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# Stroke, Dementia and Atrial Fibrillation

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Edited by

Vincenzo Russo and Riccardo Proietti

Printed Edition of the Special Issue Published in *Medicina*

# **Stroke, Dementia and Atrial Fibrillation**



# Stroke, Dementia and Atrial Fibrillation

Editors

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## About the Editors

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# Preface to “Stroke, Dementia and Atrial Fibrillation”

Stroke and dementia are among the top ten causes of death worldwide, as estimated by the World Health Organization. Atrial fibrillation (AF) is estimated to cause about 15% of all ischemic strokes and as much as 30% of strokes occurring in people in their 80s. The reduction of the burden of stroke related to AF is a difficult goal to achieve due to several clinical characteristics of AF itself: (1) Episodes of arrhythmias may be asymptomatic and misdiagnosed. (2) Stroke related to AF tends to be recurrent if an appropriate treatment is not promptly initiated. (3) During AF, silent ischemic stroke may occur that may not clinically manifest but may impact cognitive function. Indeed, silent ischemic cerebrovascular events have been recently proposed as the main pathophysiologic mechanisms linking AF with cognitive decline and dementia. (4) Finally, the disjunction between the risks of cerebrovascular events (CVE) and the burden of arrhythmias is held as a dominant concept in AF. Accordingly, the risk of CVE is not directly related to the presence of the arrhythmia but persists even during arrhythmia-free intervals. In other words, the two forms of AF classified according to duration (paroxysmal vs. persistent) of arrhythmias hold the same risk of stroke.

Given the complexity of this topic and its impact on clinical practice and public health, *Medicina* launched a Special Issue entitled “Stroke, Dementia and Atrial Fibrillation” with the aim of gathering together accurate and up-to-date scientific information on all aspects of association between cerebrovascular events, cognitive impairment and AF. The published articles not only report on the pathophysiological mechanisms underpinning this association, but also describe the results of latest clinical research about stroke prevention in AF and offer a comprehensive overview of the recent advances in understanding pharmacological interventions to prevent CVE.

**Vincenzo Russo, Riccardo Proietti**

*Editors*



Editorial

# Stroke, Dementia, and Atrial Fibrillation: From Pathophysiologic Association to Pharmacological Implications

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The impact of stroke and dementia on disability and death is a major contemporary health issue. The proportion of ischemic strokes related to atrial fibrillation (AF) ranges from one-sixth to one-third, with the highest percentage reported among octogenarians [1]. Since AF episodes may be asymptomatic and misdiagnosed, patients at increased risk of AF should be screened for the early detection of the silent AF, in order to avoid preventable cardioembolic strokes. Furthermore, both overt and silent ischemic strokes occurring in AF patients may cause vascular dementia, the more prevalent subset of dementia in this population, impacting on cognitive function [2].

Lastly, the risk of cerebrovascular events in AF patients is unrelated to the burden or persisting of arrhythmia [3]; which implies that both paroxysmal and permanent or persistent AF share the same risk of stroke and deserve anticoagulation therapy according to the patient’s CHA2DS2VASc risk score.

Until 2011, vitamin K antagonists (VKAs) represented the standard anticoagulant therapy for reducing thromboembolic risk in AF patients. However, the patient compliance to VKA treatment in real-world setting is undermined by their slow onset of action, variable pharmacologic effects, several food and drug interactions. Moreover, VKA therapy requires serial target international normalized ratio (INR) monitoring to optimize its clinical management [4,5].

To overcome these issues, non-vitamin K oral antagonists (NOACs) have been developed and are now preferred over VKA therapy in AF patients at increased risk of stroke, excluding mechanical heart valve recipients, and patients with moderate to severe rheumatic mitral stenosis [6].

NOACs have replaced VKAs therapy in several clinical settings based on phase III randomized clinical trial (RCT) results [7], and on real-world data, including AF patients with clinical features excluded from RCTs [8–11].

Moreover, NOACs are an effective and safe alternative to the best possible conventional treatment with VKAs among AF patients undergoing direct current cardioversion or percutaneous coronary interventions [12–14].

The prevalence of AF increases with advancing age, together with ischemic and hemorrhagic stroke occurrence. AF is associated with either vascular or non-vascular dementia [15], particularly among octogenarians causing their exclusion from clinical trials for doubts in adherence to treatment.

However, available data support the concept that very elderly AF patients may benefit from the increased effectiveness and safety of NOACs, likewise for the general population [16,17].

In this issue of *Medicina*, several authors gathered together the most recent evidence on the association between cerebrovascular events, cognitive impairment, and AF. Al Turki et al. produced an elegant review on the topic of subclinical AF, as detected by cardiac devices in asymptomatic patients [18]. Dual-chambered devices have the potential to identify so-called atrial high-rate episodes

(AHRE), which have been repeatedly linked to an augmented risk of stroke. The impact of duration and burden of AHRE on the risk of stroke, as well as the tendency to progress to longer episodes, are described in the review. The management of such episodes remains a matter of debate, but promising ongoing trials will soon unveil the kind of AHRE that require anticoagulation therapy according to a patient's risk profile.

Gallinoro et al. explored recent reports suggesting that AF may predict cognitive impairment and dementia, even in stroke-free patients [19]. The comprehension of the underpinning mechanisms could provide an insight into future therapeutic targets. Cerebral hypoperfusion is just one of the aspects that links AF and cognitive decline, but as far as it depends on the perpetuation of arrhythmia, the authors suggest the potential usefulness of restoring and maintaining sinus rhythm.

Poggesi et al. present the design, methodology, and preliminary results of the Strat-AF study [20]. This prospective observational study is primarily aimed at investigating how circulating biomarkers might help to further stratify the cerebral bleeding risk of AF patients on oral anticoagulation therapy. Apart from the primary endpoint, secondary outcomes include either ischemic or non-ischemic stroke occurrence and functional, cognitive, and motor status; the Strat-AF study aspires to ameliorate the available stroke prediction models by fostering the inclusion of several biomarkers.

Another important contribution by Al Turki et al. illustrates how, and in which measure, cardiovascular comorbidities may be related to AF and cognitive decline, with particular reference to metabolic disorders including diabetes mellitus and obesity [21]. The authors highlight the importance of the atrial cardiomyopathy driven by metabolic syndromes. According to this perspective, such fibrotic changes in the atria, together with chamber dilation, leads to the onset of AF and subsequently to cerebrovascular thromboembolic events. Nonetheless, cardiovascular and metabolic comorbidities prompt cognitive impairment and dementia, other than vascular, through different pathways not yet fully understood. There is mounting evidence that the antihyperglycemic therapy used for the treatment of diabetes mellitus can alter the occurrence of stroke and AF. This aspect has been extensively reviewed by Lăcătușu et al. [22], who pointed out paradoxical effects for different antidiabetic drugs, calling for new trials aimed to deepen our understanding in the field.

In conclusion, the main scope of the present Special Issue is to summarize the most updated evidence regarding the interplay between AF, cognitive impairment, and cerebrovascular events. Given the social impact of stroke and dementia, a continuous and vigorous effort from the scientific community is needed to fill substantial knowledge gaps.

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Review

# Subclinical Atrial Fibrillation and Risk of Stroke: Past, Present and Future

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**Abstract:** Subclinical atrial fibrillation (SCAF) describes asymptomatic episodes of atrial fibrillation (AF) that are detected by cardiac implantable electronic devices (CIED). The increased utilization of CIEDs renders our understanding of SCAF important to clinical practice. Furthermore, 20% of AF present initially as a stroke event and prolonged cardiac monitoring of stroke patients is likely to uncover a significant prevalence of SCAF. New evidence has shown that implanting cardiac monitors into patients with no history of atrial fibrillation but with risk factors for stroke will yield an incidence of SCAF approaching 30–40% at around three years. Atrial high rate episodes lasting longer than five minutes are likely to represent SCAF. SCAF has been associated with an increased risk of stroke that is particularly significant when episodes of SCAF are greater than 23 h in duration. Longer episodes of SCAF are incrementally more likely to progress to episodes of SCAF >23 h as time progresses. While only around 30–40% of SCAF events are temporally related to stroke events, the presence of SCAF likely represents an important risk marker for stroke. Ongoing trials of anticoagulation in patients with SCAF durations less than 24 h will inform clinical practice and are highly anticipated. Further studies are needed to clarify the association between SCAF and clinical outcomes as well as the factors that modify this association.

**Keywords:** subclinical atrial fibrillation; atrial high rate episodes; stroke

## 1. Background

Subclinical atrial fibrillation (SCAF) is a term used to describe atrial fibrillation (AF) detected by cardiac devices in an asymptomatic patient [1]. These episodes are presumed to be of relatively short duration. A more accurate term is atrial high rate episodes (AHRE) given the difficulty in establishing that these episodes are indeed SCAF. AF is the one of the common arrhythmias encountered in clinical practice and is a major cause of preventable thromboembolic disease, namely stroke [2]. Early treatment of AF is considered essential to prevent stroke [3]; in up to 20% of AF cases, stroke may be the initial manifestation [4]. Whether SCAF is associated with stroke has been the subject of several studies [1] (references 16–19 should also be cited here).

Cardiac implantable electronic devices (CIED), namely pacemakers, implantable cardioverter defibrillators and implantable monitors are increasingly implanted worldwide. In 2009, 1.3 million CIEDs were implanted with over 400,000 CIEDs implanted in North America alone [5]. Specifically,



there has been a significant increase in the implantation of pacemakers for sinus node dysfunction, which is associated with AF, as well as a significant absolute and relative increase in the use of dual-chambered pacemakers that provide an atrial lead which allows monitoring [6]. With an increased prevalence of CIEDs has come an increase in device detected AHRE (SCAF). This presents a conundrum to clinicians with regards to discussing the risk of clinical outcomes, namely stroke, with patients and whether these patients should be receiving oral anticoagulation. Does the duration of these episodes or burden of SCAF increase the risk of stroke? SCAF duration generally refers to the duration of a single episode of SCAF while SCAF burden refers to the daily burden of SCAF average over a certain period of time; the terms are sometimes used interchangeably.

Understanding the significance of SCAF is important with implications for clinical practice. This review assesses the risk of stroke associated with SCAF, the mechanisms underlying the association between SCAF and stroke as well as the effect of SCAF burden on stroke risk; finally ongoing trials that will inform clinical practice will be reviewed.

## 2. Importance of SCAF

Our initial understanding of the importance of SCAF stems from studies of patients who developed stroke. A significant proportion of strokes appeared to be of embolic origin with no clear cause after guideline-directed investigation for embolic causes [7]. This usually includes cardiac monitors for 24–48 h after the admission to screen for AF [8]. Despite extensive investigations, often no cause is found, and these patients are described to have an embolic stroke of undetermined source (ESUS) or cryptogenic stroke [7,9,10]. The Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) and the 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation after a Cerebral Ischemic Event (EMBRACE) trials have shown that with prolonged monitoring, including those via implantable cardiac devices, a significant proportion of patients with cryptogenic strokes have underlying asymptomatic AF episodes [11,12]. The importance of the detection of AF lies in its impact on subsequent management of stroke secondary prevention: Standard anti-platelet therapy if not related to AF and anticoagulation if due to AF [13]. Evidence from the EMBRACE and the CRYSTAL-AF emphasize the importance of undetected AF in terms of stroke risk [11,12]. While the majority (60%) of strokes are due to documented cerebrovascular disease, 15% are due to documented AF and 25% are due to ESUS [14]. Understanding the relationship between SCAF and stroke is thus imperative.

In the EMBRACE trial, patients were enrolled if they were 55 years or older, had experienced an ESUS event in the preceding six months which was confirmed by a stroke neurologist, and did not have AF and or another cause of stroke after extensive testing [12]. Patients were randomized in this open-label trial to undergo ambulatory electrocardiogram monitoring with a 30-day event-triggered loop recorder or one additional round of 24-h Holter monitoring [12]. Results of this trial showed AF lasting 30 s or longer was detected in 16.1% with the a 30-day event-triggered loop recorder compared to 3.2% in the control group (absolute difference, 12.9 percentage points; 95% confidence interval (CI), 8.0 to 17.6;  $p < 0.001$ ; number needed to screen, eight) [12]. In the CRYSTAL-AF trial, investigators similarly enrolled patients who were 40 years and older who had experienced an ESUS event in the preceding three months that was supported by both symptoms and brain imaging and did not have a cause of ESUS after extensive testing [11]. Patients were randomized to receive either an implantable loop recorder (REVEAL XT) or conventional follow-up. At 12 months of follow-up, AF had been detected in 12.4% who received an implantable monitor compared to 2.0% of patients who received conventional therapy (hazard ratio (HR) 7.3; 95% CI, 2.6 to 20.8;  $p < 0.001$ ) [11].

Two trials, New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source (NAVIGATE-ESUS) and Randomized, Double-Blind, Evaluation in Secondary Stroke Prevention Comparing the Efficacy and Safety of the Oral Thrombin Inhibitor Dabigatran Etexilate versus Acetylsalicylic Acid in Patients with Embolic Stroke of Undetermined Source (RESPECT-ESUS), have evaluated a strategy of empiric anticoagulation for all patients with cryptogenic stroke [9,10]. These trials failed to demonstrate the superiority of oral anticoagulation over aspirin in the reduction of recurrent strokes in patients with ESUS [9,10]. This further highlights the importance of the detection of SCAF as well as understanding which patients with SCAF should receive treatment.

### **3. Stroke Risk**

Several studies have assessed patients who had an implantable device for any indication and followed them for the development of AHRE [14–19]. These studies are summarized in Table 1. An implanted atrial lead allows for continuous detection and characterization of AHRE over a prolonged period of time [1]. Pollak and colleagues showed that a cut-off of five minutes for AHRE significantly reduces the risk that oversensing episodes are classified as SCAF [20].

**Table 1.** The incidence of subclinical atrial fibrillation (SCAF) and associated stroke in patients with cardiac implantable electronic devices (CIEDs).

| Study (First Author, Year)                  | Study Population  | Design                   | Mode of SCAF Detection                  | SCAF Criteria + Burden | Clinical Outcome            | Annual Stroke and Systemic Embolism Event Rate (%)   | Comparative Outcomes (HR, 95% CI) | F/u       | Incidence of SCAF (%) |
|---|---|--------------------------|---|------------------------|-----------------------------|--|-----------------------------------|-----------|-----------------------|
|   | 2580 patients<br>Inclusion criteria:<br>1. ≥65 years<br>2. HTN requiring medical therapy<br>3. Initial implantation of a St. Jude Medical dual-chamber pacemaker (for sinus-node or atrioventricular-node disease) or defibrillator (for any indication) in the preceding 8 weeks.<br>Exclusions: History of atrial fibrillation or flutter or an indication for oral anticoagulation | Prospective cohort study | Dual chamber pacemaker or defibrillator | > 190 bpm + ≥6 min     | Stroke or systemic embolism | SCAF = 1.69<br>No SCAF = 0.69  | 5.56,<br>1.28–4.85                | 2.5 years | 10.1                  |
| <b>ASSERT (Healey et al., 2013) [1]</b>     | 256 patients<br>Inclusion criteria:<br>1. ≥65 years AND<br>2. CHA2DS2-VASc score > 2, OR<br>3. obstructive sleep apnea, OR<br>4. BMI > 30, AND<br>5. Left atrial enlargement<br>6. OR<br>7. elevated serum N-terminal pro-brain-type natriuretic peptide level ≥ 290 pg/mL  | Prospective cohort study | CONFIRM AF subcutaneous cardiac monitor | + ≥6 min               | NA                          | 6 events occurred (4 stroke, 1 TIA and 1 systemic embolism) but none in patients who had SCAF detected | NA                                | 16 months | 34.4                  |
| <b>ASSERT II (Healey et al., 2017) [21]</b> |   |                          |   |                        |                             |  |                                   |           |                       |

Table 1. *Cont.*

| Study (First Author, Year)                          | Study Population  | Design                   | Mode of SCAF Detection                   | SCAF Criteria + Burden | Clinical Outcome               | Annual Stroke and Systemic Embolism Event Rate (%) | Comparative Outcomes (HR, 95% CI) | F/u       | Incidence of SCAF (%) |
|---|---|--------------------------|--|------------------------|--------------------------------|--|-----------------------------------|-----------|-----------------------|
| AT 500 registry (Capucci et al., 2005) [18]         | 225 patients<br>Inclusion criteria:<br>1. Bradycardia<br>2. Guideline indication for dual-chamber pacing<br>3. History of documented symptomatic atrial tachyarrhythmias  | Prospective cohort study | Dual chamber pacemaker                   | NA + 24 h              | Stroke or systemic embolism    | NA   | 3.10, 1.10–10.50                  | 22 months | NA                    |
|   | 312 patients<br>Inclusion criteria:<br>1. ≥21 years<br>2. Dual-chamber pacemaker for sinus node dysfunction<br>3. In sinus rhythm at onset of study   | Prospective cohort study | Dual chamber pacemaker                   | >220 bpm + ≥5 min      | Stroke and all-cause mortality | SCAF = 1.82<br>No SCAF = 0.48                      | 2.79, 1.51–5.15                   | 33 months | 51.3                  |
|   | 560 patients<br>All patients had heart failure and a biventricular pacemaker capable of continuous heart rhythm monitoring through home monitoring.<br>Patients in sinus rhythm (including patients with a prior history of AF) with >70% home monitored transmissions during follow up (minimum >3 months follow-up) | Prospective cohort study | Biventricular pacemaker or defibrillator | >180 bpm + ≥3.8 h      | Stroke or systemic embolism    | NA   | 9.40, 1.80–47.00                  | 12 months | 40                    |
| HOME CARE and EVEREST (Shannugam et al., 2011) [19] |   |                          |  |                        |                                |  |                                   |           |                       |

Table 1. *Cont.*

| Study (First Author, Year)                | Study Population  | Design                   | Mode of SCAF Detection | SCAF Criteria + Burden | Clinical Outcome            | Annual Stroke and Systemic Embolism Event Rate (%) | Comparative Outcomes (HR, 95% CI) | F/u       | Incidence of SCAF (%) |
|---|---|--------------------------|------------------------|------------------------|-----------------------------|--|-----------------------------------|-----------|-----------------------|
| SOS-AF (Boriani et al., 2014) [17]        | 10,016 patients<br>Inclusion:<br>CIED able to monitor for atrial high rate episodes<br>At least 3 months of follow-up<br>Device diagnostic data available<br>Did not have permanent AF  | Prospective cohort study | CIED                   | >175 bpm + ≥5 min      | Stroke                      | SCAF = 0.49<br>No SCAF = 0.31                      | 1.76,<br>1.02–3.02                | 24 months | 43                    |
| <b>TRENDS (Glotzer et al., 2009) [15]</b> | 2486 patients<br>Inclusion criteria:<br>1. Guideline indication for an implantable cardiac rhythm device capable of long-term monitoring<br>2. At least 1 risk factor for stroke<br>Exclusion criteria:<br>1. Replacement devices<br>2. Long-standing persistent AF<br>3. Known re-entrant supraventricular tachycardias,<br>4. Terminal illness<br>5. Unable or unwilling to consent<br>6. Enrolled in a conflicting drug or device study. | Prospective cohort study | CIED                   | >175 bpm + ≥5.6 h      | Stroke or systemic embolism | SCAF = 2.4<br>No SCAF = 1.1                        | 2.20,<br>0.96–5.05                | 1.4 years | 55.9                  |

SCAF = Subclinical atrial fibrillation; HR = hazard ratio; CI = confidence interval; FU = follow up; CIED = cardiac implantable electronic device; TIA = transient ischemic attack; NA = not available; HTN = hypertension; BMI = body mass index; CHA2DS2-VASc = congestive heart failure, hypertension age, diabetes mellitus, stroke, vascular disease, age and sex.

In an ancillary study of the Mode Selection Trial (MOST) trial which randomized 2010 patients with sinus node dysfunction to dual chamber versus single chamber pacing, Glotzer et al. enrolled 312 patients and followed them for 27 months (median) with the atrial detection rate programmed to 220 beats per minute for at least 10 beats [16]. Analysis was limited to episodes of at least five minutes in keeping with the data by Pollack et al. [20]. Of the patients enrolled, 51% experienced at least one episode of AHRE ( $\geq$  five minutes). In 160 patients with an AHRE, the primary endpoint of death or nonfatal stroke occurred in 33 patients (20.6%) compared to 10.5% in those without AHRE. AHRE was an independent predictor of death or stroke [16]. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT) trial enrolled 2580 patients who were  $\geq$ 65 years old, had hypertension but no history of AF who had received a CIED (from St Jude Medical) for sinus node or atrioventricular node dysfunction in the eight weeks prior to enrollment [1]. Patients were excluded if they had any history of AF or atrial flutter or if they required oral anticoagulation for any indication. These patients were then monitored for three months to assign patients into two groups, those with AHRE (defined as an atrial rate of 190 beats or more lasting more than six minutes) and those without AHRE. The patients were subsequently followed every six months for a mean of 30 months for the primary outcome which consisted of systemic embolism or stroke [1]. At the three-month monitoring period, SCAF had occurred in 10.1% of patients. SCAF was associated with a five-fold increased risk of clinical AF (HR 5.56; 95% CI 3.78 to 8.17;  $p < 0.001$ ) and a 2.5-fold increased risk of stroke or systemic embolism (HR 2.49; 95% CI, 1.28 to 4.85;  $p = 0.007$ ). After adjustment for stroke predictors, SCAF remained predictive of the stroke or systemic embolism [1]. Though the stroke risk is not as high as that seen with clinical AF, which is four to five times the general population, it is still significant at two to two-and-a-half times the general population [22]. The major limitation of the ASSERT trial is that SCAF was defined using a limited sampling period of three months post device implantation. SCAF, in that time-period may have been transient due to lead implantation (Mittal et al. 2008). These trials also do not differentiate the type of strokes due to limitations with data. The data from MOST and ASSERT clearly demonstrate that patients with SCAF have an associated risk of stroke but a risk lower than clinical AF. Further studies and analyses are required to better improve our understanding of SCAF

An important observation of the above-mentioned studies is that SCAF was detected in patients with implantable pacemaker and defibrillators who were therefore at higher risk of developing AF. Whether this risk translates into increased risk in the general population were they to be monitored remained controversial. Several studies have attempted to address this issue by having cardiac monitors implanted for the purpose of monitoring for SCAF. These studies are also included in Table 1. In an international prospective, single-arm, multicenter study (REVEAL-AF), conducted from November 2012 to January 2017, 386 patients with at least three risk factors for stroke were enrolled after initial screening [23]. Participants received an implanted cardiac monitor for a mean of 22.5 months (Reveal XT or Reveal LINQ; Medtronic). The primary end point was adjudicated AF lasting six or more minutes and was assessed at 18 months. In addition, the median time from device insertion to SCAF detection was also assessed as was the subsequent prescription rate for anticoagulation. The incidence rate of significant SCAF  $\geq$  six minutes progressively increased with longer monitoring: 6% at 30 days, 20% at six months, 27% at one year, 34% at two years and finally 40% at 30 months. The median time from insertion to detection of SCAF was three months and 72 patients (56% of those who developed SCAF at the 18-month primary end-point of the trial) received oral anticoagulation [23]. Similarly, ASSERT-II was a prospective single-arm multi-center study that enrolled 256 patients from cardiology and neurology clinics who had no history of AF and at least two risk factors for stroke [21]. In addition, patients were required to have an element of cardiomyopathy manifest as either an enlarged left atrium or elevated brain natriuretic peptides. Significant SCAF was defined as episodes lasting longer than five minutes and follow-up was for 17 months. The incidence of SCAF was 34% which was predicted by age, hypertension and an enlarged left atrium [21]. The major knowledge gap in this area is patient selection given the lack of clinical outcomes and cost-effectiveness analyses.

#### 4. SCAF Burden

Whilst SCAF was clearly associated with an increased risk of stroke, uncertainty remained as to whether longer episodes were more likely to be associated with stroke. In a scientific statement, the American Heart Association acknowledges the large knowledge gaps pertaining to AF burden. In particular, the statement notes the burden at which clinical outcomes increase remains unknown [24]. TRENDS (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics) was a prospective observational study in patients with a CIED and at least one risk factor for stroke [15]. Patients were excluded if they had long-standing persistent AF, re-entrant supraventricular arrhythmias or a terminal illness. Interestingly, patients with paroxysmal AF were included in this study. Follow-up visits occurred every three months, but the study was terminated early due to a low event rate. AHRE detection settings were set at an atrial rate of greater than 175 beats per minute lasting greater than 20 s. The authors concede that these settings would not help differentiate AF from other atrial tachyarrhythmias [15]. In addition, with such a short detection duration, the device was liable to record over-sensed events as AHRE. Patients were classified into three groups based on the longest duration of AHRE during 30-day window subsets: Zero burden, low burden ( $\leq 5.5$  h) and high burden ( $> 5.5$  h). During a mean follow-up of 1.4 years, the annualized thromboembolic (stroke and transient ischemic (TIA)) risk was 1.1% in the zero-burden group, 1.1% in the low burden group, and 2.4% in the high burden group. In comparison to those with zero-burden, the adjusted HR in the low and high burden subsets were 0.98 (95% CI 0.34 to 2.82,  $p = 0.97$ ) and 2.20 (95% CI 0.96 to 5.05,  $p = 0.06$ ), respectively [15]. The inclusion of patients with history of paroxysmal AF was a major limitation of this study. In a systematic review and meta-analysis, Mahajan et al. pooled data from seven studies. The duration cut-off for AHRE varied among the included studies. In patients with subclinical AF exceeding the defined cut-off SCAF duration of the study, the annual stroke rate was 1.89/100 person-year with a 2.4-fold (95% CI 1.8–3.3,  $p < 0.001$ ) increased risk of stroke compared to patients with subclinical AF who did not reach the cut-off duration; the absolute risk was 0.93/100 person-years [25].

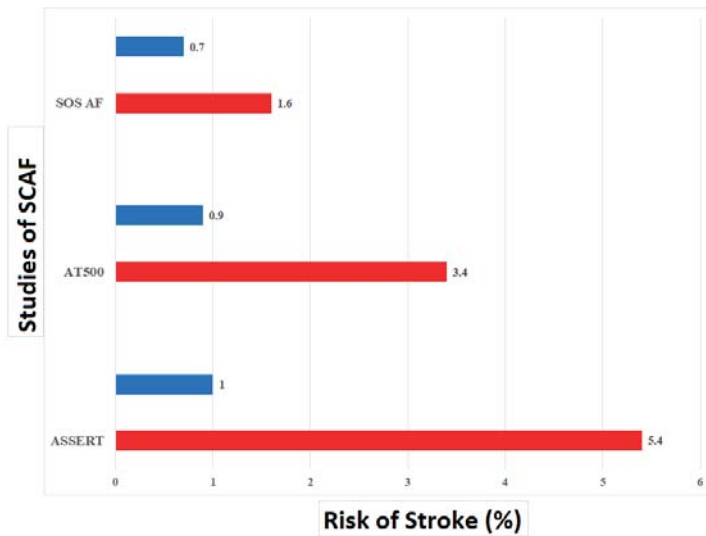
Attempts were made to assess whether increased AF burden was associated with an increased risk of stroke. Proietti and colleagues performed a systematic review and meta-analysis to assess whether SCAF burden is associated with stroke risk [26]. This analysis was limited by a small number of studies that reported such data and the varying cut-off points used in the studies. The authors concluded that a direct correlation between burden of asymptomatic AF and HR for stroke cannot be confirmed [26]. Van Gelder and colleagues performed an important analysis of the ASSERT study which showed that SCAF for a duration  $> 24$  h is associated with an increased risk of ischemic stroke or systemic embolism [27]. Patients were divided into groups depending on the duration of the single longest duration of SCAF: 19%  $>$  six minutes to 6 h, 7%  $>$  six hours to 24 h and 10.7%  $>$  24 h; patients with SCAF for  $< 6$  min were excluded from this analysis; patients were followed for 2.5 years. In patients in whom the longest episode of SCAF exceeded 24 h, there was an associated significant increased risk of stroke (adjusted HR 3.24, 95% CI 1.51–6.95,  $p = 0.003$ ). In patients with SCAF between six minutes and 24 h, the risk of stroke was not significantly different from patients without SCAF [27]. Patients who had SCAF for  $\geq 24$  h had an annual stroke risk of approximately 5% which is similar to the risk observed in patients with clinical AF. The significant increase in stroke risk with episodes  $> 24$  h was also noted in the AT500 registry [18]. These studies have informed the current practice of prescribing oral anticoagulation in patients with SCAF episodes  $> 24$  h but questions remained regarding patients with long episodes of SCAF not reaching 24 h and those who experience progression to longer SCAF episodes. Going forward, another metric, such as AF density may become clinically relevant. AF density incorporates the temporal dispersion of AF burden (Charitos et al.); further studies are needed to compare the effects of AF burden and AF density.

## 5. Progression

Whether progression to longer episodes of SCAF is associated with an increased risk of stroke is unclear. Initial data came from anticoagulation studies that compared the risk of stroke in patients with paroxysmal compared to more persistent forms of AF. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, in which patients with AF were randomized to apixaban versus warfarin, the incidence of stroke or systemic embolism was significantly higher in patients with persistent or permanent AF compared to patients with paroxysmal AF (1.52 vs. 0.98%;  $p = 0.003$ , adjusted  $p = 0.015$ ) [28]. In the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial, patients with AF were randomized to receive either rivaroxaban or warfarin. There was a significantly higher risk of stroke (2.18 vs. 1.73 events per 100-patient-years,  $p = 0.048$ ) and death (4.78 vs. 3.52 events per 100-patient years,  $p = 0.006$ ) in patients with persistent AF compared to paroxysmal AF [29]. Data from clinical AF suggests that progression to a greater AF burden increases stroke risk. De Vos showed that approximately 15% of patients with paroxysmal AF progress to persistent AF at one year of follow-up [30]; this progression is predictable using clinical risk scores such as the Hypertension, Age, Transient ischaemic attack or stroke, Chronic obstructive pulmonary disease, and Heart failure (HATCH) score [30,31] and may be preventable with catheter ablation [32]. Patients who progress are more likely to become symptomatic or experience a stroke or TIA [30].

Similar findings were found in patients with SCAF. Boriani et al. pooled patient level data from three prospective studies: TRENDS, Stroke preventiOn Strategies based on Atrial Fibrillation information from implanted devices (SOS) and Phase IV Long Term Observational Study of Patients Implanted With Medtronic CRDM Implantable Cardiac Devices (PANORAMA) [33]. Among the study population of 6580 patients, de novo AF with a SCAF burden of  $\geq 5$  min, was detected in 2244 patients (34%) during a follow-up period of  $2.4 \pm 1.7$  years. Among these patients, 1091 (49.8%) transitioned to a higher SCAF-burden threshold during follow-up. Approximately 24% of patients transitioned from a lower threshold to a daily SCAF burden of  $\geq 23$  h during follow-up. Factors associated with transition to a greater SCAF burden on multivariate analysis included male gender and a CHADS2 (Congestive heart failure, Hypertension, Age $>75$ , Diabetes mellitus and Stroke or transient ischemic attack) score of two or greater (33). Figure 1 shows the risk associated with a SCAF burden  $\geq 23$  h in various studies compared to no SCAF. Wong et al. also performed a sub study of ASSERT to assess the impact of SCAF burden progression. Patients in whom the longest SCAF episode was  $>6$  min but  $<24$  h during the first year (415 patients) were included [34]. The authors assessed the association between progression to SCAF  $>24$  h or the development of clinical AF and heart failure hospitalizations. During a mean follow-up of two years, 15.7% of patients progressed. The rate of heart failure hospitalization among patients with SCAF progression was 8.9% per year compared with 2.5% per year for those without progression. After multivariable adjustment, SCAF progression was independently associated with HF hospitalization (HR 4.58; 95% CI: 1.64 to 12.80;  $p = 0.004$ ). These results remained significant even if patients with a history of heart failure were excluded or when the analysis was limited to only progression to SCAF  $>24$  h and not clinical AF [34]. Therefore, it seems that a significant SCAF burden of greater  $>24$  h is associated not only with an increased risk of stroke but also an increased risk of heart failure hospitalizations [22]. This is consistent with the relationship seen between clinical AF and heart failure in which a vicious cycle can develop [35].

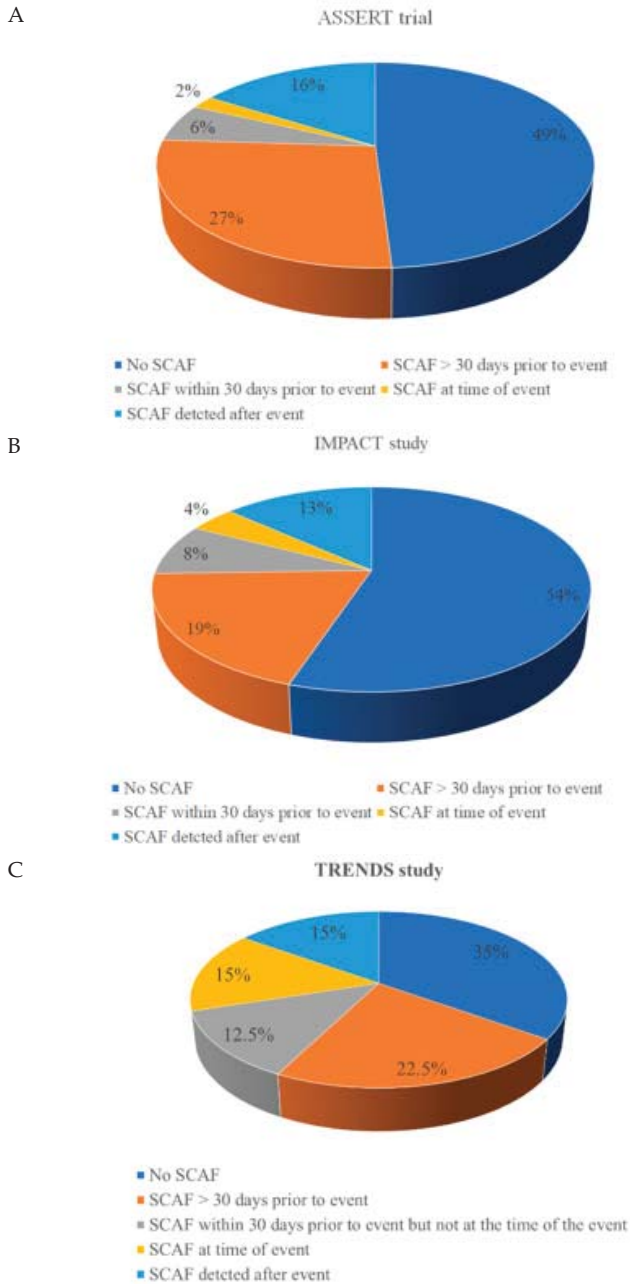




**Figure 1.** The risk of stroke associated with a SCAF burden  $\geq 23$  h in different studies compared to no SCAF. Risk of stroke in patients with SCAF  $\geq 23$  h (red) compared to no SCAF (blue). SCAF = subclinical atrial fibrillation.

## 6. Mechanism of Increased Stroke in SCAF

A direct and causal relationship between SCAF and stroke is not entirely clear. In its scientific statement the American Heart Association recognizes the presence of an important knowledge gap with regard to whether a temporal relationship exists between AF burden and stroke risk [24]. The association between AF and stroke is complex. There is a strong causal association between AF and embolic stroke but also an association with ischemic stroke [36]. In addition to causing atrial thromboembolism through stasis and clot formation, other factors such as endothelial dysfunction, left atrial fibrosis, myocyte dysfunction, chamber dilatation and left atrial appendage mechanical dysfunction may also have a role in stroke risk [37]. Brambatti and colleagues performed a sub-analysis of the ASSERT trial to assess the temporal association between SCAF and stroke and systemic embolism; the analysis included SCAF  $> 6$  min [38]. Of all the patients who experienced a stroke or systemic embolism, 51% had SCAF in keeping with previous data that shows that 50–60% of strokes are due to atherosclerosis and not thromboembolism. However, of the patients experiencing SCAF, only 16% had SCAF in the 30 days preceding the stroke or systemic embolism event [38]. A sub-analysis of the TRENDS study had similar findings; only 11 (27.5%) of the 40 patients developing clinical thromboembolism exhibited SCAF within 30 days before the event [39]. Figure 2 depicts the temporal relationship between SCAF and stroke in three studies [40].



**Figure 2.** SCAF and stroke: A temporal relationship based on data from (A) ASSERT, (B) IMPACT and (C) TRENDS. All stroke or systemic embolism events are correlated with SCAF.

There are several important points to note from this data in the context of our current understanding of AF. For the majority of stroke or systemic embolism events, there was no temporal relationship with SCAF. When a temporal relationship existed, the duration of SCAF was almost always much shorter in

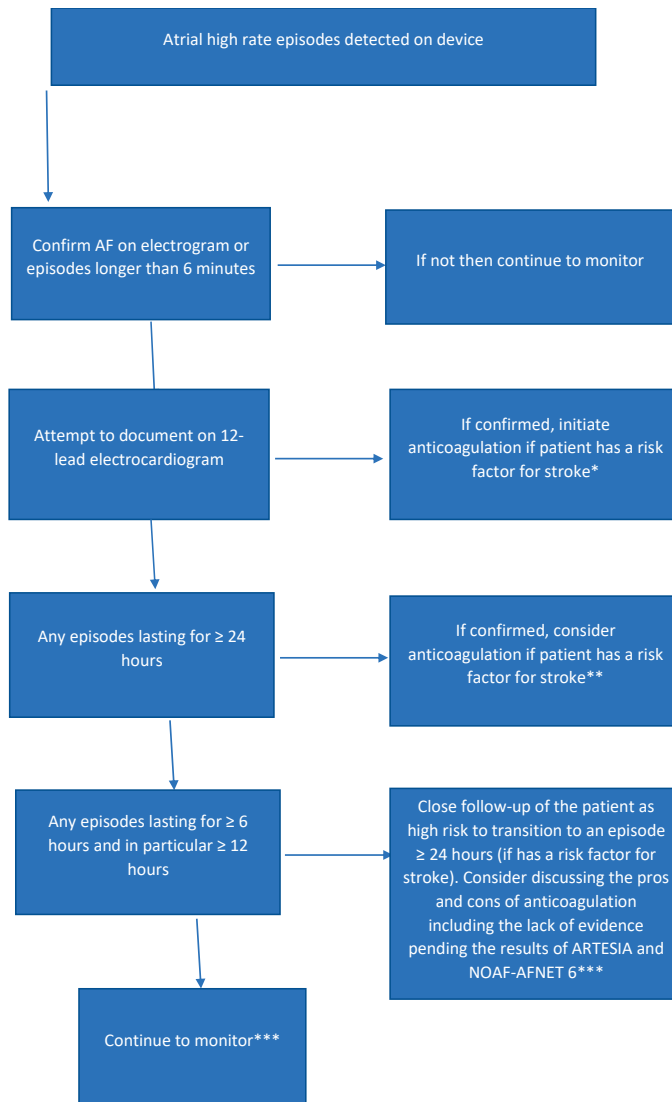
duration than the 48 h commonly believed to be the minimum duration required for thrombus to form in the left atrial appendage; this is the time period considered safe for cardioversion [41]. Furthermore, those with SCAF who experienced stroke did not require progression to longer episodes in order to develop stroke or systemic embolism. Therefore, SCAF is likely an important risk marker for stroke and systemic embolism and if there is a direct causal relationship this is not as simple as a direct predictable relationship.

## 7. Treatment

The treatment of SCAF presents several challenges due to the issues raised above. There are several factors to keep in mind when considering the treatment of SCAF. In clinical AF, oral anticoagulation is recommended regardless of AF subtype and depending on the presence of clinical factors (age, hypertension, diabetes mellitus, heart failure and stroke) which have consistently been shown to increase stroke risk [42]. Given that oral anticoagulation has been shown to significantly decrease stroke risk in clinical AF, this risk reduction should theoretically translate to SCAF. However, in SCAF the increased risk is of a lower magnitude (2–2.5 times) compared to clinical AF (5 times) and this may reduce the net clinical benefit observed with anticoagulation in SCAF. Patients with SCAF >24 h have an absolute risk profile that is similar to that observed in clinical AF and are the subgroup of SCAF most likely to derive benefit from oral anticoagulation. This is consistent with current guidelines [42]. An algorithm for the management of SCAF is proposed in Figure 3.

The equipoise in whether patients with SCAF should receive oral anticoagulation can be observed in clinical practice. Healey et al. performed a retrospective analysis of all patients at a single academic hospital who had pacemakers capable of documenting AF [43]. In 445 patients studied, SCAF was found in 55% of patients who were more likely to be older, have history of clinical AF and a large left atrium. Anticoagulants were used more frequently among patients who also had clinical AF (58.9%) compared with those without (23.7%,  $p < 0.001$ ) [43].

One strategy that was attempted is intermittent anticoagulation during episodes of SCAF with the premise that stroke risk is highest at that time-point while avoiding the risk of bleeding at other times. In the Multicenter Randomized Trial of Anticoagulation Guided by Remote Rhythm Monitoring in Patients with Implanted Cardioverter-Defibrillator and Resynchronization Devices (IMPACT) trial, 2718 patients with CIEDs were randomized to start and stop anticoagulation based on remote rhythm monitoring compared to usual office-based follow-up with anticoagulation determined by standard clinical criteria [44]. The primary endpoint was a composite of stroke, systemic embolism, and major bleeding. The trial was stopped early after a two-year median follow-up due to futility. Primary events (2.4 vs. 2.3 per 100 patient-years) were similar between the two groups (HR 1.06; 95% CI 0.75–1.51;  $p = 0.732$ ) [44]. There are multiple issues that limit inferences from this trial. Firstly, it was performed in the era of warfarin which limits the ability to provide rapid intermittent anticoagulation and which increases the risk of bleeding. In addition, because major bleeding was used in the primary endpoint composite, this may have led to the neutral result (observed and early termination. In addition, the algorithm for home monitoring was complex with poor adherence. In the end, anticoagulation use was similar in both arms [44].



**Figure 3.** Suggested clinical algorithm for the management of SCAF. \* Based on current atrial fibrillation guidelines [2,42]; \*\* based on current guidelines to consider anticoagulation when a device detected episode is for 24 h or longer [42]; \*\*\* data suggests that these patients are at high risk to transition to episodes lasting 24 h or longer [33]. \*\*\* Management for patients with an episode > 6 min is currently unclear and such patients may be eligible for enrolment in the ARTESIA and NOAF-AFNET 6 trials depending on the presence of other risk factors for stroke.

### 8. Future Directions

Current guidelines suggest that patients with AHRE (SCAF) greater than 24 h as well as at least one risk factor for stroke should receive oral anticoagulation [42]. In addition, the guidelines also suggest that patients with shorter durations of AHRE who are at high risk such as those with cryptogenic stroke should be considered for oral anticoagulation [42]. The gap in knowledge exists for patients who

have episodes between 6 min and 24 h, particularly in patients with relatively longer episodes. Given the clinical equipoise in this population, two trials are currently underway to try and provide clarity: The Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESIA) trial and the Non-vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes (NOAH-AFNET 6) trial [45,46].

ARTESIA is a prospective, multicenter, double-blind, randomized controlled trial, enrolling patients with SCAF detected by a CIED who have additional risk factors for stroke [46]. To be eligible, participants must have had at least one episode of SCAF  $\geq 6$  min in duration on device interrogation, be at least 55 years of age or older and have risk factors for stroke (the number of risk factors depends on the age with those 75 years of age or older not requiring any further risk factors) [46]. The trial will exclude patients with documented AF on a 12-lead electrocardiogram or those who have an indication for oral anticoagulant therapy. Participants will be randomized to apixaban or aspirin 81 mg daily and will receive placebo pills accordingly (aspirin and two placebo pills instead of apixaban or apixaban and placebo aspirin) [46]. The primary outcome is the composite of stroke, TIA (with magnetic resonance imaging evidence of a cerebral infarction on diffusion-weighting) and systemic embolism. The trial is aiming to recruit around 4000 patients from 230 international clinical sites. ARTESIA is expected to have 36 months of follow-up until 248 adjudicated primary outcome events have occurred [46].

NOAH-AFNET 6 is an investigator-driven, prospective, parallel-group, randomized, event-driven, double-blind, multicenter trial [45]. The trial will recruit patients with SCAF detected by a CIED with at least one risk factor for stroke. To be eligible, participants must have AHRE, be aged  $\geq 65$  years with at least one other stroke risk factor. Excluded will be patients with documented AF or an indication for oral anticoagulation. These broad inclusion/exclusion criteria were put in place to mimic clinical practice. NOAH-AFNET 6 will randomize 3400 patients to edoxaban or no anticoagulation (aspirin depending on clinical indications) in a superiority trial. The primary efficacy outcome is stroke or cardiovascular death and the primary safety outcome will be major bleeding. All patients will be followed until the 222 target primary outcomes are reached. Patients will be censored when they develop AF and offered open-label anticoagulation [45].

Further studies are needed to improve our understanding of SCAF, its clinical impact and the role of different therapies. A prospective study of well-matched patients with SCAF compared to clinical AF would provide insight into the true incidence of thromboembolic events in both groups. In addition, a greater understanding of the temporal relationship between SCAF and thromboembolic events is needed which would need a larger study. Does atrial AF burden or density significantly increase risk; and consequently, does the reduction of SCAF burden mitigate this risk? Studies in clinical AF suggest that this is unlikely to be the case. Finally, does anticoagulation therapy in patients with high SCAF burden/density, those who have significant progression of SCAF or patients with evidence of an underlying cardiomyopathy (enlarged left atrium or elevated natriuretic peptides) significantly reduce the risk of thromboembolic events?

There are several noteworthy limitations and unanswered questions regarding SCAF with current data. Not all stroke events in SCAF studies are embolic strokes and as shown above with the timing of stroke relative to the SCAF episode, SCAF may be a risk marker for stroke. Another important element to consider when discussing AF and SCAF burden is the large discrepancy between clinical and device detected categorization of the pattern of AF. Charitos and colleagues showed that while the majority of patients with AF are clinically classified as paroxysmal AF, this correlates poorly with the temporal persistence of AF based on continuous device monitoring [47]. The impact of this discrepancy on clinical practice remains unclear. Finally, the highly anticipated results of the two anticoagulation in SCAF trials should be released in 2022 with the large potential to change clinical practice.

## 9. Conclusions

Cardiac implantable electronic devices have led to the detection of SCAF which has clearly been shown to be associated with an increased risk of stroke. Based on current data, patients with episodes of

SCAF lasting for 24 h or greater and at least one risk factor for stroke should receive oral anticoagulation. Longer episodes of SCAF and progression to longer episodes also confer an increased risk of stroke. Trials are now underway to assess the efficacy and safety of oral anticoagulation in patients with SCAF lasting less than 24 h.

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Review

# Subclinical and Asymptomatic Atrial Fibrillation: Current Evidence and Unsolved Questions in Clinical Practice

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**Abstract:** Atrial Fibrillation (AF) may be diagnosed due to symptoms, or it may be found as an incidental electrocardiogram (ECG) finding, or by implanted devices recordings in asymptomatic patients. While anticoagulation, according to individual risk profile, has proven definitely beneficial in terms of prognosis, rhythm control strategies only demonstrated consistent benefits in terms of quality of life. In fact, evidence collected by observational data showed significant benefits in terms of mortality, stroke incidence, and prevention of cognitive impairment for patients referred to AF catheter ablation compared to those medically treated, however randomized trials failed to confirm such results. The aims of this review are to summarize current evidence regarding the treatment specifically of subclinical and asymptomatic AF, to discuss potential benefits of rhythm control therapy, and to highlight unclear areas.

**Keywords:** subclinical atrial fibrillation; stroke; ischemic cerebral events; catheter ablation; screening; cognitive impairment

## 1. Introduction

Atrial fibrillation (AF), the most common sustained arrhythmia [1], is associated with an increased risk of thromboembolic events such as transient ischemic attack (TIA), ischemic stroke with overt neurological sequelae [2], or micro-embolic events resulting in subclinical brain lesions (revealed by neuroimaging techniques). On the other hand, AF is independently associated with a higher risk of developing dementia [3], with up to a 30% increased risk regardless of clinical cerebrovascular events [4]. Therefore, given the high prevalence of AF in the general population and its considerable impact on both life expectancy and quality of life, correct and prompt management of the arrhythmia is mandatory. However, early diagnosis can be difficult in the case of an asymptomatic presentation, defined as sustained AF episodes in patients not presenting palpitations, dyspnea, fatigue, or other AF related symptoms [5]. The exact percentage of asymptomatic presentations among patients with AF has not been clearly established. Different studies provide estimates between 10% and 40%, according to the characteristics of the population in exam [6–10]. A higher prevalence has been reported in patients with persistent AF, males, elderly, and in the presence of relevant comorbidities [7]. However, subclinical AF can also be diagnosed in patients with fewer risk factors [10] as paroxysmal AF, for example, at the early phase of arrhythmia development and progression. Moreover, variability in terminology among studies, as later discussed, increases uncertainty related to the description of asymptomatic AF.

In the present review, we shed light on several aspects of this clinical entity, highlighting doubtful elements for which further research is needed: first, we discuss the complex pathophysiological links between AF, dementia, and stroke, focusing on the clinical impact of asymptomatic AF, which has been demonstrated not to be a benign condition. Subsequently, we address the issue of screening for AF, which is of great interest from both a clinical and population medicine point of view. Finally, we discuss management of the patient with asymptomatic and subclinical AF, considering clinical recommendations, anticoagulation, antiarrhythmic drugs (AAD) therapy, and catheter ablation.

## 2. Definitions

Despite being a widely discussed topic, terminology in literature is often inconsistent and the terms “asymptomatic AF”, “subclinical AF”, “silent AF”, and “atrial high rate episodes (AHRE)” are used to identify different entities (Table 1). Different studies define “asymptomatic AF” as AF diagnosed incidentally [11] or by ECG in patients reporting no symptoms, or, alternatively, with European Heart Rhythm Association (EHRA) score 1 [6–10,12]. Other studies [6,7,10] consider silent AF and asymptomatic AF as synonyms. The STROKESTOP trial names AF “silent AF” when the diagnosis is established through screening [13]. However, in other experiences [14–16] assessing the benefit of AF screening, the arrhythmia diagnosed through a screening program is simply referred to as AF. Conversely, AHRE are defined, with variable temporal cutoffs according to different studies, as atrial tachycardia episodes recorded by the intra-atrial electrode of implanted devices. However, when an intra-atrial electrogram is available, as in the subgroup of patients of the ARTESiA trial [17], the arrhythmia episode has been defined as “subclinical AF” and not as AHRE. Instead, the ASSERT trial refers to AHRE as subclinical AF [18]: in this study the devices were able to detect atrial arrhythmias, but it remains unclear whether the electrograms were finally analyzed to define the episodes or not. These studies, in fact, consider both asymptomatic and symptomatic AF as “clinical” only when diagnosed by surface ECG. For the purpose of this review we consider device detected atrial tachycardia without electrogram documentation as AHRE; subclinical AF refers to AF either diagnosed through screening programs, incidental findings during routine ECG, or after implanted device electrograms analysis; finally, we define asymptomatic AF in patients with a clearly established AF diagnosis, undergoing a defined clinical management and who remain asymptomatic based on physician’s evaluation. According to these definitions, subclinical and asymptomatic AF are a continuum in the diagnostic process and subsequent management of AF: in fact, once the diagnosis has been confirmed and treatment has begun, subclinical AF should be referred to as clinical asymptomatic AF.

**Table 1.** Details on the terminology used in available literature.

| Authors (Study Year)         | AHRE/Subclinical/Asymptomatic AF Diagnostic Method   | Terminology Used in the Study                            | Terminology Used in This Review |
|------------------------------|--|--|---------------------------------|
| Implanted device monitoring  |  |  |                                 |
| Glotzer et al. (2003) [19]   | AHRE: atrial rate $\geq$ 220 bpm lasting at least 5 min (detected by pacemaker)  | AHRE   |                                 |
| Glotzer et al. (2006) [20]   | AHRE: atrial rate $>$ 175 bpm lasting at least 20 s  | Device-detected atrial tachycardia (AT)/AF burden (AHRE) | AHRE                            |
| Hohnloser et al. (2006) [21] | AHRE: atrial rate $\geq$ 190 bpm lasting at least 6 min (detected by pacemaker or ICD)   | Asymptomatic AF/AHRE                                     |                                 |
| Ip et al. (2009) [22]        | AHRE: atrial rate $\geq$ 220 beat/min lasting at least 5 min,  | AHRE   |                                 |
| Kirchhof et al. (2017) [23]  | AHRE: atrial rate $\geq$ 180 bpm lasting at least 6 min  | AHRE   |                                 |
| Lopes et al. (2017) [17]     | One episode of device-detected subclinical AF lasting at least 6 min. Subclinical AF requires at least one episode of electrogram confirmation | Subclinical AF   | Subclinical AF                  |

Table 1. Cont.

| Authors (Study Year)        | AHRE/Subclinical/Asymptomatic AF Diagnostic Method   | Terminology Used in the Study | Terminology Used in This Review |
|-----------------------------|--|-------------------------------|---------------------------------|
| Non-Invasive ECG monitoring |  |                               |                                 |
| Flaker et al. (2005) [12]   | AF diagnosed with ECG or rhythm strip. Symptoms evaluated by a questionnaire   | Asymptomatic AF               |                                 |
| Rienstra et al. (2014) [10] | Recurrent persistent AF without symptoms according to a questionnaire  | Asymptomatic AF/Silent AF     | Asymptomatic AF                 |
| Boriani et al. (2015) [7]   | ECG diagnosed AF and EHRA score I  | Asymptomatic AF/Silent AF     |                                 |
| Freeman et al. (2015) [9]   | Electrocardiographically documented AF and EHRA score I  | Asymptomatic AF               |                                 |
| Bakhsai et al. (2016) [6]   | ECG diagnosed AF and EHRA score I  | Asymptomatic AF/Silent AF     |                                 |
| Siontis et al. (2016) [11]  | AF detected incidentally (routine physical examination, preoperative evaluation, emergency department or clinic visit for unrelated problem) | Asymptomatic AF               | Subclinical AF                  |
| Jaakkola et al. (2017) [15] | ECG diagnosis in a screening program   | AF                            |                                 |
| Halcox et al. (2017) [16]   | Device detected AF in a screening program  | AF                            |                                 |
| Friberg et al. (2013) [13]  | Device detected AF in a screening program and confirmed by Holter for uncertain cases  | Silent AF                     |                                 |

AF: atrial fibrillation; AHRE: atrial high rate episodes; ICD: implantable cardioverter-defibrillator.

### 3. Pathophysiological Links between AF, Dementia, and Stroke

AF confers an increased risk of cognitive decline and dementia development independently from stroke occurrence. Indeed, this has been recently demonstrated in a large cohort study conducted on 262,611 patients registered in the Korea National Health Insurance Service—Senior, 60 years of age or older and no history of valvular heart disease, stroke, dementia, and AF before enrolment [24]. After adjustment, in the incident AF population the risk of developing dementia was increased after censoring for stroke (HR, 1.27; 95% CI 1.18–1.37). Interestingly, anticoagulation therapy was associated with a lower risk of developing dementia (HR, 0.61; 95% 0.54–0.68). These results are consistent, in fact, with a recent meta-analysis showing a 30% increased risk of AF patients to develop dementia regardless of cerebrovascular events [4].

The association between AF and cognitive impairment in patients without clinical stroke has been linked to several possible mechanisms: micro-embolic events occurring in cerebral circulation may lead to silent cerebral ischemia (SCI), visible by neuroimaging techniques as magnetic resonance imaging (MRI). The correlation between SCIs and cognitive impairment has been demonstrated by ad hoc questionnaires and tests designed to examine cognitive function, both in retrospective [25] and prospective studies [26]. Additionally, a computational analysis showed that AF directly affects cerebral hemodynamic, resulting in hypoperfusions and hypertensive events, possibly associated with non-embolic SCI and microbleedings in the deep cerebral circle [27,28]. Dementia and cognitive decline, however, can also be caused by clinical strokes, a well-known and feared complication of AF. Several questions on the relation between AF and stroke are actually still unsolved: the classical mechanism, based on the Virchow’s triad [29], by which AF causes strokes is thrombus formation in the left atrium (typically in the left atrial appendage), and its subsequent embolism in a cerebral vessel. Nevertheless, studies conducted in patients with implanted devices and who suffered a thromboembolic event showed that, in a large portion of patients, no AF events occurred the months before [30,31].

The link between fibrosis and AF is rather complex, since AF causes atrial remodeling and fibrosis itself causes and sustains AF. Animal experimental models demonstrated that sustained AF induces

several structural changes in atrial myocytes, including glycogen accumulation, sarcomeres reduction, mitochondrial modification, collagen deposition, and fibrosis [32]. Late gadolinium enhancement MRI studies demonstrated that more severe atrial remodeling with extensive fibrosis is associated with more advanced disease and a higher risk of AF recurrences after catheter ablation [33]. Voltage map during invasive procedures demonstrated that the magnitude of atrial fibrosis is greater in persistent [34] in comparison to paroxysmal AF, and it predicts ablation success [35]. Finally, AF can be a marker of other atrial abnormalities including atrial dilation, left atrial appendage dysfunction, endothelial disease; all these features may cause thromboembolic stroke without an AF episode occurring prior to the cerebrovascular event. Indeed, an “atrial cardiomyopathy” exists, according to which extensive atrial disease can be, at least partially, the cause rather than the consequence of AF [36,37]. Therefore, it has been proposed [30] that AF can cause atrial remodeling and be the manifestation of an atrial disease that increases per se the risk of stroke and thrombi formation, independently from the heart’s rhythm.

Actually, the association between dementia and the different clinical presentation of AF has not been thoroughly analyzed. In fact, no published studies directly analyzed cognitive impairment in patients with asymptomatic AF. Several studies evaluated the relation between subclinical AF and the risk of stroke, focusing on subclinical atrial tachyarrhythmia detected by implanted devices. Indeed, it has been thoroughly demonstrated that evaluation of pacemakers recordings is a reliable method to detect AF [38]. The TRENDS trial [39], in fact, evaluated stroke and systemic thromboembolic events in patients with at least one stroke risk factor (defined by the CHADS2 score) by assessing pacemaker or defibrillator recordings. The study was meant to detect a difference in stroke rate among patients with a high, low burden, or no events of atrial arrhythmias/tachycardia (AHRE). Unfortunately, the study failed to show any significant differences, likely due to underpowering as the event rate was lower than expected. An ancillary analysis of the MOST study, instead, demonstrated that AHRE in patients with sinus node dysfunction conferred an increased risk of stroke, death, and to develop clinical AF [19]. Of note, patients with previously diagnosed supraventricular arrhythmia were not excluded, and a large portion of patients with AHRE presented symptoms. Nevertheless, the authors concluded that symptoms were poorly correlated with and were not reliable markers of AHRE. Analogous results were found in the ASSERT trial, which demonstrated that AHRE in patients without a history of AF confer a greater risk of developing clinical AF and are associated with a higher rate of stroke and systemic thromboembolic events [18].

Finally, also AF burden needs consideration: as thoroughly explained by Kennedy [40], AF burden defines the overall amount of AF duration among each patient, providing additional insight on the magnitude of AF episodes. Many clinical conditions (such as, genetics, obesity, hypertension, diabetes, heart failure, older age [40]) affect AF burden and have an important role in AF morbidity. Indeed, it is now clear that prompt correction of comorbidities and cardiovascular risk factors reduces AF burden [41,42] and is, therefore, recommended in all patients suffering from AF [43,44]. Several arrhythmic entities, including AHRE, detected by non-invasive ECG monitoring and implanted devices, are markers of AF and contribute to define the AF burden [40]: however, despite the association between persistent AF and worse prognosis [45–47], current guidelines suggest to base the decision of anticoagulation therapy for stroke prevention on patient’s risk factors (quantified by CHA2DS2-VASc score) and not on AF burden. In fact, an AF burden cutoff identifying an increased risk of stroke or mortality has not yet been established, and its quest is at the heart of many studies.

#### **4. Asymptomatic AF and Its Impact on Prognosis**

Whether asymptomatic presentation of AF confers a worse prognosis than symptomatic AF is still debated (Table 2). A prospective observational study conducted by Boriani et al. on 3119 patients with AF (the EORP-AF Registry) demonstrated that patients with asymptomatic AF, in comparison to symptomatic patients, have a worse prognosis and an increased risk of mortality at 1 year. At multivariate analysis, however, EHRA score I was not independently associated with a worse prognosis. Therefore, increased mortality was likely mainly driven by the differences in

patients' comorbidities and global risk rather than to the different AF presentation [7]. Another study reported that both patients with subclinical AF and atypical presentations of AF (fatigue, shortness of breath, chest pain, light-headedness, syncope, decreased exercise tolerance without palpitations) are at higher risk of cerebrovascular events (CVE) in comparison with patients with typical AF symptoms (palpitations). Moreover, the risk of cardiovascular and global mortality was greater in asymptomatic patients after adjustment for confounding factors (CHA2DS2-VASc score and age) [11]. A sub-study conducted on the PREFER in AF Registry showed that ischemic stroke and TIA occurred with similar frequency in symptomatic and asymptomatic patients [6]. These results confirm, in fact, those of a retrospective analysis of the AFFIRM trial that revealed no differences in outcomes after adjustment for baseline characteristics between patients with asymptomatic and symptomatic AF [12]. Conversely, in a sub-analysis of the RACE study, asymptomatic AF was associated with improved prognosis (lower hospitalization due to heart failure and antiarrhythmic drugs adverse effect rate) in comparison with symptomatic patients, but no differences were found on the risk of thromboembolic events [10]. However, these trials were not designed to evaluate the prognostic implications of different subtypes of AF, and AF presentation was not considered when deciding treatment throughout follow up.

**Table 2.** Summary of studies on the clinical relevance of asymptomatic and subclinical atrial fibrillation (AF).

| Authors (Study Year)        | AHRE/Subclinical/Asymptomatic AF Diagnostic Method   | Stroke and TE Incidence (%) *   | Mortality (%) *   | Correlation with Stroke or Mortality                                   |
|-----------------------------|--|---|---|--|
| Implanted device monitoring |  |   |   |  |
| Glotzer et al. (2003) [19]  | AHRE: atrial rate $\geq$ 220 bpm lasting at least 5 min (detected by pacemaker)  | AHRE: 33/160 (20.6) No AHRE: 16/152 (10.5)  | AHRE: 28/160 (17.5) No AHRE: 16/152 (10.5)  | Yes (for total mortality, stroke, and AF development)                  |
| Glotzer et al. (2009) [39]  | AHRE: atrial rate > 175 bpm lasting at least 20 s. Patients were stratified according to 30 days window monitoring in: zero, low, and high AHRE burden | Annualized TE incidence rate: zero AHRE burden 1.1%; Low AHRE burden 1.1%; High AHRE burden 2.4%  | NA  | No   |
| Healey et al. (2012) [18]   | AHRE: atrial rate $\geq$ 190 bpm lasting at least 6 min (detected by pacemaker or ICD)   | AHRE in the previous 3 months: 11/261 (4.2) No AHRE in the previous 3 months: 40/2319 (1.7)   | From vascular causes AHRE in the previous 3 months: 19/261 (7.3) No AHRE in the previous 3 months: 153/2319 (6.6) | Yes  |
| Non-Invasive ECG monitoring |  |   |   |  |
| Flaker et al. (2005) [12]   | AF diagnosed with ECG or rhythm strip. Symptoms evaluated by a questionnaire   | Asymptomatic AF: 21 Symptomatic AF: 136   | Asymptomatic AF: 60 (19) Symptomatic AF: 606 (27)   | No (in comparison with symptomatic patients)                           |
| Rienstra et al. (2014) [10] | Recurrent persistent AF without symptoms according to a questionnaire  | Asymptomatic AF: 8/157 Symptomatic AF: 28/365   | Asymptomatic AF: 9/157 Symptomatic AF: 26/365 (death from cardiovascular causes)                                  | No †   |
| Boriani et al. (2015) [7]   | ECG diagnosed AF and EHRA score I  | EHRA I: 10/962 (1.0%) EHRA II-IV: 15/1344 (1.1%)  | EHRA I: 102/1086 (9.4%) EHRA II-IV: 65/1556 (4.2%)  | Yes (for mortality compared to symptomatic patients)                   |
| Freeman et al. (2015) [9]   | Electrocardiographically documented AF and EHRA score I  | EHRA I: 99/3682 EHRA II-IV: 168/5918  | EHRA I: 311/3682 EHRA II-IV: 561/5918   | No ‡   |
| Bakhsai et al. (2016) [6]   | ECG diagnosed AF and EHRA score I  | EHRA I: ischemic stroke 8/489 (1.6) TIA 7/488 (1.4) arterial embolism 2/488 (0.4) EHRA II-IV: ischemic stroke 44/5514 (0.8) TIA 73/5510 (1.3) arterial embolism 11/5514 (0.2) | NA  | No (only EHRA score IV was associated with a higher events occurrence) |

Table 2. Cont.

| Authors (Study Year)       | AHRE/Subclinical/Asymptomatic AF Diagnostic Method  | Stroke and TE Incidence (%) *  | Mortality (%) *  | Correlation with Stroke or Mortality |
|----------------------------|---|--|--|--------------------------------------|
| Siontis et al. (2016) [11] | AF detected incidentally (routine physical examination, preoperative evaluation, emergency department, or clinic visit for unrelated problem) | HR compared to typical AF: Subclinical AF 2.60 (95% C.I. 1.10–6.11)<br>Atypical AF 3.12 (95% C.I. 1.27–7.66) | HR compared to typical AF: Subclinical AF 4.01 (95% C.I. 2.32–6.91)<br>Atypical AF 3.19 (95% C.I. 1.78–5.71) | Yes (compared to typical AF)         |

AF: atrial fibrillation; AHRE: atrial high rate episodes; NA: not applicable; TIA: transient ischemic attack; TE: thromboembolism \* If not otherwise indicated. † In this study asymptomatic AF compared to symptomatic presentation conferred a lower risk of heart failure and severe antiarrhythmic drugs adverse effects. ‡ In this study AF symptoms and decreased quality of life were associated with higher risk of hospitalization.

Bearing in mind that the first manifestation of AF can be an ischemic stroke with severe consequences (as death, dementia, and lower quality of life), that AF is first diagnosed in 11%–24% of patients with recent ischemic stroke or TIA [48,49], and that AF-associated strokes have a high risk of recurrences, interest in the screening for subclinical AF has grown during the recent years.

### 5. Screening for Atrial Fibrillation

A screening program to early detect subclinical AF entails several questions: what is the appropriate method for the screening? Who should be screened? Is a screening program cost-effective? Current European guidelines for the management of AF suggest opportunistic screening in patients older than 65 years by pulse check or single-lead ECG portable devices (Class of recommendation I). In patients with an implanted device it is recommended to evaluate the occurrence of AHRE on a regular basis: if AHRE are detected, AF must be searched by further electrocardiographic monitoring prior to starting treatment. In patients with cryptogenic ischemic stroke or TIA an initial ECG followed by electrocardiographic monitoring for 72 h is recommended (Class of recommendation I), and a long term strategy should be considered (Class of recommendation IIa) [5]. The AHA/ACC/HRS guidelines, instead, do not provide definite recommendations for screening [50]. In addition, a statement appears suggesting that ECG based screening does not improve detection rate of asymptomatic AF in comparison with a pulse palpation based approach, and there are currently no evidence to support the benefits of an ECG based screening [51,52].

Several methods have been proposed for AF screening in populations with risk factors: pulse palpation has been described as an effective method to detect subclinical AF [14]. However, pulse characteristics are seldom evaluated in primary care settings and adequately trained patients' compliance in self-monitoring is low in the long term [15]. Handheld ECG is a reliable and effective method for AF screening in at risk populations, with a fourfold increase in AF diagnosis over 12 months according to the REHEARSE-AF study [16]. This study showed that stroke and TIA incidence was not statistically different in screened and unscreened patients. However, clinical events were not considered as a primary outcome, and the study was not designed and powered to detect a significant difference in these events. The ongoing STROKESTOP trial aims at evaluating the efficacy and cost effectiveness in reducing stroke incidence of an AF screening program based on single lead discontinuous ambulatory ECG monitoring in a 75–76 years old population from two regions in Sweden [13]. An analysis of the ongoing investigation demonstrated that this strategy increased AF detection fourfold, as AF has been first diagnosed in 3% of the screened-population; 93% of patients with new detection of AF have initiated oral anticoagulation (OAC) therapy [53]. Awaiting for the conclusion of the trial and its final results, a simulation study based on the study design and available data of this trial, concluded that screening for AF with an ECG recorder is cost effective with a reduction of eight strokes, and an increase of 11 life-years and 12 quality-adjusted life years (QALYs) per 1000 screened patients [54].

In patients who suffered a cryptogenic stroke and in whom standard 24 h ECG monitoring failed to detect AF, two randomized trials, instead, demonstrated the benefits of further prolonging rhythm

monitoring. The CRYSTAL-AF trial [55,56] randomized 441 patients, 40 years of age or older, who suffered a cryptogenic stroke or TIA, without history of AF and no other indications to anticoagulant therapy, to implant a cardiac monitoring device or standard care: the AF detection rate was higher in the long term monitoring strategy group both at 6 and 12 months (HR 6.4; 95% CI 1.9–21.7; HR 7.3; 95% CI 2.6–20.8, respectively). The EMBRACE trial [57] compared standard care and 30-days non-invasive ECG monitoring to detect AF in patients over 55 years old, with cryptogenic stroke or TIA within the 6 months prior to randomization. By 90 days after the randomization AF lasting 30 s was detected in significantly more patients in the intervention group (absolute difference 12.9%, 95% CI 8.0–17.6), with a number needed to screen of eight. Moreover, in the AHA/ACC/HRS focused update of AF guidelines recommendation for the use of implantable device for AF detection after cryptogenic stroke has been implemented, according to which a more extensive and thorough long-term cardiac monitoring needs to be considered [44].

## 6. Management of Subclinical and Asymptomatic AF

### 6.1. Clinical Approach to the Patient with Asymptomatic Atrial Fibrillation

Clinical approach to a patient with asymptomatic AF is indeed complex and needs to take into account several aspects of the arrhythmia and presence of comorbidities. First, it must be taken into consideration that asymptomatic AF patients are not always truly asymptomatic, since they may undergo progressive involuntary lifestyle restriction or suffer unrecognized anxiety or depression; moreover, a large portion of AF patients may already present cerebral ischemic lesions (about four out of 10 according to results of the prospective observational SWISS-AF study [58]) which have been demonstrated to affect cognitive functions [26,58]. To assess definitively whether a patient is truly asymptomatic, cardioversion should be performed, and symptoms and quality of life evaluated after sinus rhythm restoration; subsequently, in those who felt improvement after sinus rhythm restoration, a rhythm control strategy should be pursued. It has been demonstrated that catheter ablation for AF significantly improves quality of life and symptoms [59,60]: however subanalysis of these studies demonstrated that, once the patients were divided according to symptoms intensity, the observed benefit was mostly driven by patients with more severe symptoms, whereas those who at baseline were barely symptomatic had little or no improvement after ablation. Therefore, patients' symptoms (not only typical AF symptoms such as palpitations, but also fatigue and dyspnea) and exercise tolerance should be thoroughly examined and a quality of life questionnaire administered; comorbidities should be evaluated, since they can be a cause of symptoms experienced by the patient, and promptly treated. Control of cardiovascular risk factors, hypertension, smoke habit, sedentary life, and obesity should be also encouraged and recommended, as they worsen symptoms and play a role in disease progression [44]. Finally, a regular cardiological follow-up is recommended, including clinical examination for heart failure signs and echocardiographic control of ejection fraction; the latter, in fact, is a crucial aspect to promptly recognize and address patients with a reduced ejection fraction to rhythm control strategy by catheter ablation in order to prevent further heart failure progression [5] and reduce mortality, as suggested by the recent CASTLE-AF findings [61].

Treatment strategies for prevention of cognitive decline are, instead, debated [62]: in addition to physical exercise and optimal control of cardiovascular risk factors, appropriate anticoagulation therapy is recommended; non-vitamin K antagonist oral anticoagulants (NOAC) should be preferred because of the higher safety profile. Moreover, a rhythm control strategy, including catheter ablation, is indicated; nevertheless, it should be borne in mind that the benefit of restoring sinus rhythm may be partially offset by subclinical cerebral lesions occurring during the procedure [63,64].

### 6.2. Anticoagulation Therapy

The cornerstone of AF therapy for prevention of stroke and systemic thromboembolic events is OAC therapy. The 2016 ESC guidelines recommend to initiate OAC therapy upon evaluation of



the individual stroke risk based on the number of CHA2DS2-VASc risk factors; in the absence of contraindications, OAC therapy is recommended when the CHA2DS2-VASc score is  $\geq 2$  in male patients or  $\geq 3$  in female patients and it should be considered with CHA2DS2-VASc scores 1 or 2 respectively. Whereas vitamin K antagonists are the only recommended anticoagulants for valvular AF patients, i.e., patients with mechanical heart valve or moderate to severe mitral stenosis, NOAC should be preferred in non-valvular AF patients [5]. The net benefit of CHA2DS2-VASc-guided OAC therapy in preventing stroke occurrence and recurrence in AF patients has been thoroughly demonstrated [65,66]. A large meta-analysis showed the superiority of NOAC over VKA with respect to safety and efficacy [67].

As far as OAC therapy in subclinical AF or AHRE is concerned, there is actually no direct evidence that early initiation of OAC treatment in this setting can improve hard clinical endpoints without significantly increasing bleeding risk [51]. It has been proposed that intermittent OAC might provide a better balance between stroke prevention and bleeding risk than uninterrupted OAC therapy. Nevertheless, the IMPACT trial, which evaluated intermittent versus OAC initiated upon standard physician’s indication after detection of AHRE at implanted defibrillator follow-up sessions, failed to show clinical benefit regarding the composite outcome of stroke, systemic embolism, and bleeding events (HR 1.06; 95% CI 0.75–1.51; *p* value: 0.732) [68]. In this perspective, two ongoing clinical trials are designed to assess the feasibility of continuous OAC therapy in patients with subclinical AF or AHRE recorded by implanted devices (Table 3). The randomized, double-blind, multicenter NOAH-AFNET 6 study, including older patients (>65 years old) with at least one additional CHA2DS2-VASc risk factor but without clinical AF nor any other indication to OAC therapy, will evaluate the efficacy of edoxaban compared to aspirin or no antithrombotic therapy in preventing stroke, cardiovascular death, and systemic embolism after AHRE detection by implanted devices’ recordings; the primary safety endpoint will be major bleeding [23]. The ARTESiA trial is a prospective, multicenter, double-blind, randomized controlled trial, which enrolls patients with risk factors for stroke and subclinical AF detected by implanted devices; patients will be randomized to either apixaban or aspirin with a primary composite endpoint of stroke, TIA, and systemic thromboembolic events during an estimated follow-up of 3 years [17].

**Table 3.** Details of ongoing trials.

| Name of Study              | Number of Patients  | Study Arms   | Primary Endpoints  | Secondary Endpoints   |
|----------------------------|---|--|--|---|
| STROKESTOP (NCT01593553)   | 7173 (in screening)<br>14,381 (controls not screened)   | Intervention group: ECG screening for AF using intermittent ECG recorder.<br>Control group: standard of care | Composite of ischemic and hemorrhagic stroke, systemic embolism, major bleeding requiring hospitalization, and all-cause mortality | Each single component of the composite primary outcome; dementia; cardiovascular mortality; hospitalization due to cardiovascular disease; cost-effectiveness; OAC initiation and compliance; AF detection; pulmonary embolism and deep vein thrombosis   |
| NOAH-AFNET 6 (NCT02618577) | 2686 (3400 estimated) patients ( $\geq 65$ years old and $\geq 1$ additional CHA2DS2-VASc factor) with AHRE documented by implanted devices | Intervention group: Edoxaban (standard AF dosing) Control group: ASA or placebo                              | Composite of stroke, systemic embolism and cardiovascular death (measured as time from randomization to event occurrence)          | MACE (cardiac death, MI, acute coronary syndrome), all-cause death, major bleeding events, quality of life changes at 12 and 24 months, patient satisfaction at 12 and 24 months, cost effectiveness and health resource utilization, autonomy status changes in patients affected by stroke during study participation, cognitive function at 12 and 24 months |
| ARTESiA (NCT01938248)      | $\approx 4000$ patients with subclinical AF at high risk for stroke (estimated)   | Intervention group: Apixaban (standard AF dosing) Control group: ASA (81 mg/die)                             | Efficacy outcome: composite of stroke (including TIA) and systemic embolism.<br>Safety outcome: major bleeding                     | Ischemic stroke; MI; vascular death; total death; composite of stroke, MI, systemic embolism and total death; composite of stroke, MI, systemic embolism, total death, and major bleeding.  |

Table 3. Cont.

| Name of Study             | Number of Patients  | Study Arms   | Primary Endpoints  | Secondary Endpoints  |
|---------------------------|---|--|--|--|
| EAST<br>(NCT01288352)     | 2789 patients with new AF (<1 year) and risk factors for stroke   | Intervention group: guidelines-based therapy and early rhythm control therapy (AAD or PVI) Control group: usual care | First coprimary outcome: composite of cardiovascular death, stroke (including TIA), acute coronary syndrome, and worsening of heart failure. Second coprimary outcome: nights in hospital per year | Cardiovascular death, stroke, worsening of heart failure, acute coronary syndrome, time to recurrent AF, cardiovascular hospitalizations, all-cause hospitalizations, left ventricular function, quality of life, cognitive function   |
| OCEAN<br>(NCT02168829)    | 1572 patients free from AF for at least 1 year after catheter ablation for non-valvular AF (estimated)          | Active Comparator: rivaroxaban 15 mg/die Active Comparator: ASA 75–160 mg/die  | Composite of clinically overt stroke, systemic embolism, and covert stroke detected by brain MRI   | Each single component of the composite primary outcome; major bleeding, clinically relevant non-major bleeding, minor bleeding and their composite; overt intracranial hemorrhage; microbleedings as detected by MRI; TIA; all-cause mortality; net clinical benefit; occurrence of nonprimary endpoint MRI changes; correlation of AF burden/recurrence to occurrence of clinical or covert stroke; neuropsychological testing; quality of life |
| OAT<br>(NCT01959425)      | 100 patients free from AF for at least 3 months after catheter ablation and at high risk for stroke (estimated) | Intervention group: OAC discontinuation Control group: OAC continuation  | Composite of any major thromboembolic event and major hemorrhagic complication   | Bleeding; hospitalization; mortality; quality of Life; AF recurrence; repeat ablation  |
| SWISS-AF<br>(NCT02105844) | 2415 AF patients  | NA   | Stroke or systemic embolism  | Hospitalization for heart failure  |

AAD: antiarrhythmic drugs; AF: atrial fibrillation; AHRE: atrial high rate episodes; ASA: acetylsalicylic acid; MACE: major adverse cardiovascular events; MI: myocardial infarction; MRI: magnetic resonance imaging; NA: not applicable; OAC: oral anticoagulant; PVI: pulmonary veins isolation; TIA: transient ischemic attack.

### 6.3. Anti-Arrhythmic Drug Management

A rhythm control approach in the subset of patients with subclinical and asymptomatic AF is perhaps even more controversial than the previously discussed OAC therapy. The AFFIRM [69,70] and RACE [71] trials demonstrated no advantage on mortality and stroke in pursuing a rhythm control over a rate control strategy in AF patients. Nevertheless, the CASTLE-AF [61] study showed a clear benefit in cardiovascular death and hospitalizations for worsening heart failure in patients with heart failure and paroxysmal or persistent AF treated by catheter ablation. According to current European guidelines, rhythm control therapy is recommended in symptomatic patients presenting with recent onset AF in order to improve quality of life [5].

Some considerations are needed in this regard. First, a subanalysis of the AFFIRM [72] study showed that maintaining sinus rhythm confers half the risk of death compared to AF persistence. AAD, however, were associated with increased mortality after adjustment for sinus rhythm restoration, therefore the authors concluded that the beneficial effects of AAD in maintaining sinus rhythm were offset by their adverse effects, resulting in no net survival advantage. Similarly, an observational study [73] comparing stroke and TIA incidence in patients treated with either rate or rhythm control strategy ( $n = 41.193$  and  $16.325$  respectively) showed that rhythm control strategy was associated with a lower risk of stroke and TIA during a mean follow-up of 2.8 years at multivariate analysis (HR 0.80; 95% CI 0.74–0.87). After stratification for CHADS2 score, absolute stroke and TIA incidences were reduced only in patients with CHADS2 score  $\geq 2$ .

#### 6.4. Catheter Ablation

The aforementioned studies compared only AAD with rate control therapy, but AF catheter ablation has now become an effective and widespread option for rhythm control: indeed, ESC guidelines do recommend catheter ablation as a first-line alternative to AAD in symptomatic patients with paroxysmal AF. A large meta-analysis [74] including 1481 patients with AF and 11 randomized controlled trials compared the efficacy and safety of catheter ablation versus AAD therapy ( $n = 785$  and  $696$  respectively): catheter ablation was associated with lower AF recurrences (RR, 0.40; 95% CI 0.31–0.52;  $p$  value = 0.00001) both as first- and second-line approaches (RR, 0.52; 95% CI, 0.30–0.91;  $p$  value = 0.02 and RR, 0.37; 95% CI, 0.29–0.48;  $p$  value < 0.00001, respectively), but there was a significant increase of adverse events incidence (RR, 2.04; 95% CI, 1.10–3.77;  $p$  value = 0.02). However, after stratification by date, no difference in safety endpoints was found considering only the results of the studies conducted after 2009 (RR, 1.51; 95% CI, 0.55–4.15;  $p$  value = 0.42). This finding may be due to increased experience and improved technology in catheter ablation, leading to lower complications and adverse events.

Since catheter ablation proved more effective than AAD therapy in maintaining sinus rhythm [74], it has been hypothesized that indication to this procedure could reflect into better long-term prognosis. However, the recent CABANA trial [75], which was supposed to shed light on this clinical dilemma, failed to demonstrate a statistically significant superiority of catheter ablation over both rhythm and rate control pharmacological therapy for a composite primary endpoint including death, disabling stroke, serious bleeding, or cardiac arrest (HR, 0.86; 95% CI 0.65–1.15;  $p$  value = 0.30). A detailed analysis of the results, however, shows that the study was characterized by a greater than expected cross-over between treatment groups, with 301 (27.5%) patients assigned to medical therapy switching to catheter ablation. Indeed, in the 12-month per-protocol analysis of the results, patients who had undergone catheter ablation presented a reduced risk of meeting the primary endpoint than those managed pharmacologically (HR 0.73; 95% CI 0.54–0.99).

Several other investigations, albeit limited by their unrandomized nature, provided evidence in favor of catheter ablation. One study comparing patients with similar CHADS2 scores showed that catheter ablation confers a risk of ischemic stroke similar to that of the population without AF, but the details on OAC treatment were lacking [76]. A multicenter study conducted by Hunter et al. [77] compared patients undergoing AF ablation with a cohort treated with medical therapy and an AF-free cohort representing the general population; of note, in the medical therapy cohort CHADS2 score was higher than in catheter ablation group ( $1.6 \pm 1.2$  and  $0.7 \pm 0.9$  respectively). After a mean follow-up of 3.1 years, catheter ablation was associated with a lower risk of stroke and death in comparison with medical therapy, presenting a stroke rate comparable to the general population. Moreover, freedom from AF was a protective factor against stroke at multivariate analysis (HR 0.33; 95% CI 0.17–0.67). Discontinuation of OAC therapy occurred in 64% of patients who underwent pulmonary veins (isolation (85% of these were on single antiplatelet agent therapy) and it was more frequent in patients without AF recurrences in comparison to patients with AF recurrences, despite a small difference in CHADS2 score between the two groups ( $0.7 \pm 0.9$  vs.  $0.9 \pm 0.9$ , respectively). These findings confirm those of another observational study [78] which reported no statistically significant difference between patients who stopped or continued OAC after AF ablation. Along with history of stroke, and unlike OAC interruption, except in intermediate risk patients, recurrent AF was a predictor of thromboembolic events, whereas OAC continuation was associated with an increased risk of bleeding. Another multicenter observational study [79] recruiting 1500 AF patients compared rate control and OAC therapy with catheter ablation associated with either OAC continuation or discontinuation after the procedure: no differences were found as for thromboembolic events incidence (2.2% in rate control strategy and OAC, 1% in catheter ablation with OAC, 1.4% catheter ablation and OAC discontinuation,  $p$  value = 0.45), whereas OAC discontinuation after catheter ablation conferred a lower risk of hemorrhagic events (2.4% in rate control strategy and OAC, 1.8% in catheter ablation with OAC, and no events in catheter ablation and OAC discontinuation,  $p$  value < 0.001).

Based on the aforementioned studies, preservation of sinus rhythm, achieved by AAD therapy or catheter ablation, holds the potential to confer an improved clinical outcome in the general population. Among patients with fewer risk factors and lower event rates than those with heart failure, a longer follow-up and greater sample sizes are possibly needed to identify a statistically significant benefit in hard clinical end-points. Indeed, maintenance of sinus rhythm can prevent atrial structural remodeling process accompanying the arrhythmia, hampering disease progression. In this perspective, the currently ongoing EAST [80] trial will assess if rhythm control therapy in the early phase following AF diagnosis can improve prognosis in comparison with a more conservative approach; the trial primary endpoint is a composite of cardiovascular death, stroke, worsening heart failure and myocardial infarction; cognitive function will be evaluated as a secondary outcome as in the STROKESTOP, NOAH-AFNET 6, and OCEAN studies. Additionally, two ongoing trials will shed light on another quandary in clinical management of AF patients: the open, multicenter, randomized OCEAN trial [81] will compare rivaroxaban and acetylsalicylic acid efficacy in reducing stroke, systemic embolism and subclinical brain lesions incidence among high-risk patients free from AF for at least 1 year after pulmonary veins isolation after a 3 years follow-up period. In the OAT trial (NCT01959425) patients without AF recurrences three months after catheter ablation will be randomized to suspend or continue OAC. Should these trials meet their outcomes, a rhythm control strategy with catheter ablation in an early phase of the disease would be recommended aiming to interrupt disease progression and prevent AF-related complications. Moreover, it would be possible to consider catheter ablation in asymptomatic patients as well; as a matter of fact, as thoroughly explained by Kalman et al. [82], subclinical AF can become symptomatic with arrhythmia progression, therefore it may prove useful to treat the arrhythmia in this early “window of opportunity” in order to prevent symptoms onset and atrial remodeling. Finally, patients’ compliance to OAC therapy for AF diagnosed after a single ECG in the absence of any symptoms is of great concern in clinical practice; in this scenario catheter ablation may be a valid tool potentially providing the expected benefits (Figure 1).

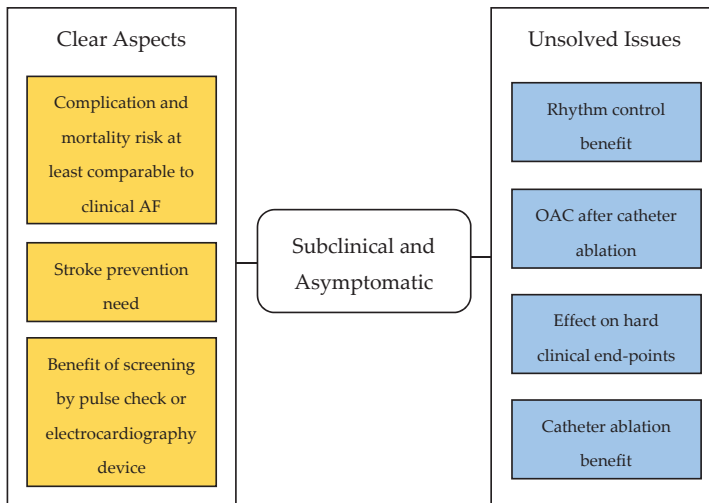


Figure 1. Current certainties and doubts on the management of subclinical and asymptomatic AF.

## 7. Conclusions

The treatment of asymptomatic AF patients should be personalized, evaluating individual risk factors and comorbidities as well as patient’s own preference. High risk individuals with heart failure, should be promptly treated, and catheter ablation should be offered due to the strong evidence supporting AF ablation in this setting. As for patients with early-diagnosed asymptomatic AF and no

comorbidities, ongoing clinical trials will assess the benefits of catheter ablation and pharmacological rhythm control therapy, but currently there is not enough evidence to clearly support this approach.

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Review

# Association of Antihyperglycemic Therapy with Risk of Atrial Fibrillation and Stroke in Diabetic Patients

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**Abstract:** Type 2 diabetes mellitus (DM) is associated with an increased risk of cardiovascular disease (CVD). Atrial fibrillation (AF) and stroke are both forms of CVD that have major consequences in terms of disabilities and death among patients with diabetes; however, they are less present in the preoccupations of scientific researchers as a primary endpoint of clinical trials. Several publications have found DM to be associated with a higher risk for both AF and stroke; some of the main drugs used for glycemic control have been found to carry either increased, or decreased risks for AF or for stroke in DM patients. Given the risk for thromboembolic cerebrovascular events seen in AF patients, the question arises as to whether stroke and AF occurring with modified incidences in diabetic individuals under therapy with various classes of antihyperglycemic medications are interrelated and should be considered as a whole. At present, the medical literature lacks studies specifically designed to investigate a cause–effect relationship between the incidences of AF and stroke driven by different antidiabetic agents. In default of such proof, we reviewed the existing evidence correlating the major classes of glucose-controlling drugs with their associated risks for AF and stroke; however, supplementary proof is needed to explore a hypothetically causal relationship between these two, both of which display peculiar features in the setting of specific drug therapies for glycemic control.

**Keywords:** diabetes mellitus; atrial fibrillation; stroke; metformin; thiazolidinediones; GLP-1 receptor agonists; SGLT-2 inhibitors

## 1. Introduction

Cardiovascular disease (CVD) is the main cause of morbidity and mortality in type 2 diabetes patients. The increased cardiovascular risk seen in diabetic patients cannot be mitigated with a monofactorial intervention of plasma glucose control, requiring a multi-factorial control of all cardiovascular risk factors [1,2]. Some of the newer classes of antihyperglycemic drugs have the potential to improve other risk factors beyond glycemic levels, and to protect against major cardiovascular events. Hence, the presence of CVD has become one of the key decision factors in the international guidelines counseling the choice of second-line antidiabetic medication after metformin [3].

Among all potential clinical forms of diabetes-associated obstructive artery disease, cerebrovascular disease is a serious condition, inducing major disabilities and a shortened life span. In a large meta-analysis of 102 prospective studies, diabetes mellitus was associated with a 2.27-fold increase in the risk for ischemic stroke when compared with a non-diabetic status [4].

Accumulating clinical evidence also seems to connect diabetes mellitus with an increased risk for atrial fibrillation (AF) [5]. Diabetes mellitus may induce structural and electrical alterations of the left atrium (deposition of advanced end-glycation products and connexin-mediated fibrosis), and stimulate the production of pro-coagulant factors (von Willibrand factor, soluble P-selectin, and other molecules exerting pro-inflammatory and pro-oxidative actions or favoring platelet activation and aggregation) [6]. All these changes promote clotting in the left atrial appendage and subsequent thromboembolism [6].

In a turning point in diabetes-related clinical research, several older or newer drugs used to control glycemic values in diabetic patients were recently shown—mostly in observational studies, post-hoc analyses of the major trials, or various meta-analyses—to display different levels of risk for either AF or stroke [7,8]. Such evidence exists for all classes of antidiabetic drugs included in the major international guidelines [3,7,8]. These drugs are summarized in Table 1. The body of evidence accumulating for each of these two new facets of antidiabetic medications is continuously increasing, and may represent far more than a random coincidence, even though no studies have been drafted to investigate a specific cause-effect relationship between the AF and stroke risks associated with use of various antihyperglycemic agents. Therefore, the aim of the present review is to gather, for the first time in the literature, the current knowledge on the risks of each of the antihyperglycemic drugs advised by current guidelines for both AF and stroke, raising the question as to whether they are causally interconnected.

**Table 1.** Classes of antihyperglycemic drugs included in current guidelines [3].

| Drug   | Mechanism of Action   |
|--|---|
| Insulin  | Activation of insulin receptor; various effects on multiple metabolic pathways                                |
| Metformin  | Reduced insulin resistance, mostly by decreasing gluconeogenesis  |
| Sulfonylureas (SU)                                 | Insulin secretagogues by activation of SUR (SU receptor) unit of ATP-sensitive potassium channels             |
| Thiazolidinediones (TZD)                           | Insulin sensitizers by the activation of peroxisome proliferator-activated receptor (PPAR)- $\gamma$          |
| Dipeptidyl peptidase-4 (DPP-4) inhibitors          | Inhibition of DPP-4 and subsequent conservation of native human GLP-1 in its active form                      |
| Glucagon-like peptide-1 (GLP-1) receptor agonists  | Activation of GLP-1 receptor at high pharmacological concentrations   |
| Sodium-glucose cotransporter-2 (SGLT-2) inhibitors | Inhibition of active reabsorption of glucose and sodium performed by SGLT-2 in the proximal convoluted tubule |

## 2. Antihyperglycemic Drugs, Atrial Fibrillation and Stroke

Recently published research has frequently depicted various classes of antihyperglycemic agents as being associated with modified levels of risk for either AF or stroke. Stroke episodes in AF patients frequently have a thromboembolic nature; hence, the question arises as to whether a specific risk for AF in one or the other of the antidiabetic drugs would reflect an accordingly modified risk for cerebral thromboembolism, and thus stroke. Unfortunately, the major clinical trials have not yet distinguished between the ischemic or hemorrhagic nature of stroke episodes, and least of all, between the atherothrombotic or thromboembolic etiology of ischemic strokes [9,10]. In the absence of dedicated studies using electrocardiogram (ECG) technologies to monitor the heart rhythm, a high number of asymptomatic AF and/or paroxysmal, recurrent episodes of AF may go unrecognized; this may underlie the inconstant associations between diabetes and incidences of AF or stroke seen in clinical studies, especially those not reporting AF as a specific outcome [11]. We searched Medline and Scopus databases using the logical string “atrial fibrillation” OR “stroke” AND “antihyperglycemic”

AND “diabetes” to identify these key terms in the title or abstract of English-written articles published before June 2019. Clinical studies or trials, meta-analyses, and systematic reviews focusing on human subjects were selected. After eliminating duplicates, this initial search returned 14 results. We screened all titles and abstracts to select papers that could be considered relevant to the aim of our review. This operation led to a further reduction to only 11 titles. A second search using the same algorithm and replacing the key term of “antihyperglycemic” with “insulin” OR “metformin” OR “sulfonylurea (SU)” OR “thiazolidindione (TZD)” OR “dipeptidyl peptidase-4 (DPP-4) inhibitor” OR “glucagon-like peptide-1 (GLP-1) receptor agonist” OR “sodium-glucose cotransporter-2 (SGLT-2) inhibitor” issued 28 supplementary papers, which were also included in our review. When potential mechanical explanations were useful, we also referred to other relevant review papers, selected by the same two search algorithms; as an only exception, we included a case report which filled a gap in an area of scarce evidence. The following sections summarize the data related to the risk of AF and stroke for each class of antihyperglycemic agents.

### 2.1. *Insulin*

In a case-control study on Taiwan registries, insulin therapy was associated with a higher risk of new-onset AF in diabetic patients than with other antihyperglycemic medications [12]. Among patients in the PREvention of thromboembolic events—European Registry in Atrial Fibrillation (PREFER in AF) registry, insulin users, but not diabetic patients treated with non-insulin antihyperglycemic drugs, were shown to have a higher risk of stroke compared with non-diabetic individuals [13]. In a Medicare analysis on 798,592 AF patients, insulin-requiring diabetic subjects also had a higher risk of stroke than diabetic patients not requiring insulin therapy or non-diabetic individuals; use of insulin therapy was associated in this registry study with an attenuation in the efficacy of anticoagulant drugs [6]. However, the association between insulin therapy and this pro-arrhythmic status may be biased by the longer duration of type 2 diabetes usually seen in patients treated with insulin. Such subjects may have experienced years of suboptimal glycemic control on other non-insulin therapies, and may have had the time to develop significant comorbidities [12]. The real possibility exists that hyperinsulinism (either due to insulin resistance or, in this case, having an iatrogenic component) may be associated with an increased anti-fibrinolytic status, as insulin stimulates the Plasminogen Activator Inhibitor-1 (PAI-1) production in adipocytes [14].

### 2.2. *Metformin*

In a cohort study on 645,710 Taiwan patients, monotherapy with metformin was associated with a 19% reduction in the risk of AF compared with the use of other antihyperglycemic medications during a 13-year follow-up. Metformin users had the lowest AF incidence rates in the first two years after diagnosis, but the protective effect tended to fade afterward [15]. Possible explanations accounting for the favorable effect of metformin include its actions on adenosine monophosphate-activated kinase, and the drug-induced reduction of the oxidative stress and the myolysis in the atrial tissue [15,16]. The loss of its protective effect over time may be underlain by the progressive deterioration of  $\beta$ -cell function typically observed in type 2 diabetes, which may lead to a worsened glycemic control, or by the gradual remodeling of the atrial wall [15]. In the above-mentioned case-control study, also originating from Taiwan registries, biguanides, of which metformin is the main representative today, were also associated with a lower risk of developing AF [12].

Current evidence suggests that metformin also has a protective effect against ischemic stroke, even though specific outcome studies analyzing a potential cause–effect relationship between the protective role of metformin against AF development and the rate of thromboembolic events are lacking in the medical literature. The results of the United Kingdom Prospective Diabetes Study (UKPDS) suggested that intensive blood glucose control with metformin, compared with the use of sulfonylureas or insulin, significantly reduced the risk of stroke [17]. After a four-year follow-up,

the administration of metformin within the antihyperglycemic therapy was associated with a 54% reduction in the risk of stroke, with the best results observed in the highest risk patients [18].

### 2.3. Sulfonylureas

Most researchers analyzing the risk of AF development have considered SU therapy as only a control to report comparative AF outcomes of other antidiabetic medications. Among the few studies making an exception, the previously mentioned Taiwan case-control study found SUs to not be associated with an increased risk of new-onset AF [12].

Research on the stroke risk associated with SU use generally precedes the publication of most studies using these drugs as an active comparator for other medications' AF risk. This class of hypoglycemic drugs acts on the SU receptor (SUR) unit of the ATP-sensitive potassium channels. In normal conditions, these ionic channels may play a protective role against neuronal ischemia. SUs were therefore feared by some authors to inhibit this neuroprotective mechanism, and thus to increase the risk of stroke [19–21]. Initial results of clinical studies were contradictory, varying between reports of potential benefits [22], neutral effects [23], or even detrimental effects [24]. A subsequent meta-analysis of 27,705 diabetic patients from 17 trials found SUs to be associated with a higher relative risk for stroke than other antihyperglycemic drugs administered for glycemic control [20].

### 2.4. Thiazolidinediones

Thiazolidinediones are insulin sensitizers acting primarily on the peroxisome proliferator-activated receptor (PPAR)- $\gamma$  and, in the case of pioglitazone, also exerting a weak agonist activity on PPAR- $\alpha$ . Their action on these nuclear receptors is associated with anti-inflammatory and anti-oxidant benefits, potentially due to favorable effects on Transforming Growth Factor (TGF)- $\beta$ , Tumor Necrosis Factor (TNF)- $\alpha$ , Atrial Natriuretic Peptide (ANP), superoxide dismutase (SOD), malonyldialdehyde, nicotinamide adenine dinucleotide phosphate (NADPH) oxidase subunits, or voltage-dependent calcium channels [25]. Reports of an increased risk of hydro-saline retention, heart failure, and cardiovascular events seen with rosiglitazone [26,27] drastically limited their use in diabetic patients. As a direct effect of these reports, regulatory agencies subsequently requested proof of cardiovascular safety for the newer generations of antihyperglycemic drugs by means of dedicated trials.

These conflicting features of TZDs led to research on their association with atrial fibrillation and stroke. In an observational study on 12,605 patients with insulin-naïve type 2 diabetes, the risk of developing AF was reduced by 31% after a five-year follow-up in patients treated with TZD [28]. In another smaller observational study following the arrhythmic outcomes of catheter ablation, pioglitazone was also reported to be associated with a reduced risk of post-procedural AF [29]. A better recovery to sinus rhythm was reported in isolated cases of patients with paroxysmal AF and diabetes who received rosiglitazone [30]. The use of TZDs was associated with a lower risk of developing AF in the Taiwan case-control study that was previously mentioned [12]. A large cohort study of 108,624 diabetic, AF-free Danish patients, treated with either metformin or sulfonylureas as first-line antihyperglycemic therapy, showed a 24% risk reduction in the incidence of AF when TZDs were used as a second-line drug for glycemic control, compared with other antidiabetic drugs [31]. Post hoc analyses on the incidence of AF in the PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) and BARI 2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trials did not show significant differences in the number of patients developing AF [32,33]. However, neither of these two randomized studies were designed to include AF between their specific endpoints, so they did not systematically search for its existence using any ECG-monitoring device. The number of patients receiving TZDs who developed AF was lower than their counterparts in both studies [32,33]. A meta-analysis including 130,854 patients from three randomized clinical trials and four observational studies found a 30% reduction in the AF risk in patients treated with TZD, with significantly reduced incidences of both new-onset AF and recurrent AF [34]. In this meta-analysis, results were observed predominantly with pioglitazone, but not with rosiglitazone, and were driven by the data in the

observational studies, as the pooled analysis of the results from the three randomized clinical trials showed no statistical differences in the AF incidence [34].

Similar to the case of metformin, no specific evidence links the potentially protective role of TZDs against AF and the effect of these drugs on the risk of cerebrovascular events. However, some data indicate a real possibility that TZDs have the ability to protect diabetic patients against stroke development. In another sub-analysis of the PROactive study, the risk for fatal or non-fatal stroke was significantly reduced with pioglitazone in type 2 diabetes patients with a history of previous stroke, but not in those without a history of cerebrovascular events [35]. In the Insulin Resistance Intervention after Stroke (IRIS) trial, performed in non-diabetic but insulin-resistant patients with a history of stroke or transient ischemic attack, pioglitazone was able to lower the risk for recurrent stroke or myocardial infarction compared with placebo therapy [36]. Finally, a meta-analysis on three randomized controlled trials, incorporating 4980 subjects with previous stroke and either insulin resistance, prediabetes, or type 2 diabetes mellitus, found the use of pioglitazone to be associated with a 32% lower risk of stroke recurrence compared with a placebo [37].

### 2.5. DPP-4 Inhibitors

In a cohort study on 90,880 patients with type 2 diabetes previously treated with metformin as a first-line antihyperglycemic drug, the add-on of DPP-4 inhibitors (mostly sitagliptin) as a second-line therapy was found to be associated with a lower risk of AF development than the use of other drugs (mainly SUs) as the second antidiabetic medication [38]. The use of DPP-4 inhibitors was associated with neither an increased nor a decreased risk of new-onset AF in the case-control study on Taiwan registries that was previously mentioned [12].

These positive or neutral results on AF risk raised the question of potentially protective effects of DPP-4 inhibitors against stroke. In another longitudinal observational Taiwan study on 123,050 type 2 diabetes patients that were newly initiated on oral antidiabetic drugs, the use of DPP-4 inhibitors was associated with a lower risk for ischemic stroke compared with meglitinides or insulin; however, their risk for stroke was comparable to that observed in metformin users, and higher than the risk observed in patients treated with pioglitazone [39]. None of the cardiovascular outcome trials with DPP-4 inhibitors identified a reduced risk for stroke with any of these medications [40–44]. When a meta-analysis was performed on 19 small randomized trials and the first three cardiovascular outcome trials with DPP-4 inhibitors that were published, a non-significant trend toward protection against stroke was found, but this trend disappeared when only the cardiovascular outcome trials were introduced into another pooled analysis [45]. Likewise, a meta-analysis of the five cardiovascular outcome trials with DPP-4 inhibitors available at the end of 2018 showed a neutral effect on the risk for stroke, similar to the profile of safety, but showed a lack of benefits in terms of the risk for myocardial infarction, cardiovascular death, or heart failure [46]. Similar to the case with other drugs, none of the cardiovascular outcome trials or meta-analyses with DPP-4 inhibitors published so far have differentiated between stroke events of hemorrhagic or ischemic origin, least of all between atherothrombotic or thromboembolic events.

### 2.6. GLP-1 Receptor Agonists

A side effect of GLP-1 receptor agonists includes a moderate increase in heart rate [47], which may be due to either an effect of the direct stimulation of the GLP-1 receptor found on sino-atrial cells, or a compensatory response to the relative lowering of blood pressure levels seen with GLP-1 receptor agonists [48,49]. Acknowledgement of this effect on the heart rate led to concerns that GLP-1 receptor agonists may be associated with a higher risk for AF, especially after a pooled analysis of the phase 2b and phase 3 trials in the Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes) program with albiglutide showed a statistically significant increase in the AF incidence with this drug [50]. However, the cardiovascular outcome trials with lixisenatide, liraglutide, or semaglutide found no differences in the AF incidence between any of

the active drugs and the placebo comparator [51–53]. As cardiovascular outcome trials are specifically designed to follow major cardiovascular events, it is plausible to think that an AF episode—even though not counting as a pre-defined endpoint—should be more recognized in such studies than in trials with metabolic outcomes, to therefore offer a better statistical accuracy. Since these three cardiovascular outcome trials included patients with pre-existing cardiovascular disease, it is also presumable that such subjects would be treated with  $\beta$ -blockers, thus reducing the probability of AF occurrence and reducing the number of cases below the limit of statistical significance. Subsequently, a meta-analysis of all trials available in 2017 with GLP-1 receptor agonists (including studies with albiglutide, but also with exenatide, lixisenatide, liraglutide, dulaglutide, and semaglutide) showed no increase in the risk of AF with these drugs [54].

However, aside from speculations about the risks of AF, GLP-1 receptor agonists are definitely not associated with a higher risk for stroke. All GLP-1 receptor agonists developed from the human GLP-1 backbone (liraglutide, injectable semaglutide, albiglutide, and dulaglutide) are able to lower the risk for the composite outcome of major cardiovascular events (cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke) [53,55–57]. When endpoints included in the composite outcome were analyzed separately in each of these trials, liraglutide and albiglutide demonstrated non-significant differences opposite to the placebo in terms of the risk of stroke [55,56], whereas injectable semaglutide showed a significant 39% reduction [53], and dulaglutide was associated with a 24% reduction in the calculated risks for non-fatal stroke [57]. In a previously mentioned meta-analysis, including, in this case, the four cardiovascular outcome trials with GLP-1 receptor agonists available at the end of 2018, this class of drugs was associated with a 13% reduction in the risk for non-fatal stroke, even if atherothrombotic, thromboembolic, and/or hemorrhagic events were not differentiated [46].

### 2.7. SGLT-2 Inhibitors

SGLT-2 inhibitors exert their actions by inhibiting the active reabsorption performed by this specific co-transporter of sodium and glucose at the level of the proximal convoluted tubule. As a result, glucose, sodium, and water are lost in the final urine, lowering blood pressure and blood glucose levels, and creating a negative energy balance that induces weight loss. Based on these direct effects on multiple cardiovascular risk factors, but also on other adjunctive metabolic actions, SGLT-2 inhibitors seem able to lower the cardiovascular risk in diabetic patients. In the dedicated cardiovascular outcome trials, empagliflozin and canagliflozin were shown to reduce the progression to the composite outcome of major cardiovascular events [58,59], whereas dapagliflozin reduced the risk for the composite outcome of cardiovascular death and hospitalization for heart failure [60]. Currently, no research on the risk of AF development with any of the SGLT-2 inhibitors has been published, but a sub-analysis of the Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose (EMPA-REG OUTCOME) acknowledged a slightly increased incidence of stroke in the empagliflozin treatment group, even though not reaching statistical significance [61]. A subsequent meta-analysis of 57 studies using seven different approved or unapproved SGLT-2 inhibitors reported a 30% higher risk of non-fatal stroke [62]. Hypothetical explanations attribute this negative effect either to chance or to the relative increase in hematocrit, leading to a higher blood viscosity, as these agents exert an effect of osmotic diuresis [63]. However, another meta-analysis of trials with SGLT-2 inhibitors, this time including studies lasting at least 24 weeks and reporting at least one cardiovascular outcome, did not confirm an increased risk of stroke, thus assuring a reasonable level of cerebrovascular safety with this class of drugs [64]. The above-mentioned pooled analysis, including all three available cardiovascular outcome trials with SGLT-2 inhibitors, revealed no supplementary risk of stroke with SGLT-2 inhibitors compared with placebo comparators [46].

### 3. Conclusions

Current evidence supports the existence of a relationship between diabetes mellitus and an increased risk for atrial fibrillation and stroke. In these high-risk patients, several reports linking

antidiabetic medications to modified risks for atrial fibrillation, stroke, or both, have been published in the last years. The most relevant of these results are summarized in Table 2.

**Table 2.** Summary of the main current evidence on the association of current antihyperglycemic drugs with risks of atrial fibrillation (AF) and stroke.

| Drug                    | Risk for AF  | Risk for Stroke   |
|-------------------------|--|---|
| Insulin                 | Increased [12]   | Increased [6,13]  |
| Metformin               | Reduced [12,15]  | Reduced [17,18]   |
| Sulfonylureas           | Unchanged [12]   | Reduced [22], unchanged [23], or increased [20,24]  |
| Thiazolidinediones      | Reduced [12,28,29,31,34] or unchanged [32,33]  | Reduced [35–37]   |
| DPP-4 inhibitors        | Reduced [38] or unchanged [12]   | Reduced [39] or unchanged [40–46]   |
| GLP-1 receptor agonists | Increased with albiglutide [50], unchanged with semaglutide, liraglutide, and dulaglutide, or in meta-analyses [51–54] | Reduced in meta-analyses [46] and with semaglutide [53], unchanged with liraglutide, albiglutide, and dulaglutide [55–57] |
| SGLT-2 inhibitors       | Data not available   | Increased in some meta-analyses [62], unchanged in others [46,64]   |

The cause–effect relationship between the modified risk for atrial fibrillation of these drugs and cerebrovascular disease due to thromboembolic events has not yet been analyzed in studies with dedicated outcomes. However, depicting the ability of some specific antihyperglycemic therapies in reducing the risks for both atrial fibrillation and stroke as completely separate mechanisms would mean allowing the existence of slightly too much coincidental evidence. Trials searching for a potentially causal triangular relationship between antidiabetic drugs, risks for atrial fibrillation, and cerebral thromboembolism are needed to fill in a gap in evidence, and to potentially supplement the adaptation of the recommendations of current guidelines to prevent the negative outcomes of cardiovascular disease in diabetic patients as much as possible.

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Review

# The Role of Cardiovascular and Metabolic Comorbidities in the Link between Atrial Fibrillation and Cognitive Impairment: An Appraisal of Current Scientific Evidence

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**Abstract:** Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice with implications on long-term outcomes. Metabolic disorders including diabetes mellitus and obesity are independent predictors of atrial fibrillation and present therapeutic targets to reduce both the incidence and duration burden of atrial fibrillation. The presence of pericardial fat in direct contact with cardiac structures, as well the subsequent release of proinflammatory cytokines, may play an important role in this connection. Atrial fibrillation is an independent predictor of cognitive impairment and dementia. While clinical stroke is a major contributor, other factors such as cerebral hypoperfusion and microbleeds play important roles. New evidence suggests that atrial fibrillation and cognitive impairment may be downstream events of atrial cardiomyopathy, which may be caused by several factors including metabolic syndrome, obesity, and obstructive sleep apnea. The mechanisms linking these comorbidities to cognitive impairment are not yet fully elucidated. A clearer understanding of the association of AF with dementia and cognitive impairment is imperative. Future studies should focus on the predictors of cognitive impairment among those with AF and aim to understand the potential mechanisms underlying these associations. This would inform strategies for the management of AF aiming to prevent continued cognitive impairment.

**Keywords:** atrial fibrillation; metabolic syndrome; obesity; cognitive impairment; dementia

## 1. Introduction

Atrial fibrillation (AF) is the most common significant arrhythmia and is increasingly prevalent [1]. Hospitalization due to AF has increased by 60% in the United States in the last 20 years and is expected to affect 20 million Americans by 2030 [2]. AF may be complicated by thromboembolic events and heart failure, and it is associated with an increase in mortality [3]. Metabolic disorders including hypertension and diabetes have been shown to significantly increase the risk of these complications in those with AF [4]. In addition, obesity and obstructive sleep apnea have also been associated with AF [5].

Cognitive decline and dementia have emerged as associated risks in patients with atrial fibrillation [6]. A significant portion of this risk is attributable to cerebrovascular thromboembolic

events that lead to vascular dementia [7]. However, AF has been shown to be a risk factor for cognitive impairment and dementia independent of stroke [8]. In this review, we will examine the association between metabolic disorders and AF as well as the possible role of these cardiovascular and metabolic comorbidities in the pathogenesis of cognitive impairment in patients with AF.

## 2. Obesity and Metabolic Syndrome

Atrial fibrillation is associated with heart failure, obesity, diabetes, hypertension, and hyperthyroidism [9]. Obesity has been shown to be an independent risk factor for AF [10], and this association has been observed in multiple studies thus far [11–13]. Wang et al. [11], analyzed the data of the Framingham Heart Study, a long-standing, multigenerational, longitudinal study of cardiovascular disease, and found that body mass index (BMI) independently predicted AF when adjusted for other risk factors [11]. Each BMI unit increase was associated with a 4% risk increase of AF. Overall, obese men and women had a 52% and 46% greater risk of AF, respectively, when compared to nonobese participants. One of the largest studies to date was a nationwide, prospective cohort from Denmark of 47,589 individuals, where each increase in BMI per unit increased the risk of AF by 8% and 6% in men and women, respectively [14]. In individuals with a BMI over 30, the adjusted hazard ratio for AF was 2.35 in men and 1.99 in women [14]. The association between obesity and AF is independent of ethnicity. In two large cohort studies of 28,449 Japanese individuals and 14,598 American individuals, a significant association between obesity and AF was shown [15,16]. Umetani et al. [17], reported a three-fold risk of AF in individuals with BMI > 25, after adjusting for age and left atrial (LA) size, and that obesity was the strongest metabolic risk factor for AF [17]. In the Atherosclerosis Risk in Communities (ARIC) study, 20% of incident AF could be attributed to obesity. Wanahita conducted a meta-analysis of 16 studies and found a 49% increase in the risk of AF in individuals with a BMI above 30 [13].

Adipose tissue is known to release multiple compounds, many of which are proinflammatory cytokines [18]. Central obesity is strongly associated with insulin resistance [19]. In addition, obesity is associated with the activation of the sympathetic nervous system and renin-angiotensin system, leading to hypertension [20]. These elements define the metabolic syndrome. Metabolic syndrome can practically be considered as a collection of cardiovascular and metabolic imbalances that are associated with a higher risk of developing cardiovascular atherosclerotic disease. Key features include abdominal obesity, dyslipidemia, hypertension, and insulin resistance [21]. Metabolic syndrome has an estimated prevalence of 20% in North America [22], which underlines the need to identify, manage, and prevent potential complications [21].

Metabolic syndrome has been shown to be associated with atrial remodeling and fibrosis, atrial synchronicity, autonomic abnormalities, mitochondrial dysfunction, and increased LA size [23,24]. An electrophysiological study of patients with AF has shown that left atrial low-voltage zones were identified more commonly in patients with metabolic syndrome (46%) than in patients without metabolic syndrome (8.2%). Metabolic syndrome was an independent predictor of left atrial low voltage with 11 times the odds [20]. Each component of metabolic syndrome has been demonstrated to be associated with an increased risk of AF [23]. It is not only the diagnosis of diabetes mellitus that has an association with AF, but increased fasting glucose also independently predicts the risk of AF. Each increase of 18 mg/dL is linked with a 33% increased risk of AF [25].

One mechanism in which obesity may lead to AF is through the presence of pericardial fat, which is of importance because of its contiguity with the heart and a shared blood supply [26]. Pericardial fat is highly metabolically active and releases proinflammatory cytokines. Critically, pericardial fat is more strongly associated with metabolic risk than BMI. Thus, pericardial fat may play a major role in the risk of AF observed with obesity [26].

## 3. Obesity as a Therapeutic Target to Decrease Metabolic Comorbidities

From a pharmacological perspective regarding weight loss, there is little evidence of the benefit in reducing the risk of AF with medications used in diabetes that induce significant weight loss and

improve insulin sensitivity, such as glucagon-like peptide -1 receptor agonists, sodium-glucose transport protein 2 (SGLT2), and dipeptidyl peptidase-4 (DPP-4) inhibitors [23]. Osteopontin, a proinflammatory adhesion protein that is upregulated in obese individuals with hypertension, may be a pharmacological target to prevent atrial remodeling [27].

Interventions of weight management have been shown to affect atrial remodeling in a proportional manner and to reduce AF burden. The benefits of weight loss were seen from the structural perspective in a study conducted by Abed and colleagues that showed a significant decrease in the left atrial area and interventricular septal thickness in subjects that lost 14.3 kg, compared to the control group that lost 3.6 kg [28]. In addition, patients who lost significant amounts of weight also experienced a reduction in AF, as well as AF symptom-related frequency and severity [28]. However, there appears to be a minimal threshold of weight loss for AF burden to decrease [23]. The Long-Term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort (LEGACY) study aimed to assess the long-term impact of weight loss on AF rhythm control in patients who were obese, as defined by a BMI of 27 kg/m<sup>2</sup> [29]. Similarly, in the LEGACY study, subjects with BMI > 27 that lost >10% of body mass had a six-fold decrease of arrhythmias compared to individuals that lost less than 10% of body mass. Patients that lost >5% of body mass, but did not reach the 10% threshold, actually had a two-fold increase in arrhythmia recurrence [29].

Weight control measures that involve medical interventions, rather than exercise or diet, have also been shown to be effective. Bariatric surgery is able to produce significant weight loss that is more sustainable in comparison to nonsurgical interventions [30]. This has been shown to have dramatic effects on metabolic comorbidities, such as hypertension and diabetes mellitus, and may return the patient to a normotensive and normoglycemic state. Reductions in cholesterol have also been noted. This mirrors the effect of weight loss by nonsurgical interventions [28,29]. Interestingly, bariatric surgery has been shown to decrease incident AF as well as reduce the burden of AF in obese individuals [31]. In the Swedish Obese Subjects study, investigators compared 2000 individuals that underwent bariatric surgery to a matched cohort of 2000 patients that received usual care [31]. After a median 19 years follow-up period, incident AF had occurred in 12.4% of patients that underwent bariatric surgery compared to 16.8% of those that received usual care with a 29% relative risk reduction in incident AF [31]. Lynch and colleagues replicated this finding [32].

#### 4. Fibrotic Atrial Cardiomyopathy

Metabolic syndrome, which results in hypertension, inflammation, endothelial dysfunction, and myocardial steatosis, leads to left atrial fibrosis and dilatation [23]. Inflammation is the main driver of atrial fibrosis; a proposed mechanism in metabolic syndrome is through the accumulation of intracellular triglycerides and free fatty acids. These deposits appear to be toxic to the atrial myocytes, leading to myocardial apoptosis and fibrosis. The resulting atrial fibrosis leads to structural and electrical remodeling of the left atrium. Atrial dilatation leads to the activation of the renin-angiotensin-aldosterone system, which in itself leads to further myocyte fibrosis, apoptosis, and vasoconstriction by angiotensin II and aldosterone [24]. Atrial fibrosis causes the development of electrical remodeling by delaying interatrial conduction with prolongation of atrial activation time and cycle length, and these changes are enhanced by augmented atrial stretch from obesity. Atrial stretch causes prolongation of the action potential and shortens refractory periods which allow physiological rhythm to be overtaken by reentrant wave fronts from the pulmonary veins, which result in atrial fibrillation. Recurrent episodes of AF enhance atrial remodeling that will promote further events in time.

Atrial cardiomyopathy, therefore, is hypothesized to be the result of these multiple metabolic derangements including hypertension, diabetes, and metabolic syndrome [33]. In turn, AF may also independently be associated with strokes and cognitive decline. This notion is supported by findings seen in patients with subclinical AF in whom studies found a significant increase in stroke risk [34]. The classical theory is that AF causes blood to stagnate in the left atrium that leads to a stroke. However, data from patients with subclinical device-detected AF put this theory into question. There was



no temporal relationship between AF episodes and stroke events, with the majority of AF episodes occurring >30 days prior to the stroke event [35,36]. This lends credence to the notion that atrial hypocontractility and impaired atrial endothelial function in the context of atrial cardiomyopathy contribute significantly to stroke events and do not require the presence of AF [33]. In a recent consensus document by the European Heart Rhythm Association that examined the current literature on the subject, hypertension, obesity, and diabetes mellitus were noted to lead to atrial cardiomyopathy through the promotion of changes to the cardiac myocyte, fibrosis, and noncollagenous infiltration [37].

## 5. Atrial Fibrillation (AF) and Cognitive Function

Both atrial fibrillation and dementia are common diseases that share similar risk factors, but the association between them appears to be independent of shared risk factors. Table 1 summarizes the current body of literature demonstrating the association between AF and dementia. An improved understanding of the predictors of cognitive impairment in patients with AF, and the potential underlying mechanisms, is critical for the management of AF with the aim to prevent adverse outcomes in these patients [38].

Several studies have documented the association of AF and cognitive impairment. In 935 participants of the ARIC study with no prior history of strokes, incident AF was associated with a more rapid decline in executive function and verbal fluency [39]. The association was only found in those with subclinical strokes, which suggested a thromboembolic cause of the association. Ott and colleagues assessed data from a cross-sectional study with 6584 participants, of whom 9.6% had cognitive impairment and 4.2% had dementia [40]. The most common causes of dementia were Alzheimer's disease (75%), vascular dementia (15%), and undefined dementia (11%). Participants with AF had twice the odds of having dementia compared to those without AF.

Other studies have shown that the association between AF and cognitive decline goes beyond thromboembolic disease. Marzona and colleagues performed a combined post hoc analysis of two prospective multicenter trials, Telmisartan, Ramipril, or Both in Patients at High Risk for Vascular Events (ONTARGET) and The Telmisartan Randomised Assessment Study in ACE intolerant subjects with cardiovascular Disease (TRANSCEND), which comprised 31,506 patients aged 55 years and older with cardiovascular disease or diabetes [41]. At baseline, 3.3% had AF, while 6.5% developed AF during follow-up (median 56 months). AF was associated with a 14% increased risk of cognitive decline and a 16% increased risk of new-onset dementia; these results were independent of any history of overt stroke [41]. Santangeli published a systematic review of eight prospective studies that included over 77,000 patients. The risk of dementia in AF patients was increased by 40% (hazard ratio (HR) 1.42, 95% confidence interval (CI) 1.17–1.72,  $p = 0.002$ ) [6]. Kim and colleagues analyzed data from a large population-based cohort. The association between incident AF and subsequent incident dementia was assessed in 262,611 participants aged 60 years and older that were free of stroke and dementia in Korea between 2005 and 2012. Incident AF was observed in 10,435 participants over a time frame of 1,629,903 person-years at a rate of 0.64% per year. During that time period, incident dementia occurred at a rate of 4.1 and 2.7 per 100 person-years in those with incident AF and a propensity score-matched AF-free group, respectively. Incident AF increased the risk of dementia by 50% (HR 1.52; 95% CI 1.43–1.63). Incident AF was associated with an increased risk of both Alzheimer's (HR 1.31, 95% CI 1.20–1.43) and vascular dementia (HR 2.11, 95% CI 1.85–2.41). Oral anticoagulation in patients who developed incident AF was associated with a reduced risk of incident dementia (HR 0.61, 95% CI 0.54–0.68), while higher CHA<sub>2</sub>DS<sub>2</sub>-VASc scores were associated with an increased risk of dementia [42].

AF is associated with an increased risk of progressive cognitive impairment in patients who have not suffered from a stroke. In a secondary analysis of the Cardiovascular Health Study, patients with AF had a more rapid decline of cognitive function compared to patients with sinus rhythm [43], as assessed by the Mini Mental State Exam. Cognitive impairment risk is greater in AF patients with heart failure, diabetes, and kidney disease [44]. A higher risk of dementia in patients with AF that have not suffered from strokes is found in both men and women. In a large study of 35,608 patients without

a history of AF or dementia, of whom 40.4% were women, the five-year rates of AF were higher in men than women (14.0% in men versus 11.9% in women;  $p < 0.0001$ ). However, dementia rates (1.1% in women versus 0.9% in men;  $p = 0.09$ ) were similar in women and men. Among the patients who developed AF, the five-year rate of dementia in women was 2.9%, versus 2.3% in men ( $p = 0.180$ ) [45].

Multiple mechanisms of cognitive dysfunction due to atrial fibrillation have been postulated. The most intuitive mechanism is ischemic stroke causing cognitive decline. The risk of ischemic stroke is four to five times greater in individuals with atrial fibrillation. Subclinical strokes contribute significantly to cognitive decline. AF is significantly associated with subclinical strokes, which has been shown to confer a two- to seven-fold increase in odds [8]. Chronic brain hypoperfusion is believed to be a second mechanism of cognitive decline in AF. Cardiac output can decrease as a result of beat-to-beat variability, leading to hypoperfusion and hypoxia of the brain. Animal models have shown that hypoperfusion of the brain reduces clearance of amyloid beta, which may lead to Alzheimer's dementia [7]. In a modeling analysis performed to assess the hemodynamic effect of AF on brain perfusion, the variance in R-R intervals as well as loss of atrioventricular synchrony led to a reduction in cerebral blood flow that led to repetitive hypoperfusions [46]. Lastly, systemic inflammation is increased in patients with AF, as evidenced by elevated markers such as C-reactive protein and tumor necrosis factor and may lead to cognitive impairment via cerebrovascular dysfunction [7]. Systemic inflammation may cause cerebral microinfarction with subsequent cognitive dysfunction via endothelial dysfunction, tissue factor release, and platelet activation [38]. Intensive lipid-lowering treatment with 40 mg atorvastatin and 10 mg ezetimibe, which has been shown to have anti-inflammatory properties, slows neurocognitive deterioration and cortical volume loss [47].

**Table 1.** Important studies in the association between atrial fibrillation and dementia.

| Study First Author (Year) | Study Details   | Outcomes   |
|---------------------------|---|--|
| Bunch et al., [48]        | Prospective database<br>3-year follow-up<br>16,848 with AF and 16,848 age/gender matched controls without AF.   | 0.9% of the AF patients and 0.5% of the no AF patients   |
| Dublin et al., [49]       | Prospective cohort study.<br>A population-based sample of 3045 community-dwelling adults aged 65 and older without dementia or clinical stroke followed from 1994 to 2008.<br>AF identified using codes             | 572 participants (18.8%) developed dementia (449 with Alzheimer's disease). The adjusted hazard ratio associated with AF was 1.38 (95% confidence interval (CI) = 1.10–1.73) for all-cause dementia and 1.50 (95% CI = 1.16–1.94) for possible or probable Alzheimer's disease). |
| De Bruijn et al. [50]     | Prospective cohort study<br>6514 dementia-free participants in the prospective population-based Rotterdam Study<br>20 years of follow-up<br>Clinical criteria   | Incident AF was associated with an increased risk of dementia in younger participants (<67 years: 1.81; 1.11–2.94 vs. ≥67 years: 1.12; 0.85–1.46; $p = 0.02$ for interaction)  |
| Ding et al. [51]          | Prospective cohort study<br>2685 dementia-free participants from the Swedish National Study on Aging and Care who were regularly examined from 2001–2004 to 2010–2013.<br>9 years of follow-up<br>Clinical criteria | AF was significantly associated with an increased risk of all-cause dementia (HR = 1.40, 95% CI: 1.11–1.77) and vascular and mixed dementia (HR = 1.88, 95% CI: 1.09–3.23)   |
| Marzona et al. [41]       | Post-hoc analysis of two randomized controlled trials, TRANSCEND and ONTARGET<br>31,506 participants<br>56 months follow up<br>Clinical outcomes  | AF was associated with an increased risk of incident dementia (HR 1.30, 95% CI 1.14–1.49)  |
| Rusanen et al. [52]       | 2000 participants who were randomly selected from four separate, population-based samples originally studied in midlife<br>25 year follow up<br>Clinical outcomes   | AF in late-life was an independent risk factor for dementia (HR 2.61, 95% CI 1.05–6.47; $p = 0.039$ ) and AD (HR 2.54, 95% CI 1.04–6.16; $p = 0.040$ )   |

## 6. Future Directions

Given the increased prevalence of AF, metabolic syndrome, and cognitive impairment, it is imperative that our understanding of the associations and interactions of these entities also increases. Prospective studies with well-defined and adjudicated predictors and outcomes are needed. This includes clear criteria for the subdivisions of dementia and prolonged screening for AF prior to the commencement of studies. New technology that allows continuous ambulatory monitoring of AF will significantly increase our ability to screen for AF. The Apple Heart Study, which enrolled 419,093 participants, disclosed the preliminary findings that 2161 participants (0.5%) received a pulse notification for AF. These patients were then invited to wear an electrocardiogram patch, and AF was identified in 34% of participants [53]. Studies assessing the efficacy of a variety of treatment modalities for prevention and treatment of cognitive impairment in the context of AF will inform future clinical practice. Ongoing trials such as Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in AF (BRAIN-AF) (NCT02387229) will assess whether anticoagulation is effective in patients without traditional risk factors for stroke. Ongoing improvement in imaging may allow further characterization of cerebral changes and explain mechanisms of the association between AF and dementia.

## 7. Conclusions

AF is associated with cognitive impairment and dementia via stroke-dependent and independent mechanisms. Metabolic comorbidities are independent predictors of AF and may be a cause of atrial cardiomyopathy, which would in turn contribute to AF as well as non-stroke-related mechanisms. Further studies are required to elucidate and identify predictors of this association. Such knowledge may inform future management of AF.

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Review

# Cognitive Function and Atrial Fibrillation: From the Strength of Relationship to the Dark Side of Prevention. Is There a Contribution from Sinus Rhythm Restoration and Maintenance?

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**Abstract:** Atrial fibrillation (AF) is the most common chronic cardiac arrhythmia with an increasing prevalence over time mainly because of population aging. It is well established that the presence of AF increases the risk of stroke, heart failure, sudden death, and cardiovascular morbidity. In the last two decades several reports have shown an association between AF and cognitive function, ranging from impairment to dementia. Ischemic stroke linked to AF is a well-known risk factor and predictor of cognitive decline. In this clinical scenario, the risk of stroke might be reduced by oral anticoagulation. However, recent data suggest that AF may be a predictor of cognitive impairment and dementia also in the absence of stroke. Cerebral hypoperfusion, reduced brain volume, microbleeds, white matter hyperintensity, neuroinflammation, and genetic factors have been considered as potential mechanisms involved in the pathogenesis of AF-related cognitive dysfunction. However, a cause-effect relationship remains still controversial. Consequently, no therapeutic strategies are available to prevent AF-related cognitive decline in stroke-free patients. This review will analyze the potential mechanisms leading to cognitive dysfunction in AF patients and examine the available data on the impact of a sinus rhythm restoration and maintenance strategy in reducing the risk of cognitive decline.

**Keywords:** atrial fibrillation; cognitive decline; anticoagulation; rhythm control; microbleeds; cerebral ischemia

## 1. Introduction

Atrial fibrillation (AF) is a common chronic cardiac arrhythmia with an increasing prevalence over time mainly because of population aging, peaking at 10–17% incidence from the age of 80 years and older [1,2]. The presence of AF increases the risk of stroke up to five-fold [3], heart failure [4,5] and death [6,7]. Epidemiological evidence indicates an association between AF, cognitive impairment and dementia [8–13]. The great impact of this issue is demonstrated by the several articles that have been published only in the last 12 months from the present review paper by Heart Rhythm Associations [14] and others [10–12,15–22]. Stroke-related AF is a well-known risk factor and predictor of cognitive impairment and dementia [23]. However, clinically recognized strokes represent only the tip of an iceberg. Some observations suggest that AF-induced brain ischemia and silent brain infarcts [24–26] detected by neuroimaging [27] are more frequent than clinical stroke and together with microinfarcts (beyond the power resolution of the conventional neuroimaging techniques) are associated with cognitive impairment and dementia [28,29]. Based on recent observations AF may also be a predictor of cognitive impairment and dementia in the absence of stroke [30,31]. Moreover, taking into account



the different patterns of AF (paroxysmal, persistent, long-stand persistent, permanent, non-valvular, and incident [1,32]), it seems clear that the association between AF and cognitive function becomes more difficult to elucidate. In addition, a full understanding of the mechanisms by which AF may lead to cognitive impairment also in patients without any evidence of stroke remain not completely understood [33]. Cerebral hypoperfusion, chronic inflammation and endothelial dysfunction have been considered potentially involved in the pathogenesis of AF-cognitive impairment [11,20,34–36]. Currently, no therapeutic strategies are available to prevent cognitive dysfunction in stroke-free patients with AF; therefore, clarifying the potential underlying mechanisms of cognitive impairment in AF without stroke might be a critical issue.

This review, starting from the available literature, focuses on the relationship between AF and cognitive impairment, exploring both stroke and non-stroke related mechanisms that lead AF-patients to the development of progressive cognitive dysfunction. Moreover, the examination of the potential basic mechanisms provides an insight into the possible therapeutic implications. Finally, the potential benefit of a sinus rhythm restoration and maintenance strategy is explored.

## 2. Current “Views” on Atrial Fibrillation-Related Stroke

As reported by the majority of epidemiological studies the presence of AF implies up to five-fold increased risk of ischemic stroke [3,37,38], but the causal relationship of this correlation still remains not completely understood [33]. Moreover, this risk increases if other pathological conditions, such as hypertension [39], diabetes mellitus, valvular heart disease [6], heart failure [5], coronary heart disease [6,40], chronic kidney disease [6,32], inflammatory disorders [41,42], sleep apnea [43], and tobacco use [44] are present. To date some of these comorbidities are also included in the CHA2DS2-VASc score used to calculate the annual risk of stroke [1].

### 2.1. Possible Mechanisms of AF-Related Stroke

The current hypothesis postulates that uncoordinated myocytes activity could explain the impaired/loss of atrial contraction seen in AF patients, and the resulting blood stasis would cause the increased thromboembolic risk [33,45]. Despite a direct correlation between AF and stroke found in many studies, this is not consistent among all available data: according to some reports, the risk of embolic stroke seems not to be directly related to the duration of dysrhythmia [46–50]. This evidence seems to demonstrate the lack of a direct association between the burden of AF and the prevalence of stroke. Furthermore, it is important to note that a single brief episode of subclinical AF is associated with a 2-fold higher risk of stroke in older patients with vascular risk factors, whereas young and otherwise healthy patients with clinically apparent AF do not face a significantly increased stroke risk [51,52]. These data support the role of other concomitant risk factors apart from dysrhythmia in the determination of AF-related stroke. If AF causes thromboembolism, it should be specifically associated with embolic strokes [53]. However, almost 10% of patients with lacunar strokes have AF, and large-artery atherosclerosis is twice common in AF patients, suggesting a possible contribution from other factors [54]. Moreover, if dysrhythmia is the only cause of thromboembolism, maintaining a normal rhythm should eliminate stroke risk. However, in a meta-analysis of eight randomized clinical trials, a rhythm-control strategy had no effect on stroke risk (odds ratio, 0.99; 95% confidence interval, 0.76–1.30) [55], and it is unlikely that this result could reflect a failure to maintain sinus rhythm because rhythm-control strategies showed substantial success in maintaining normal sinus rhythm (odds ratio, 4.39; 95% confidence interval, 2.84–6.78). Atrial fibrillation coexists with other alterations, such as endothelial dysfunction [56], fibrosis [57], and mechanical dysfunction of left atrial appendage [58]. These factors have been associated to stroke. Some authors have proposed a novel up to date model of AF-related stroke, based on the severity of atrial cardiopathy rather than the duration of dysrhythmia [33]. According to this new hypothesis, AF and thromboembolism occur as separate downstream effects of atrial cardiopathy [33,38,59]. Briefly, this model highlights the interaction between systemic vascular risk factors, atrial substrate and rhythm suggesting that these factors with

the aging finally result in atrial cardiopathy, thus increasing the risk to develop AF and consequently thromboembolism. The role of atrial cardiopathy in thrombogenesis should be considered similar to the post myocardial infarction and heart failure related ventricular cardiopathy. In both of these diseases, thromboembolism can occur even in the absence of dysrhythmia. Once developed, AF causes contractile dysfunction and stasis because of dysrhythmia, which further increases the risk of thromboembolism [37,45]. In addition, long-standing persistent AF (a pattern that lasts at least a year without interruption) [1] causes atrium remodeling, thereby worsening atrial cardiopathy and increasing thromboembolic risk even further. On the other hand, systemic risk factors participate to increase risk of stroke via non atrium-related mechanisms, such as in situ cerebral small-vessel occlusion, atherosclerosis of the large-artery, and ventricular systolic dysfunction [60]. Finally, once stroke occurs, AF risk may transiently increase because of autonomic changes and post-stroke inflammation [61].

## 2.2. AF and Stroke-Related Cognitive Impairment: The Visible Side of the “Moon”

The relationship between AF and cognitive impairment/dementia has been reported in several studies [11,15–17,19,20,62,63]. The large cross-sectional Rotterdam Study was one of the first pieces of evidence to describe this association [64]. Of the 6584 participants, 635 (9.6%) had cognitive impairment without dementia, whereas 4.2% were diagnosed with dementia. In 75% of the affected patients, the most common form of dementia was Alzheimer’s disease, whereas 15% had vascular dementia and 11% undefined dementia. Of the patients with Alzheimer’s disease, almost 20% had concomitant cerebrovascular disease. Dementia was reported to be up to 2-fold more common in patients with AF than in those without it. A significant positive association between cognitive impairment and AF was also described, but this association was weaker [64]. Stratification for sex showed that these findings were restricted to women and patients younger than 75 years old [64]. Furthermore, a systematic review including more than 77,000 patients with normal baseline cognitive function and not suffering an acute stroke, showed that AF significantly increases the risk of incident dementia (HR 1.42, CI 1.17–1.72,  $p = 0.002$ ) [30]. Three meta-analyses have shown a higher risk of dementia in patients with AF who have a stroke (RR 2.43–2.70) [30,65,66]. The risk of incident dementia and cognitive decline was more modest in those without stroke at baseline than in patients with AF and previous history of stroke. AF patients have up to a 2-fold higher risk of silent or subclinical strokes than those without AF [28]. In AF patients, subclinical stroke has been clearly associated to long-term rates of cognitive dysfunction and dementia compared to patients who do not have a stroke, and there is a direct correlation between the impairment of cognitive function and the number of silent cerebral lesions at MRI [26,28].

Of note, patients with persistent AF (defined as at least seven days of arrhythmia that may or may not end on its own [1]) have a significantly higher number of lesions than those with paroxysmal pattern, in which irregular heartbeat may last anywhere from several seconds to a week, but usually ends spontaneously within 24 h [1] ( $41.1 \pm 28.0$  vs.  $33.2 \pm 22.8$ ,  $p = 0.04$ ) [28]. Cognitive performance, assessed by well-validated tests, was significantly worse in patients with persistent and paroxysmal AF than in controls (Repeatable Battery for the Assessment of Neuropsychological Status scores  $82.9 \pm 11.5$ ,  $86.2 \pm 13.8$ , and  $92.4 \pm 15.4$  points, respectively,  $p < 0.01$ ) [28].

Many of the previously cited studies were limited by the short duration of the follow-up. The Atherosclerosis Risk in Communities, a prospective cohort study with a 20-year follow-up, showed that participants who developed incident AF (defined as the first occurrence of hospitalization with a primary discharge diagnosis of AF or  $\geq 2$  ambulatory visits for AF [32]) had greater cognitive decline over 20 years, compared to participants who did not develop AF. The AF-related decline in the global score was 16% greater and was augmented after accounting for attrition. In addition, incident AF was associated with 23% higher risk of dementia. Although adjustment for prevalent and incident ischemic stroke attenuated the associations slightly, they remained significant [8]. AF-related cognitive impairment was characterized by a greater decline in cognitive tests associated to language and executive function rather than memory tests [8]. While Alzheimer’s disease is mainly characterized by memory deficits [67–69], AF shares with other vascular risk factors a preferential impairment of

visuospatial ability [28]. The study by Gaita et al. [28] evaluated the distribution of silent cerebral lesions in patients with paroxysmal or persistent atrial fibrillation, reporting bilateral distribution with cortical and subcortical areas of silent cerebral ischemia. These lesions showed a frontal spotted pattern which is in contrast with the hippocampal and temporal lobe involvement of Alzheimer's disease. The cardiac origin of the embolic particles was suggested by distribution and size of the embolic material. Emboli of cardiac origin are generally smaller than those due to atherothrombotic material and cause lesions widely distributed, on both sides, of the brain [70–72]. The cerebral MR pattern described in 50% and 67% of the patients with paroxysmal and persistent AF, respectively, was characterized by small, sharply demarcated lesions, often in clusters, with a bilateral distribution, prevalently in the frontal lobe, strongly supporting the non-atherothrombotic origin of the silent cerebral ischemia.

Finally, another cross-sectional study reported that AF was not associated to cognitive decline in patients without prevalent silent cerebral ischemia and/or subclinical cerebral infarct [73].

### 2.3. Effects of Anticoagulation Therapy

Despite the well-documented role of anticoagulants in cardioembolic stroke prevention [1,74], it is not clear if the risk of AF-related dementia can be significantly reduced by oral anticoagulation [11,16,75–77]. Prior studies have found that oral anticoagulation in stroke free patients was associated with dementia [78]. Intracranial hemorrhage has been considered the major concern with anticoagulation use, and the risk was higher in patients with leukoaraiosis (white matter changes) [79]. In warfarin-treated patients, the maintenance of an international ratio between 2 and 3 for most of the time-period (defined as time in therapeutic range [80]) is essential for stroke prevention [1]. It has been reported that chronic undercoagulation as well as overcoagulation might be linked to increased risk of cognitive impairment (HR 1.017 CI 1.007–1.027,  $p = 0.001$  and HR 1.018 CI 1.006–1.031,  $p = 0.005$ ; respectively) [81]. This trend was found significant only in younger patients (<80 year old), most probably because of a longer anticoagulation regimen overtime [81]. A retrospective study from a Swedish Patient Register showed lower incidence of dementia among patients with oral anticoagulation than patients without anticoagulants (1.14 vs. 1.78 per 100 patients/year at risk,  $p < 0.001$ ) [82]. The use of anticoagulation at baseline was associated with 29% lower risk of dementia than in patients without anticoagulant drugs (HR 0.71, 95% confidence intervals 0.68–0.74 and 48% lower risk analyzed on treatment (HR 0.52, 95% CI 0.50–0.55) [82].

In the last decade, the use of novel anticoagulants (direct inhibitor of coagulation factor Xa or thrombin, named DOACs) that do not require lab monitoring has greatly improved the prevention of AF-related cardiac embolism [83], even in elderly [84,85] and in patients undergoing cardioversion [86,87], because of a better compliance and a uniform time in therapeutic range [59,83,88]. Based on the current literature, risk of undercoagulation as well as overcoagulation should be overcome [83]. The risk of dementia appeared to be lower with DOACs (HR 0.48, 95% CI 0.40–0.58) than warfarin (HR 0.62, 95% CI 0.60–0.64), but direct comparison showed no significant differences [76,82,89]. A recent meta-analysis including 471,057 AF patients under oral anticoagulants has shown that anticoagulation was associated with a significant reduction in cognitive impairment [90]. Moreover, comparison of DOACs with warfarin-based treatment showed that the novel agents-based group has a significantly lower occurrence of dementia with an increased risk of bleeding in warfarin group [89,90]. Furthermore, in the DOAC-treated group, a low combined risk of dementia and stroke was also reported [89].

However, pre-specified blind and randomized clinical trials are warranted to verify the role of oral anticoagulation in the prevention of dementia and resolved the current controversies. Actually, the Blinded Randomized Trial of Anticoagulation to Prevent Ischemic Stroke and Neurocognitive Impairment in AF (BRAIN-AF) (NCT02387229) is ongoing [91]. It is enrolling patients with non-valvular AF (defined as arrhythmia that is not caused by any moderate to severe heart valve disease [1]) that will be screened for dementia prior to randomization by mini-mental state examination and other tests. The efficacy and safety of rivaroxaban 15 mg will be evaluated for stroke reduction, transient

ischemic attack and neurocognitive decline [91]. Another trial entitled “Impact of Anticoagulation Therapy on the Cognitive Decline and Dementia in Patients with Non-Valvular Atrial Fibrillation (CAF—NCT03061006)”, randomized, will compare the use of dabigatran vs. warfarin in 120 AF patients to assess the cognitive decline through neurological examination and cognitive testing [77].

Based on the current evidence, it has been suggested that DOACs would be a better choice for prevention of dementia than warfarin [92]. The lower rate of intracerebral bleeding has been suggested to be one possible mechanisms involved in this protective effect [92], but further studies are needed in order to investigate the role of DOACs in prevention of AF-related cognitive impairment and in the definition of a cause-effect relationship rather than a simple epidemiologic association.

### 3. Atrial Fibrillation and Non-Stroke-Related Cognitive Decline: The Submerged Part of the Iceberg?

In the last decade, new evidence supported the role of AF as independent risk factor for cognitive impairment and dementia even in patients with no history of stroke as assessed by two meta-analysis including large samples of patients [30,66] as well as by a perspective post-hoc analysis of two randomized clinical trials: the ONTARGET and the TRASCEND [31]. Large longitudinal studies also provided data supporting this association. Chen et al. [8] analyzed the results from a cohort of more than 12,000 patients enrolled in the ARIC study and evaluated the association of incident AF with 20-year change in cognitive performance considering the incidence of dementia and the cognitive decline: In conclusion, AF increased the risk of cognitive impairment and dementia independently from ischemic stroke (global cognitive Z score = 0.115, 95% confidence interval, 0.014–0.215) [8]. Similarly, De Bruijn et al. [62] evaluated the association of incident and prevalent AF and incident dementia in 6514 dementia-free participants in the prospective population-based Rotterdam Study over a 20-year follow-up period showing that prevalent and incident AF increases the risk of dementia (HR 1.33; 1.02–1.7 for prevalent AF and 1.23 (0.98–1.56) for incident AF, 95% CI) especially in younger patients (<67 year old) and in those with longer duration of AF [62].

#### *Linking Mechanisms of AF to Cognitive Dysfunction in Stroke-Free Patients*

Despite this epidemiological evidence, the pathophysiological mechanisms correlating AF and cognitive dysfunction in stroke-free patients are not completely elucidated. It is widely known that microbleeds, which are often the result of hypertensive vasculopathy/fibrohyalinosis and cerebral amyloid angiopathy, are associated with cognitive impairment [93]. In some AF patients, anticoagulation therapy may favor the occurrence of microbleeds, a condition that, at least in part, could explain the progressive cognitive impairment observed in AF [94]. However, to date there is a lack of studies about microbleeds and cognitive function in stroke-free patients affected by AF.

Brain white matter hyperintensity detected by MRI evaluation are associated with AF and poor cognitive performance [95]. However, the pathogenesis of white matter hyperintensity remains not completely understood, and its occurrence may be associated to cerebral hypoperfusion, arterial hypertension, aging, and cerebrovascular disease [96]. Neuroinflammation may be another possible explanation of the cognitive impairment in AF [41,97]. Several inflammatory markers are elevated in patients with AF such as C-reactive protein, tumor necrosis factor- $\alpha$ , interleukin-2, interleukin-6, and interleukin-8 and they may trigger cerebral micro-infarction and subsequent cognitive dysfunction by inducing a prothrombotic state through endothelial activation/damage, production of tissue factor from monocytes, increased platelet activation, and increased expression of fibrinogen [98]. Lappegard et al. demonstrated that anti-inflammatory therapy through intensive lipid-lowering treatment with 40 mg atorvastatin and 10 mg ezetimibe can modify the deterioration of neurocognitive function, and the loss of volume in certain cerebral areas in older patients with AF [99]. Reduced brain volume has been considered another potential risk factor linking AF and cognitive function. In a cross-sectional analysis of 4252 participants without dementia, AF was associated with a lower volume of gray and white matter ( $p < 0.001$  and  $p = 0.008$ , respectively) [100]. The association was reported to be even stronger in patients with persistent AF compared to paroxysmal AF [100]. A smaller hippocampal

volume, evaluated by structural MRI, has been associated with neurocognitive decline and progression towards Alzheimer disease in patients with mild cognitive impairment [101,102]. In a cross-sectional analysis, led by Knecht et al. on 122 patients, patients with AF without stroke showed worsening in tasks of learning and memory ( $p < 0.01$ ) as well as attention and executive functions ( $p < 0.01$ ) compared to subjects without AF; corresponding to the memory impairment, hippocampal volume was reduced in AF patients [103]. Genetic risk factors predisposing to dementia and cognitive impairment have been extensively studied but whether these factors may link AF and cognitive dysfunction is not well established. In the study by Rollo et al. 112 Caucasian patients with AF and dementia were matched 1:1 with patients with AF and without dementia resulting in an association between PITX2 loci, rs2200733, and dementia (OR = 2.15,  $p = 0.008$ ) [104]. However further studies are warranted to confirm these results and clarify the role of genetic factors which may influence development of cognitive dysfunction in AF patient. Most of the mechanisms involved in AF-related cognitive dysfunction are summarized in Figure 1

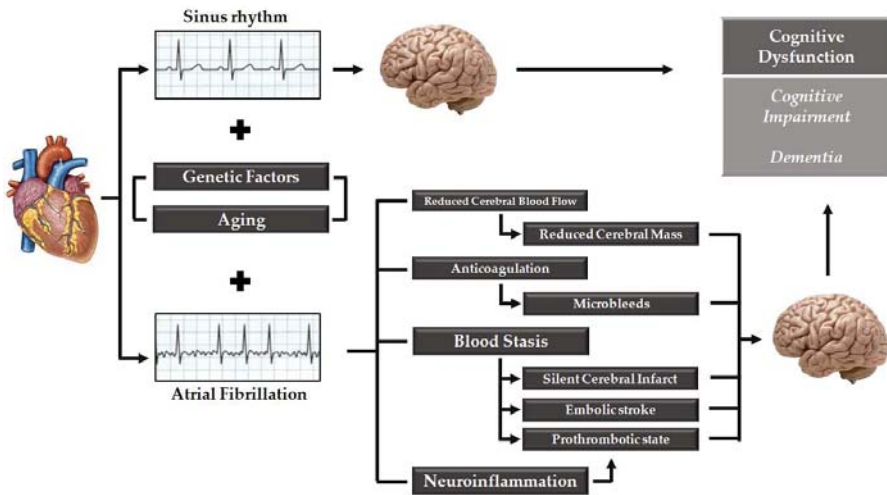


Figure 1. View of the mechanisms involved in cognitive dysfunction in patients affected by atrial fibrillation.

#### 4. Rhythm Control Strategy and Cognitive Impairment: The Dark Side of the Prevention?

The management of AF patients has been the subject of intensive investigations especially in the 1980s and early 1990s. It is well documented that compared with patients in sinus rhythm, the development of AF increases the risk of stroke [3] and worsen cardiovascular outcomes in patients with heart failure (HF) [5]. Nevertheless, it has to be taken into account that AF is a marker of more severe disease, and thus, evaluation of the coexisting comorbidities and their respective contribution to the worsening of long-term prognosis in AF patients should be carefully evaluated [5,32,39].

It seemed to be logical that restoration and maintenance of sinus rhythm might improve cardiovascular outcome. However, the analysis of the large clinical trials evaluating the impact of either rate or rhythm control strategy on mortality or combined end point of mortality and morbidity have demonstrated no benefits [105–109], resulting in a rethinking of the appropriate way in which to treat a patient with AF when the therapeutic options include both strategies, rate or rhythm control [110]. To date, this question still remains a matter of debate [111,112].

##### 4.1. AF, Cerebral Blood Flow, and Possible Contribution to Cognitive Impairment

Among older adults, lower cardiac index is associated with reduced cerebral blood flow in the cerebral gray matter, especially in lobes [113]. This mechanism seems to be associated with incident

dementia and Alzheimer's disease [114]. It is well documented that AF can reduce cardiac output [115,116]. Thus, by reducing cardiac output, AF could induce chronic brain hypoperfusion, which could be linked to AF-related cognitive impairment [104]. However, despite the association between AF and a reduction of almost 20% of the total cardiac output, cerebral blood flow has been reported by some evidence to be substantially unchanged, due to autoregulation mechanisms [117].

Currently, cardioversion of AF can be easily and safely performed because of DOACs [87,118–120]. A recent study has evaluated the impact of AF and sinus rhythm on cerebral blood perfusion [121] reporting that mean cerebral flow rates in AF and sinus rhythm are similar, even considering cerebral autoregulation (but not other associated pathologies). The authors concluded that a well-functioning cerebral autoregulating system is able to ensure a normal cerebral blood flow both during AF and sinus rhythm [121]. These findings are apparently in contrast with the hypothesis that AF is associated to chronic brain hypoperfusion. Flow variability is higher in AF compared to sinus rhythm, with a peak at arteriolar and capillary levels, thus resulting in local hypoperfusion [121]. Taking in to account these observations, the hemodynamic cerebral effect of AF could be a relevant mechanism into the genesis of AF-related cognitive impairment/dementia. In fact, deep white matter could undergo an ischemic damage because of two possible mechanisms: (1) the transient hypoperfusion as indicated above or (2) as a consequence of being exposed to transient hypertensive events (by arteriolosclerosis and capillary loss/bleeding), laying the basis for a potential AF-related vascular subcortical dementia [122]. On this matter, a cross-sectional study evaluating an unselected elderly cohort showed that AF is associated with decreased total cerebral blood flow compared to those who were in sinus rhythm, assessed by on phase-perfusion MRI and a reduction in total brain volume [123]. Brain perfusion was lowest in the persistent AF group compared to the paroxysmal AF group (46.4 mL/100 g/min vs. 50.9 mL/100 g/min;  $p < 0.05$ ) and those with no AF (52.8 mL/100 g/min;  $p < 0.001$ ) [123]. Although the hemodynamic effects on brain are complex, evidence suggests that a decreased cerebral blood flow may play a role in reducing brain volume and inducing decline in cognitive function seen in AF patients [100]. Of note, patients with paroxysmal AF who were in sinus rhythm at the time of MRI had higher cerebral blood flow and higher relative brain volume compared to those with permanent AF suggesting that as longer is the persistence in AF as low is the cerebral perfusion [123]. There is also evidence supporting that both cerebral blood flow and brain perfusion, assessed by phase-contrast MRI, improve after cardioversion [124,125]. This evidence further supports the hypothesis that also the time-period in AF may influence the risk to develop cognitive impairment [17].

#### 4.2. Rhythm Maintenance Strategy: Do We Have Supporting Evidence?

Data regarding the impact of rate control in AF and the incidence of cognitive dysfunction and dementia are still not conclusive. In the observational study from Bunch et al. the impact of effective AF ablation on the risk of cognitive decline and dementia was evaluated [126]. A total of 37,908 participants were enrolled from the large ongoing prospective Intermountain AF study and divided in three cohorts: (1) patients who underwent AF ablation (4212); (2) age/gender-matched controls with AF (no ablation, 16,848); and (3) age/gender-matched controls without AF (16,848). These cohorts were followed for at least 3 years. Authors reported a significant reduction of Alzheimer's dementia in AF-ablated patients (0.2%) compared to AF patients who did not undergo ablation (0.9%) and patients without AF (0.5%) [126]. Patients treated with catheter ablation for AF have long-term rates of death, stroke, and dementia similar to patients without AF. Other types of dementia occurred in 0.4% of the AF-ablated patients compared to 1.9% of the AF patients not undergone ablation and 0.7% of the control patients [126]. A recent report by Damanti et al. [22] seems to shed more light on this issue, supporting the protective role of rhythm control strategy on cognitive function. Specifically, in their retrospective analysis, 1082 individuals aged 65 and older with AF before hospital admission (for any cause) were enrolled. Logistic regression evaluation adjusted for age, sex, education, antithrombotic therapy, and comorbidities found that the rhythm control strategy and education were associated with less probability of cognitive impairment.

In Table 1 are reported the published data on the putative role of sinus rhythm of cognitive function. However, based on this available literature, the impact of sinus rhythm restoration and maintenance on the cognitive decline should be further investigated in pre-specified randomized clinical trials. The major limitation for such investigation will be the need of many thousands of patients to enroll and a longer follow-up to be run for at least 10 years. Therefore, because it is unlikely that such trials will ever be funded, the real role of sinus rhythm restoration and maintenance will remain a pathophysiological based strategy but with a dark side in prevention of cognitive impairment.

**Table 1.** Studies comparing impact of sinus rhythm vs. atrial fibrillation on cognitive function.

| Author              | Type of Study (N. of Patients)          | Design and Aim of the Study  | Study Results   |
|---------------------|---|--|---|
| Damanti [22]        | Retrospective Study<br>1802 individuals | Evaluation of cognitive performance using the Short Blessed Test according to rhythm and rate control strategy, antithrombotic therapy, age, education, and comorbidities.   | In the absence of optimal anticoagulation, a rhythm control strategy is associated with lower probability of cognitive impairment.  |
| Anselmino [108]     | Experimental model                      | Two coupled lumped-parameter models (systemic and cerebrovascular circulations, respectively) were used to simulate sinus rhythm (SR) and AF. For each simulation 5000 cardiac cycles were analyzed and cerebral hemodynamic parameters were calculated                                | Higher cerebral flow variability in AF rather than SR may lead to subcortical vascular dementia   |
| Gardarsdottir [110] | Cross-sectional study<br>2291 patients  | Blood flow in the cervical arteries was measured with phase contrast MRI and brain perfusion. Individuals were divided into three groups at the time of the MRI: persistent AF, paroxysmal AF, and no history of AF  | Reduced Brain perfusion in persistent AF compared to paroxysmal AF and SR. Patients with persistent AF had the smallest relative brain volumes when compared with the paroxysmal AF group and to those with no history of AF. |
| Gardarsdottir [111] | Observational study<br>26 patients      | To measure cerebral blood flow (CBF) and brain perfusion (BP) with phase-contrast (PC) magnetic resonance imaging (MRI) and arterial spin labelling (ASL) MRI in patients with AF before and after cardioversion.  | Cerebral blood flow and brain perfusion both improved after cardioversion to SR as opposed when patients continued to be in AF  |
| Bunch [113]         | Observational study<br>37,908 patients  | Three groups of patients were enrolled: those who underwent AF ablation were compared to age/gender matched controls with AF (no ablation) and age/gender matched controls without AF. Impact of effective AF ablation on the risk of cognitive impairment and dementia was evaluated. | AF ablation patients have a significantly lower risk of death, stroke, and dementia in comparison to AF patients without ablation.  |

### 5. Hypertension: A Non-Stroke-Related Mechanism of Cognitive Decline in Atrial Fibrillation?

While hypertension is a known risk factor for AF [39,127] the contribution of hypertension on cognitive decline in combination with AF is not well defined in literature. Among patients with

established AF, hypertension is present in  $\approx 60\%$  to  $80\%$  of individuals [128]. In the ARIC study (Atherosclerosis Risk in Communities), hypertension was the main contributor to the burden of AF, explaining  $\approx 20\%$  of new onset of dysrhythmia [129]. However, the effect of an intensive control of blood pressure on the risk of new onset of AF in hypertensive patients remains unclear [39]. As reported by the post-hoc analysis of the ONTARGET and TRANSCEND trials the association of AF and cognitive impairment was independent of treatment with antihypertensive drugs [31]. However, other studies seem to confirm the contribution of hypertension in the cognitive impairment [130]. In a 5-year longitudinal study of 353 community-dwelling persons, mean age 72 years, increased blood pressure variability was associated with poorer cognitive function [131]. In addition, another study involving 1373 French participants aged 59 to 71 years, the risk of cognitive impairment at 4-year assessment was increased 2.8-fold in hypertensive patients [132]. It has been reported that because of hypertension, the structure and function of cerebral blood vessels is impaired, leading to ischemic damage of white matter regions that is critical for cognitive function [130]. However, whether hypertension treatment might reduce the risk for AF and the associated cognitive impairment remains unclear [39]. It has to be considered that in AF patients, the improvement of cognitive function related to the restoration and maintenance of sinus rhythm might be partially lost by an uncontrolled hypertensive status [130]. To date, despite the lack of evidence in the relationship between hypertension treatment and cognitive impairment, the uncontrolled blood pressure remains a major epidemiological contributor to cardiovascular disease and neurological disorders, and thus, an aggressive approach, as suggested by the current guidelines [133], is highly recommended.

## 6. Discussion

Several studies have evaluated the association between AF and cognitive dysfunction, ranging from cognitive impairment to dementia. Although the strongest evidence supports the role of stroke as the principal risk factor for cognitive impairment, it has been also established that AF is a risk factor for cognitive dysfunction independently from stroke [8,63]. Various mechanisms linked to cognitive impairment in AF patients, apart from stroke, have been discussed, involving microbleeds, white matter hyperintensity, neuroinflammation, reduced brain volume, cerebral hypoperfusion and genetic factors (as shown in Figure 1). However, a clear cause-effect relationship between these putative mechanisms and cognitive dysfunction is still controversial. Some of these mechanisms (i.e., microbleeds, reduced brain volume and cerebral hypoperfusion) might be linked to a common pathophysiological substrate which might be the impact of rhythm control over a rate control strategy on brain damage. First, since AF, through the loss of atrial systole contribution in left ventricle filling, reduces cardiac output and cerebral blood flow, restoration of sinus rhythm could improve brain perfusion, thus resulting in better cognitive outcome. Second, cerebral hypo-perfusion might be related to beat-to-beat variation in stroke volume in AF [100,123]. Decreased cerebral perfusion has been associated with a reduction in both grey and white matter although the effect may be greater on the grey matter due to higher metabolic demand [123]. However, reduction in grey matter is heterogeneous in the brain, since some areas appear to have higher vulnerability to cerebral hypoperfusion [134]. In some studies, a correlation between volume reduction in specified brain area (such as hippocampus) in AF patients and neurocognitive impairment and dementia has been reported [103]. Other investigations have linked the cerebral hypoperfusion AF-related and the reduction of brain volume [123]. Of note, the reduction in brain volume, especially in grey matter volumes of temporal and hippocampal areas, has been clearly associated with the risk of dementia [135]. Moreover, also white matter hyperintensity, linked with AF and cognitive impairment, may lead to cerebral hypoperfusion [95]. Taken together, these data are consistent with the “hemodynamic hypothesis” of AF related dementia and, as a consequence, restoration and maintenance of sinus rhythm might be associated to an improved brain perfusion, thus potentially avoiding most of the “risk factors” associated to cognitive impairment.



Further evidence linking AF and cognitive impairment comes from the SWISS-AF trial, a prospective multicenter national cohort study of 2400 patients across 13 sites in Switzerland [136]. In this study, patients with documented AF underwent to extensive phenotyping and genotyping, repeated assessment of cognitive functions, quality of life, disability, electrocardiography and cerebral magnetic resonance imaging. Authors reported that four in ten patients with AF but no history of stroke or transient ischemic attack had clinically unrecognized ‘silent’ brain lesions or other structural brain abnormalities such as white matter lesions, microinfarctions or microbleeds that could serve a substrate for the cognitive decline [136].

The question whether a rapid restoration of sinus rhythm in AF patients may reduce the risk for AF-related cognitive impairment remains a matter of debate. Further studies specifically designed to compare patients in a rhythm control intervention vs. rate control strategy are warranted to define the role of these two therapeutic approaches in the cognitive outcome overtime. Moreover, evaluation over time of specific parameters, such as cerebral blood flow, brain mass, neuroinflammation and others, will be of great importance to identify the contributing factors involved in cognitive impairment in stroke-free patients and the putative role of a rhythm restoring/rate control strategy in the prevention of cerebral damage. However, the major limitation in testing the effect of sinus rhythm restoration and maintenance in preventing cognitive decline and dementia is the need of larger (with many thousands of patients to enroll) and longer (to run for more than 10 years) prospective randomized trials. Therefore, it is unlikely that such trials might be ever funded.

## 7. Conclusions

AF is an independent predictor for cognitive dysfunction ranging from cognitive impairment to dementia. Apart from stroke and ischemic substrate, other mechanisms have been studied to explain the risk for cognitive dysfunction in AF patients. By the pathophysiological point of view, restoration and maintenance of sinus rhythm might represent an additional intervention to reverse some of the pathological alterations that serve as substrate for cognitive impairment, thus with potential effect in prevention. However, this aspect remains to be better supported by stronger evidence.

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Review

# Atrial Fibrillation and Stroke. A Review on the Use of Vitamin K Antagonists and Novel Oral Anticoagulants

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**Abstract:** Atrial fibrillation (AF) is the most common arrhythmia, ranging from 0.1% in patients <55 years to >9% in octogenarian patients. One important issue is represented by the 5-fold increased ischemic stroke risk in AF patients. Hence, the role of anticoagulation is central. Until a few years ago, vitamin K antagonists (VKAs) and low molecular weight heparin represented the only option to prevent thromboembolisms, though with risks. Novel oral anticoagulants (NOACs) have radically changed the management of AF patients, improving both life expectancy and life quality. This review aims to summarize the most recent literature on the use of VKAs and NOACs in AF, in light of the new findings.

**Keywords:** NOACs; non vitamin K oral anticoagulants; atrial fibrillation; stroke; oral anticoagulation

## 1. Introduction

Atrial fibrillation (AF) is the most common arrhythmia, ranging from 0.1% in patients aged <55 years to >9% in octogenarian patients. One of the most important issues is represented by the 5-fold increased risk of ischemic stroke in AF patients [1].

Atria are excited in a chaotic, disorganized manner, with a frequency of activation variable from 400 to 650 beats/min. The atrioventricular node (AVN) receives much more impulses from the atrium than it is able to conduct, thus exercising a filter function which transmits a not excessively high number of beats to the ventricles. In fact, numerous impulses penetrate only partially into the AVN and then they are trapped inside.

The patient is often symptomatic at onset. The most common symptom is palpitation, but, in the case of the concomitant presence of an organic heart disease, the loss of effective atrial systole, as well as tachycardia, favor a hemodynamic decompensation. Less frequently, AF runs asymptomatic.

The diagnostic suspicion may already arise at the evaluation of the radial pulse and/or the cardiac auscultation, and then confirmed by an electrocardiogram (ECG) characterized by the absence of regular and morphologically similar atrial activation waves, with a totally irregular interval of the QRS complexes of ventricular activation.

AF treatment has 4 main approaches:

1. Heart rate control with either beta blockers (Bisoprolol, Metoprolol), non-dihydropyridine calcium antagonists (Verapamil, Diltiazem), digoxin (less used due to the possible risk of toxicity, especially in patients with renal insufficiency) or, as a last resort, Amiodarone;
2. Either electrical or pharmacological cardioversion with class antiarrhythmics III (Amiodarone, Ibutilide) or I-C (Flecainide, propafenone, in the absence of cardiac structural damage);

3. AF deletion through catheter ablation, either by acting on its trigger points or by altering the arrhythmogenic substrate. In either case, the risk of relapse still persists, especially during the first 6–12 months after the procedure;
4. The control of thrombo-embolic complications by using anticoagulants (novel oral anticoagulants (NOACs), vitamin K antagonists (VKAs), heparin).

A more in-depth analysis of the latter point, in fact, shows that the reduction of blood flow in the atrial chambers, caused by the reduced ventricular depletion (consequent to the reduction of diastolic time and the loss of atrial contraction, as well as, sometimes, the reduction of myocardial contractility secondary to tachycardia) makes more likely the formation of thrombi in the left atrium (LA), including the left atrial appendage (LAA).

The occurrence of this condition significantly increases when arrhythmia lasts for over 48 h, with an embolic thrombus risk increased even more significantly at the reestablishment of the sinus rhythm. A risk stratification in these patients may be estimated by using the CHA2DS2-VASc score, for which a score is assigned to each risk factor, finally providing a sum which represents the overall risk of stroke per year for the patients (Table 1).

**Table 1.** Risk stratification of stroke by the CHA2DS2-VASc score [2].

| Risk Factors               | Score | CHA2DS2-VASc Score | Stroke Risk Per Year |
|----------------------------|-------|--------------------|----------------------|
| Congestive Heart Failure   | 1     | 0                  | 0%                   |
| LV Dysfunction             | 1     | 1                  | 1.3%                 |
| Hypertension               | 1     | 2                  | 2.2%                 |
| Age ≥ 75 years             | 2     | 3                  | 3.2%                 |
| Diabetes Mellitus          | 1     | 4                  | 4.0%                 |
| Stroke/TIA/Thromboembolism | 2     | 5                  | 6.7%                 |
| Vascular Disease           | 1     | 6                  | 9.8%                 |
| Age 65–74                  | 1     | 7                  | 9.6%                 |
| Female                     | 1     | 8                  | 6.7%                 |
| Total                      | 9     | 9                  | 15.2%                |

LV: Left Ventricle, TIA: Transient Ischemic Attack.

## 2. Atrial Fibrillation (FA) Cardioversion and Anticoagulation

Current ESC guidelines for patients with AF, for less than 48 h, with a CHA2DS2-VASc score of either 0 in men or 1 in women, recommend the administration of heparin, a factor Xa inhibitor or a direct thrombin inhibitor, versus no anticoagulant therapy, without the need for post-cardioversion oral anticoagulation. Conversely, an AF for 48 h or more, needs an appropriate anticoagulation for at least 3 weeks or a negative transesophageal echocardiogram (TEE), followed by 4 weeks anticoagulation after cardioversion. In the case of a rescue cardioversion due to hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion, unless contraindicated [2].

A recent meta-analysis comparing warfarin and novel oral anticoagulants (NOACs) on 7588 AF patients undergoing electric cardioversion (CV) showed overlapping risks of ischemic stroke, major bleeding, mortality and hemorrhagic stroke [3]. In this subset of patients, several real-world studies have confirmed a favorable clinical outcome [4–8].

Though an appropriate therapy, the risk of systemic embolism in elective cardioversion is still present. In fact, a transesophageal echocardiogram may highlight the presence of a thrombus in LA or LAA in 5% of patients, despite adequate anticoagulation with both vitamin K antagonists (VKAs) or NOACs [9]. Data from real-world studies have highlighted a similar incidence of LA thrombus before performing CV, both among the use of different NOACs and in the case of VKA treatment [10,11]. Additionally, the importance of practicing TEE in patients at high risk of LA/LAA thrombus (e.g., CHA2DS2-VASc score >3) has been pointed out [12].

The average stroke rate <1% makes it reasonable to assume a lower prevalence of thromboembolism during cardioversion or, maybe, that not every stroke is clinically diagnosed. Moreover, it is not surprising that patients with a very high-risk score for thromboembolism could be refractory to standard anticoagulation [12].

The use of NOACs compared to VKAs treatment has shown, both in trials and in real-world settings, a reduction in the timing to CV, with a consequent higher satisfaction of patients and cost savings for clinical facilities [13–15].

In patients in whom sinus rhythm has been restored, the same drugs used for cardioversion may be used to prevent arrhythmia relapses. Among these drugs, amiodarone has been shown to be the most effective antiarrhythmic, though not without long term side effects [16].

### 3. Oral Anticoagulation with Vitamin K Antagonists

VKAs were the first anticoagulants used in AF patients. Their discovery was completely random and dates back to the 1920s, when in the U.S., sweet clover was used to feed livestock, which was stored in silos. The fermentation of the clover produced bis-hydroxycoumarin. The anticoagulant effect of this by-product determined the consistent death of herds of cattle on farms in Wisconsin, due to hemorrhagic syndromes. The fear that warfarin could be excessively toxic to humans initially led to only being used as rat poison. The drug with the trade name of Coumadin was approved only in 1954, though the skepticism of the medical community remained until 1955, when President Eisenhower, struck by coronary artery disease (CAD), requested to be treated with the most powerful “antithrombotic” drug of the time.

VKAs (warfarin and acenocoumarol) are indirect anticoagulants, which interfere with the hepatic production of dependent vitamin K coagulation factors. The lag time between drug intake and pharmacological action varies between 3 and 7 days, the time required for activated coagulation factors to be deleted and/or exhausted. On the other hand, prothrombin time (PT) can be lengthened in a short time due to the inhibition of short-life coagulation factors, such as factor VII.

The dosage of oral anticoagulants, due to the individual variability of their pharmacokinetics and pharmacodynamics, should be established based on the determination of the International Normalized Ratio (INR), given by the ratio between the PT of each patient and the PT of a healthy subject. In the case of AF, INR must be maintained between 2 and 3 [2].

Vitamin K represents the antidote of dicoumarols in the case of major bleeding, but it can also be found in several vegetables (e.g., tomatoes, spinach, cabbages, turnip greens), as well as in some dairy and animal products. Therefore, a reduction of the intake of these foods is strongly recommended to improve the time in therapeutic range (TTR).

The use of VKAs is limited by the narrow therapeutic interval, which needs frequent monitoring, dose adjustments and attention to drugs interaction (e.g., nonsteroidal anti-inflammatory drugs (NSAIDs) may lead to hemorrhage due to pharmacokinetic interactions and to their antiplatelet effect) [2].

VKAs efficacy and safety have been established over time and all over the world by several studies [17,18], and currently represent the first-choice treatment in AF patients with rheumatic mitral valve disease and/or a mechanical heart valve prosthesis [19]. Conversely, the use of NOACs in AF patients undergoing valves replacement and transcatheter aortic valve replacement (TAVR) is only supported by few and limited data [1,20].

In a meta-analysis, patients under VKAs therapy showed a relative risk reduction of ischemic stroke of 67%, with no significant difference between primary and secondary prevention, and 25% of all-cause mortality rate compared to controls (either aspirin or placebo). Also, the risk of intracranial hemorrhage was mild [21].

The fact that antiplatelet agents may play a preventive role during AF has been investigated by several studies. For example, Lip et al. [22], in a meta-analysis, demonstrated a 22% relative reduction in the risk of thromboembolism in AF with AP monotherapy compared to placebo. In addition, the

authors also showed a 36% risk reduction with warfarin compared to aspirin. Several studies have compared warfarin to AP monotherapy and dual AP therapy (aspirin + clopidogrel), with a lower effectiveness of AP therapy and either a similar or increased risk of bleeding [23–25].

Thus, the most recent ESC guidelines have discouraged a routine use of AP monotherapy for stroke prevention in AF patients [26].

The Garfield AF registry shows how the administration of AP monotherapy in newly diagnosed AF has slowed down over the years, though a consistent number of patients are still under treatment (about 20% of the 51,270 patients analyzed are under AP monotherapy with no indication) [27].

Furthermore, AF patients cannot be treated with indirect anticoagulants if they are pregnant or breastfeeding, if they have bleeding diathesis or in the case of invasive surgical procedures. In addition, in fragile and/or cardiac and/or hepatic insufficient patients, closer INR controls are required.

#### 4. Novel Oral Anticoagulants (NOACs): A Future Already Present

Until a few years ago, as shown in the previous sections, anticoagulant therapy with VKAs represented, along with the use of low molecular weight heparin (LMWH), the only therapeutic aid to reduce thromboembolic risk [28].

NOACs selectively inhibit only one factor of the coagulation cascade: thrombin, in the case of dabigatran, or activated factor X (Xa), in the case of rivaroxaban, apixaban and edoxaban.

Their pharmacodynamics are predictable, with little variability even at the individual level and there are no relevant interactions with both food and drugs. The half-life is well defined, but its increase with age and with the reduction of the renal filtrate should always be considered.

Their action is fast and their effect quickly ends after interruption and, in either case, can be predicted based on a few easily calculable variables (mainly the time from the last dose taken, type of molecule, age and the glomerular filtrate).

These characteristics make the monitoring of the coagulative structure superfluous (and confounding). In this way, the induction of the anticoagulant effect is eased without having to resort to the administration of heparin [28,29]. Moreover, both the safety and efficacy of NOACs have been positively tested in a randomized clinical trial [30] and confirmed by several clinical real-world casuistries [1,31–35].

For this reason, in recent years, NOACs have become a valid alternative to VKAs to prevent stroke in AF patients and have emerged as the first choice, especially in patients who are new to anticoagulants.

It is of fundamental importance to remember how some specific subpopulations of AF patients cannot be treated with NOACs. Among these are the wearers of cardiac mechanical prostheses, patients with severe mitral stenosis on a rheumatic basis and patients with aneurysms [22]. However, subjects with biological valve prostheses, subjected to mitral valvuloplasty three months after implantation, and those with hypertrophic cardiomyopathy have been granted by the 2018 EHRA PRACTICAL GUIDE update and 2016 ESC guidelines, the possibility of using NOACs [22,36].

Four large phase III trials assessed the non-inferiority of NOACs compared to VKAs. The overall assessment of the findings from the four trials allowed for establishing how NOACs are able to, with respect to conventional VKAs therapy, further reduce the combined risk of stroke and embolic events by 19% and the risk of all-cause mortality.

The prescription of the most appropriate NOAC must be based on the knowledge of the clinical characteristics of each patient and of the pharmacological characteristics of the different NOACs.

The recommended dosages for the treatment of AF patients are listed in Figure 1. To understand the profile of each NOAC, it is necessary to know the findings from the most important clinical trials which led to their registration.

|                      | 95 mL/min                | 60 mL/min          | 50 mL/min             | 40 mL/min | 30 mL/min  | 15 mL/min | Dialysis |
|----------------------|--------------------------|--------------------|-----------------------|-----------|------------|-----------|----------|
| Creatinine Clearance |                          |                    |                       |           |            |           |          |
| Dabigatran           | 2x150 mg                 |                    | 2x150mg or 2x110 mg * |           | Red        |           |          |
| Rivaroxaban          | 20 mg                    |                    | 15 mg                 |           | 15 mg      | Red       |          |
| Edoxaban             | 60 mg                    | 60 mg <sup>†</sup> |                       | 30 mg     | 30 mg      | Red       |          |
| Apixaban             | 2 x 5 mg or 2 x 2.5 mg * |                    |                       |           | 2 x 2.5 mg |           | Red      |

**Figure 1.** Use of non-vitamin K antagonists (VKAs) according to renal function. \* 2 × 110 mg in patients at high risk of bleeding (per SmPc). # Other dose reduction criteria may apply (weight ≤60 kg, concomitant potent P-Gp inhibitor therapy). <sup>§</sup> 2 × 2.5 mg only if at least two out of three fulfilled: age ≥80 years, body weight ≤60 kg, creatinine ≥1.5 mg/dL (133 mmol/L). Orange arrows indicate cautionary use (dabigatran in moderate renal insufficiency, FXa inhibitors in severe renal insufficiency, edoxaban in ‘supranormal’ renal function). [36].

The randomized open-label RE-LY clinical trial assessed the non-inferiority of dabigatran 150 mg bid (reduced to a 110 mg bid in elderly patients and in those with reduced renal function) compared to warfarin (INR 2 to 3) in AF patients. The study showed a statistically significant reduction in systemic stroke/embolism, hemorrhagic stroke and vascular mortality. The major bleeding rates were, instead, comparable. In addition, a significant reduction in the total number of bleedings, life-threatening bleeding for the patient and intracranial bleeding, as well as a statistically significant increase in gastrointestinal major bleeding with dabigatran 150 mg were observed [37].

In the ROCKET-AF double-blind randomized clinical trial, rivaroxaban was shown to be not inferior to Warfarin in the prevention of either stroke or systemic embolism, without significant difference between the two groups for overall mortality or differences between two drugs in the risk of major bleeding or major bleeding plus the clinically relevant ones. Even in the ROCKET-AF, however, a statistically significant increase in gastrointestinal major bleeding was observed [38].

Two trials, ARISTOTLE and AVERROES, instead assessed the efficacy and safety of apixaban 5 mg bid (reduced to 2.5 mg bid in elderly patients and in those with reduced renal function). Apixaban emerged statistically superior to Warfarin in the prevention of stroke and systemic embolisms, major bleeding, including intracranial ones, and no major clinically relevant ones, as well as in reducing all-cause mortality. Comparable outcomes emerged for major gastrointestinal bleeding [39,40].

Finally, edoxaban. The ENGAGE AF-TIMI 48 trial demonstrated the non-inferiority of edoxaban 60 mg vs. warfarin in preventing stroke or systemic embolic events, with a statistically significant reduction in hemorrhagic stroke, vascular mortality, major bleeding and the number of intracranial bleedings and a statistically significant increase in major gastrointestinal bleedings [41].

The meta-analysis of Dentali et al. states that all NOACs directly act on the final phase of the coagulation cascade, and therefore, differ from the VKAs mechanism of action [42].

In the prevention of stroke during AF, NOACs overall, compared to VKAs, significantly reduce (1) stroke and systemic embolism, (2) major bleeding, (3) intracranial bleeding, (4) cardiovascular and (5) global mortality.

Despite the several advantages of NOACs with respect to VKAs therapy, a careful decision-making process is required in each case to ensure the safety of the choice of one option over another.

As more findings emerge from clinical studies and real-world evidence, the use of NOACs is becoming increasingly varied, replacing VKAs therapy in many contexts as a safe, reliable and effective therapeutic approach [9,12,16–18,21,43]. However, VKAs still play an important role in countless contexts, including situations where NOACs are contraindicated [36].

At present, the difference between each NOAC depends on the preferences of the physician (evaluating the risk profile of each patient compared to that present in the groups treated in each study), the pros and cons of each molecule, and the costs. An indirect comparison between the four drugs can lead to the suggestion of which one would be preferred for each individual patient. A recent

meta-analysis, including all of the four major clinical trials, showed that NOACs reduce ischemic events compared to warfarin in patients with AF, but at the cost of increased gastrointestinal bleeding [44]. The comprehensive results from all of these studies show a significant reduction in cases of stroke and systemic embolism (relative risk, RR, 0.81), mainly due to a reduction in hemorrhagic strokes (RR 0.49). There was also a small number of all-cause deaths, compared to warfarin, during follow-up (RR 0.90), though this did not affect myocardial infarction. Intracranial hemorrhages were less frequent with NOACs (RR 0.48), while gastrointestinal ones had a higher incidence (RR 1.25) [43].

In AF patients at high ischemic risk, who have undergone percutaneous coronary intervention (PCI) with stenting for acute coronary syndrome (ACS), dabigatran etexilate 110 mg twice daily versus VKAs, in association with DAPT (aspirin plus clopidogrel) showed a safer profile and a lower cumulative incidence of major bleeding, as well as a lower hospitalization rate for cardiovascular events in real-world settings [45,46].

## 5. Bridging Therapy

Perioperative management of AF patients receiving NOACs is an extremely sensitive issue. The strategy not to initiate the so-called “bridge therapy” is comparable to “bridge therapy” in terms of prevention of thromboembolic events, though it translates into a greater reduction in the risk of major bleeding. This requires a more in-depth consideration of the advantages of both pharmacokinetic and pharmacodynamic aspects of the different anticoagulation regimens in each individual patient [36].

Therefore, the management of patients who need to interrupt oral anticoagulant therapy (OAT) to undergo either surgery or invasive procedures is particularly complex and requires collaboration among the different medical figures. The American College of Cardiology Anticoagulation Work Group, in order to assess the current clinical practice, devised a specific survey. Several professionals, including cardiologists (in different sub-specialties), internists, gastroenterologists and orthopedists, were asked how to manage patients taking oral anticoagulant therapy (OAT), candidates for invasive procedures and surgical procedures [47].

With the advent of NOACs in most recent years, the decision-making process has become even more complicated, since guidelines on this issue only provide general recommendations. The BRIDGE study, published in the New England Journal of Medicine, attempted to address this issue. The study found that the no bridging strategy was inferior to the low molecular weight heparin bridging therapy for the prevention of thromboembolic events, while at the same time, it determined a reduction in the risk of major bleedings [48].

In particular, the BRIDGE study assessed how the different professional figures managed, in the common clinical practice, patients taking OAT as candidates for invasive procedures. From the findings of the study, the most frequently involved professional class was that of cardiologists. The study also showed that among the most commonly used parameters to identify patients with an increased risk of thromboembolic events during OAT interruption is the presence of a mechanical heart valve, a history of previous stroke or transient ischemic attack (TIA) and an elevated CHA<sub>2</sub>DS<sub>2</sub>-VASc score. With regard to this latter finding, it was emphasized that, frequently, this score is used in clinical practice to refer patients to the use of bridge therapy, though this approach has never been validated in this field. Despite many patients at low risk of thromboembolic events, that are referred to invasive procedures, being considered as low risk for bleeding without OAT interruption, the study showed that several doctors still prefer bridge therapy, exposing patients to a high risk of bleeding. Moreover, the variability in the choice of both dose and duration of parenteral anticoagulant therapy was also confirmed.

The study also underlined the problem of the management of patients on anticoagulant therapy with NOACs. A similar use of bridging therapy was observed for patients who were candidates for either surgical interventions or invasive procedures, treated with VKAs and with NOACs despite the extremely different pharmacokinetic characteristics of the drugs. In patients taking NOACs, however, in the case of an intermediate risk of thromboembolic events and in procedures with a low risk of bleeding, bridging therapy was used infrequently. Conversely, the use of parenteral anticoagulant

therapy in high-risk patients treated with NOACs subjected to procedures with a higher risk of bleeding, requiring the interruption of anticoagulant therapy for a long period, has remained uncertain [49].

One of the drugs usable in the case of urgent procedures in subjects treated with dabigatran, who either had severe bleeding or required an urgent procedure, is the idarucizumab monoclonal antibody, studied in a trial of 503 patients, in the RE-VERSE AD study. Idarucizumab has received full FDA approval [50]. In addition, Andexanet alfa, a genetically modified and recombinant protein designed to serve as an antidote against direct factor Xa inhibitors, has also been reported to reverse the effects of rivaroxaban and apixaban and was approved according to the FDA's accelerated approval process, based on the effects in healthy volunteers [51].

Furthermore, in a special subpopulation of patients undergoing coronary angiography with or without PCI, a meta-analysis by Kowalewski et al. showed a comparable safety of uninterrupted (UAC) and interrupted OAT (IAC). This safety also appeared higher in the case of IAC with bridging [52].

## 6. Anticoagulant Therapy: An Upcoming Challenge

AF is commonly diagnosed in the setting of active malignancy [53]. Cancer is associated with the hypercoagulable state, with an increased risk of thromboembolism, regardless of the CHA<sub>2</sub>DS<sub>2</sub>-VASc score [54]. Moreover, these patients, in particular the ones affected by either primary or metastatic intracranial tumors or hematological malignancies, also present an increased risk of bleeding. Other important issues should also be taken into account, such as drug–drug interaction with cancer treatment, changes in renal and hepatic function, dietary and nutritional status, chemotherapeutic toxicity and disease state. All these conditions may determine a fluctuation of INR values.

Up until now, VKAs have represented the gold standard in long term treatment. However, this class of drugs is burdened by the need to maintain the INR at target. In the last few years, with the advent of NOACs, several studies have assessed the safety and efficacy in this specific population [32,55–58]. Nevertheless, the limited sample size and the wide spectrum of malignancies render it necessary to conduct further in-depth studies.

Thus, anticoagulation with both NOACs and VKAs for AF related thromboembolism in patients affected by malignancies is challenging.

## 7. Conclusions

In conclusion, given the extreme complexity of this scenario, which involves multiple professional figures, it would be worthwhile establishing standardized protocols and research models oriented towards the development of clinical pathways. In this way we could improve the management of patients under OAT, candidates for interventions surgical and invasive procedures, especially in light of the new commercial oral anticoagulants.

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Review

# Management of Direct Oral Anticoagulants in Patients with Atrial Fibrillation Undergoing Cardioversion

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**Abstract:** Atrial fibrillation the most common cardiac arrhythmia. Its incidence rises steadily with each decade, becoming a real “epidemic phenomenon”. Cardioversion is defined as a rhythm control strategy which, if successful, restores normal sinus rhythm. This, whether obtained with synchronized shock or with drugs, involves a periprocedural risk of stroke and systemic embolism which is reduced by adequate anticoagulant therapy in the weeks before or by the exclusion of left atrial thrombi. Direct oral anticoagulants are safe, manageable, and provide rapid onset of oral anticoagulation; they are an important alternative to heparin/warfarin from all points of view, with a considerable reduction in bleedings and increase in the safety and quality of life of patients.

**Keywords:** direct oral anticoagulants (DOACs); atrial fibrillation (AF); electrical cardioversion (EC)

## 1. Introduction

Atrial fibrillation (AF) is the most common cardiac arrhythmia worldwide. It is nowadays a real “epidemic phenomenon” considering an incidence of approximately 25% in patients aged >40 years with high prevalence in elderly patients [1–6]. The worldwide prevalence of atrial fibrillation in the near future will necessitate mandatory, safe, and effective management [5,6].

Cardioversion is defined as a rhythm-control strategy that, if successful, restores normal sinus rhythm. There are two types of cardioversion: pharmacological (the preferred strategy in patients presenting with recent-onset AF; within 48 h) and electrical (the preferred strategy when AF is prolonged). Cardioversion is very important in the management of AF [7,8]; indeed, delays in cardioversion promote atrial remodeling and difficult sinus rhythm restoration, increasing the likelihood of postcardioversion AF recurrence and adding further thromboembolic risk [8–10]. In fact, sinus rhythm restoration, either obtained with electrical cardioversion or with drugs, carries a periprocedural risk of stroke and systemic embolism which is decreased by adequate anticoagulation in the weeks before cardioversion or excluding left atrial thrombi before the procedure [1,9–14] (see Figure 1). For these reasons, prophylactic anticoagulation represents a cornerstone of peri-cardioversion management in patients with AF [1–12], even if, in patients with datable AF (less than 48 h), it is usual to perform cardioversion without transesophageal echocardiogram (TEE) or antecedent oral anticoagulant therapy (OAT) [12–14]. Randomized controlled trials (RCTs) comparing direct oral anticoagulant (DOAC) therapies in patients with AF duration of <48 h are not available. The same applies to patients with hemodynamic instability and AF that can undergo cardioversion immediately [12]. Long-term OAT after cardioversion should be based on the long-term risk of stroke using the CHA2DS2-VASc

(Congestive Heart failure, hypertension, Age  $\geq 75$  – doubled-, Diabetes, Stroke –doubled-, Vascular disease, Age 65–74, and Sex female) risk score. If the duration of AF lasted more than 48 h, or its onset is not evaluable, the periprocedural risk of thromboembolism can be as high as 5–7% without anticoagulant therapy [12,14]. In this clinical situation, current guidelines recommend therapeutic anticoagulation for at least 3 weeks before and at least 4 weeks after cardioversion [12–14] (see Figure 1). It is important to underline that the highest risk of thromboembolism is within the first 7 days after cardioversion (>80% of events) with the greatest risk within the first 72 h [15]. An embolic event after cardioversion can be due both to the fact of left atrial thrombi migration or to the subsequent formation and migration of de novo thrombi caused by postcardioversion atrial stunning [8]. The single biggest risk factor for thrombus formation is inadequate anticoagulation [1,12–16]. In the current European Society of Cardiology (ESC) Guidelines for the management of AF [12], the recommendation for anticoagulation with warfarin before cardioversion is in first class for a time  $\geq 3$  weeks and must be continued for  $\geq 4$  weeks after the procedure, based on pathophysiological and observational data [12]. Compared to vitamin K antagonist (VKA) therapy, the use of DOACs offers potential advantages in the setting of cardioversion, although their use is recommended in Class IIa in the last ESC Guidelines [12]. These advantages include a faster onset of therapeutic anticoagulant effects, avoidance of heparin bridging, and improved quality of life avoiding the mandatory blood sample to control international normalized ratio (INR) range when vitamin K antagonist are used [14].

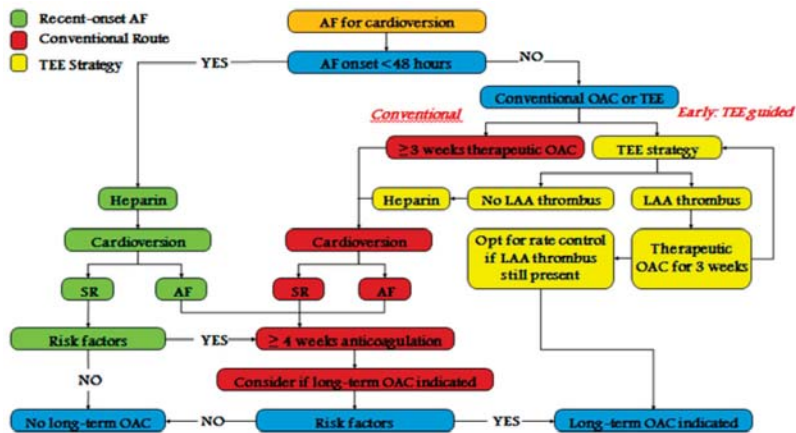


Figure 1. Suggested flow chart for atrial fibrillation (AF) cardioversion on the basis of the current European Society of Cardiology (ESC) Guidelines. Transesophageal echocardiogram (TEE), anticoagulant therapy (OAT), left atrial appendage (LAA), sinus rhythm (SR).

The use of DOACs in this setting of patients is based on subgroup analyses of Randomized Evaluation of Long-Term Anticoagulation Therapy trial (RE-LY) for dabigatran [16], from Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation trial (ROCKET AF) for rivaroxaban [17], and from Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial (ARISTOTLE) for apixaban [18]. Moreover, recent important studies on DOACs suggest new possibilities in cardioversion and deserve to be examined [13,14,19]. These important pieces of evidence have been considered by the American Heart Association (AHA), American College of Cardiology (ACC), and the Heart Rhythm Society (HRS) in the recent 2019 Focused Update of the 2014 AF Guideline [13]. Thus, the aim of this review was to summarize the state-of-the-art methods regarding the use of DOACs in relation to cardioversion.

## 2. DOACs for Cardioversion in Atrial Fibrillation

From a purely academic and explanatory point of view, we consider four different scenarios regarding cardioversion, which we examine point by point:

- Cardioversion of AF patient treated for >3 weeks with DOACs: we consider the subgroup analyses from RE-LY (dabigatran), ROCKET-AF (rivaroxaban), and ARISTOTLE (apixaban), including important news from the “eXplore the efficacy and safety of once-daily oral riVaroxaban for the prevention of caRdiovascular events in patients with nonvalvular aTtrial fibrillation scheduled for cardioversion trial” (X-VeRT study) [20].
- Cardioversion of AF of >48 h in a patient not on DOACs: we consider the X-VeRT study [20] and “Edoxaban versus enoxaparin–warfarin in patients undergoing cardioversion of atrial fi brillation trial” (ENSURE AF) [21].
- Cardioversion of recent onset AF in an anticoagulation-naive patient: in this scenario, the results of the “Eliquis evaluated in acute cardioversion coMpared to usuAl treatmeNts for AnticoagulaTion in subjects with atrial fibrillation trial” (EMANATE trial) are very important [22].
- Patients with evidence of left atrial appendage (LAA) thrombus: we consider the few studies available in the literature on this scenario.

### 2.1. Cardioversion of AF Patient Treated for >3 Weeks with DOACs

The initial data on the use of DOACs in a clinical setting for cardioversion came from the post-hoc subgroup analysis of randomized control trials (RCTs) RE-LY [16], ROCKET AF [17], and ARISTOTLE [18].

In the RE-LY trial [16,23,24], from a total of 1983 cardioversions, patients received dabigatran 110 mg BID, dabigatran 150 mg BID, and warfarin. It was recommended that patients assigned to dabigatran receive at least 3 weeks of therapy before cardioversion. Stroke and systemic embolism rates at 30 days were 0.77 for dabigatran 110 mg BID, 0.60 for warfarin, 0.30 for dabigatran 150 mg BID, without significant differences among the treatment groups (dabigatran 110 mg versus warfarin,  $p = 0.71$ ; dabigatran 150 mg versus warfarin,  $p = 0.40$ ). Stroke and systemic embolism rates were similar in patients undergoing TEE before cardioversion (25% of patients assigned to dabigatran and 13% of patients assigned to warfarin) and in patients not performing TEE. Major bleeding rates were 1.7% for dabigatran 110 mg group, 0.6% for dabigatran 150 mg, and 0.6% for warfarin (dabigatran 110 mg versus warfarin,  $p = 0.06$ ; dabigatran 150 mg versus warfarin,  $p = 0.99$ ).

The ROCKET AF post-hoc analysis [25] investigated patient outcomes with both cardioversion and catheter ablation procedures; 143 patients underwent electrical cardioversion, 142 underwent pharmacological cardioversion, and 79 underwent catheter ablation. The incidence of stroke or systemic embolism (1.88% versus 1.86%) and death (1.88% versus 3.73%) were similar in the rivaroxaban-treated and warfarin-treated groups. No data were available regarding the use of TEE pre-cardioversion. Major bleeding rates were 18.75% in the rivaroxaban group and 13.04% in the warfarin group. It is important to consider and remember that elective cardioversions were excluded by the enrolling protocol in ROCKET AF, i.e., patients who underwent cardioversion or ablation due to the fact of hemodynamic instability, progressive heart failure, or refractory symptoms despite optimal medical therapy [25].

In the ARISTOTLE trial [18,26], we found 540 cardioversions, and 265 patients received apixaban and 275 received warfarin. A TEE pre-procedural was performed in about 27% of cases. In the first 30 days after cardioversion, no patients experienced a thromboembolic event; one myocardial infarction (MI) and one major bleeding (MB) event occurred in each group, with two deaths in each group. In most cases, cardioversion occurred after months of treatment, with a mean time from enrolment to cardioversion of  $243 \pm 231$  days for patients assigned to warfarin and of  $251 \pm 248$  days for patients assigned to apixaban, far longer than the 3 weeks recommended by international guidelines [27].



Subgroup analyses from RE-LY, ROCKET-AF, and ARISTOTLE underline that electric cardioversion in patients treated with DOACs had a low and similar thromboembolic risk than patients treated with warfarin. According to these data, cardioversion without TEE seems reasonably safe under regular and continued DOAC intake.

2.2. Cardioversion of AF of >48 h in a Patient Not on DOACs Therapy

The X-VerT, ENSURE-AF, and EMANATE studies [20–22] were evaluated in the context of DOAC-naïve patients, respectively, with rivaroxaban (57% of patients), edoxaban (47%), and apixaban (61%) (see Figure 2).

|               | ENSURE-AF | X-VerT | EMANATE | Tot |      |
|---------------|-----------|--------|---------|-----|------|
| # of patients | DOAC      | 1095   | 978     | 753 | 2826 |
|               | VKA       | 1104   | 492     | 747 | 2343 |
| All Strokes   | DOAC      | 2      | 2       | 0   | 4    |
|               | VKA       | 3      | 2       | 6   | 11   |
| Major Bleed   | DOAC      | 3      | 6       | 3   | 12   |
|               | VKA       | 5      | 4       | 6   | 15   |

Figure 2. Summary of X-VerT, ENSURE-AF, and EMANATE trials results.

The X-VerT study [20] is the first prospective randomized trial of DOACs in patients with atrial fibrillation undergoing elective cardioversion. Rivaroxaban was compared with dose adjusted VKA in the prevention of cardiovascular events in 1504 patients with non valvular atrial fibrillation (NVAf) scheduled for early or delayed cardioversion at the discretion of the local cardiologist investigator. In the early approach, oral anticoagulant therapy was given 1–5 days before cardioversion and, in the rivaroxaban arm, a cardioversion was performed at least 4 h after the first dose. In the delayed cardioversion approach, patients were anticoagulated for a range of 3–8 weeks before the procedure. Prophylaxis with rivaroxaban was considered adequate if the pill count was ≥80% in the three weeks preceding the cardioversion. The procedure was TEE guided in 65% of patients treated with an early strategy, whereas a TEE-guided cardioversion was performed in 10% of patients using a delayed strategy, with no significant difference in the rate of TEE employment among the two treatment groups. Primary efficacy endpoints were a composite of stroke and transient ischemic attack (TIA), non-systemic embolism, MI, CV death, while primary safety endpoints were MB. The primary efficacy endpoint occurred in 0.51% of patients in the rivaroxaban arm and 1.02% of patients in the VKAs arm (risk ratio 0.50; 95% CI 0.15–1.73). Major bleeding (MB) occurred in 0.6% of patients in the rivaroxaban group and in 0.8% of patients in the VKAs group (risk ratio 0.76; 95% CI 0.21–2.67). Rivaroxaban was associated with low rates of adverse outcomes similar to those of VKAs even when data from the early and delayed strategies were analyzed separately. An important difference was found among the two strategies in terms of median time to cardioversion. This data were similar in the early strategy but significantly shorter in the delayed strategy using rivaroxaban versus warfarin (22 days rivaroxaban arm versus 30 days in VKA arm). Only 36% of patients anticoagulated with VKA were cardioverted as scheduled as the INR was not in range, in comparison with 77% in the rivaroxaban arm. According to data from X-VerT, rivaroxaban can be considered as an effective and safe alternative to VKAs in patients with AF addressed to cardioversion, irrespective of the timing of the procedure. Moreover, X-VerT showed that rivaroxaban may overcome critical limitations of VKA treatment in the setting of cardioversion, including a significant reduction in time to cardioversion and a considerable reduction of economic expenditure.

In the ENGAGE AF-TIMI 48 trial [28] few patients underwent electrical cardioversion and, therefore, we have limited data about edoxaban in the setting of procedures. Further data about anticoagulation with edoxaban in patients undergoing cardioversion are provided by the ENSURE-AF [21] which is the largest prospective randomized clinical trial of anticoagulation for cardioversion of patients with non-valvular atrial fibrillation. In this trial, 2199 patients scheduled for cardioversion were randomized (1:1) to edoxaban or enoxaparin/warfarin. As in the X-VeRT trial, patients were stratified in two different approaches. In the TEE-guided group, the TEE and cardioversion had to be executed within 3 days of randomization and patients randomly addressed to the edoxaban group had to begin treatment at least 2 h before electrical cardioversion. In the non-TEE-guided group, electrical cardioversion was executed at a minimum of 21 days following the start of anticoagulation. The primary endpoint (PE) was a composite of stroke, systemic embolic event (SEE), MI, and cardiovascular (CV) mortality, while the primary safety endpoint was a composite of major and non-major but clinically relevant bleeding (CRNM). The primary endpoint was similar with edoxaban compared to enoxaparin/warfarin in patients undergoing electrical cardioversion of NVAf (<1% edoxaban arm versus 1% enoxaparin/warfarin, odds ratio (OR) 0.46, 95% CI 0.12–1.43) and was independent of TE or previous anticoagulant therapy. The composite of the PE was numerically lower for edoxaban versus enoxaparin/warfarin and the main difference was due to the cardiovascular mortality, (0.1% in the edoxaban group versus 0.5% in the enoxaparin–warfarin). The primary safety endpoint occurred in 1.5% and 1.0% of patients in the edoxaban versus the enoxaparin/warfarin arm, respectively, and the results were statistically non-significant. There were numerically more major bleedings in the enoxaparin/warfarin arm, while more CRNM bleedings were found in the edoxaban arm. The net clinical outcome (composite of stroke/systemic embolism/myocardial infarction/cardiovascular death/major bleeding) was numerically lower in the edoxaban arm versus the enoxaparin/warfarin arm, but the result was statistically non-significant. In contrast with the X-VeRT study, there was no difference in time to delayed cardioversion among the two treatment groups. This probably means that the ENSURE-AF trial compared edoxaban with the optimized standard care of enoxaparin, bridging the pending therapeutic warfarin. The results suggest that edoxaban may be an effective and safe alternative to enoxaparin/VKA strategy and may allow prompt cardioversion to be performed when following a TEE-guided approach (edoxaban almost 2 h before ECV).

### 2.3. Cardioversion of Recent Onset AF, in an Anticoagulation-Naive Patient

In this very important scenario, a key role is represented by EMANATE study [22]; this was the first study in anticoagulation-naive patients scheduled for cardioversion. All patients received <48 h anticoagulation and 61% were not anticoagulated prior to randomization. One thousand and thirty-eight patients underwent cardioversion, whereas 300 spontaneously restored sinus rhythm; 162 patients were not cardioverted; and in only 855 patients was imaging test (TEE or CT) performed. In some patients randomized to apixaban, according to the investigator, before the cardioversion, a single 10 mg loading dose of apixaban could be administered to achieve exposure at 2 h similar to steady state. Instead the maintenance dose was down titrated to 5 mg. Cardioversion could be performed 2 h after administration of the loading dose; 342 of patients received a loading dose of apixaban. The result of apixaban versus heparin/VKA group showed in EMANATE trial was: 0 versus 6 strokes ( $p = 0.0164$ ), 3 versus 6 major bleeds, 2 versus 1 deaths, and no systemic embolic events in both groups. Among 342 patients receiving the loading dose of apixaban, there were 0 strokes, 1 major bleed, and 1 death. Finally, imaging identified left atrial appendage thrombi in 61 patients; all continued anticoagulation. Among those who underwent second imaging examination ( $37 \pm 11$  days after the initial imaging) thrombi resolved in 52% versus 56% in the apixaban and heparin/VKA groups. The EMANATE study supports the use of apixaban in patients with AF undergoing cardioversion. The novelty of this trial was the exclusive enrolment of anticoagulant-naïve patients (62% not receiving, 38% < 48 h) with recently detected AF (new onset or first diagnosed) with a focus on enrolling those amenable to early cardioversion. Also unique to the study, if an immediate cardioversion was planned, there was

administration of a loading dose (10 mg) of apixaban at least 2 h before cardioversion. For this reason, potential participants were actively identified in hospital emergency departments which encouraged but did not mandate imaging (TEE or CT).

#### 2.4. Management of a Patient with Documented Left Atrial Appendage Thrombus

The left atrial appendage is the site with the highest blood stasis which causes thrombus formation during atrial fibrillation [29]. In fact, about 90% of intracardiac thrombi in patients with cardioembolic events originally develop in the LAA. In patients with evidence of LAA thrombus cardioversion should not be performed. In patients with AF VKA, current guidelines recommend therapy for 3 weeks after diagnosis of an LA/LAA thrombus and long-term therapy for those with a documented residual thrombus [12,30]. Although relevant studies showing differences between DOAC and VKA (small data, although very interesting and encouraging, can be derived from the EMANATE study) do not yet exist, in the past few years, there some evidence has emerged supporting the use of DOACs for LA/LAA thrombus resolution, even if the data are limited to case studies or small case series [31]. The X-TRA study was the first prospective, multicenter study examining thrombus resolution with rivaroxaban in VKA-naïve patients or patients receiving suboptimal or ineffective VKA therapy [31]. This study showed that resolution or reduction of thrombus after rivaroxaban treatment was comparable to the results obtained with VKA therapy according to prior retrospective observational case series and the retrospective CLOT-AF registry [31]. The results suggest that rivaroxaban seems to be a potential option for the treatment of TEE-detected LA/LAA thrombi in patients with AF [31]. Even dabigatran has generated encouraging data regarding its use for LA/LAA thrombus resolution [32]. In a small study with a total of 58 AF patients with LAA thrombus, Xiao et al. [32] demonstrated that dabigatran was effective in the dissolution of LAA thrombus in patients with AF. Ongoing trial RE-LATED-AF will make further clarifications about the use of DOACs in this complex and poorly studied scenario [33].

### 3. Conclusions

For several years, warfarin has been the primary oral anticoagulant used for patients with AF [34], affirming its superiority over acetylsalicylic acid in reducing thromboembolic risk [1,11–13]. Since 2009 until 2013, the four DOAC registered RCTs have paved the way for a more optimal prevention of thromboembolic risk in patient with AF, reducing hemorrhagic risk; in particular, all DOACs significantly reduced the risk of intracranial hemorrhage (ICH), principally in more complex categories of patients such as in the elderly, frail, and patients with comorbidities (Figure 2) [5,6,35].

Direct oral anticoagulants (DOACs) offer several potential advantages over warfarin therapy in the setting of cardioversion, including removing the need for routine laboratory monitoring and heparin bridging therapy (the latter of which is very important, especially in the case of surgical interventions), as well as having predictable pharmacokinetic and security pharmacodynamic profiles.

Finally, DOACs demonstrated good predictable onset of anticoagulation (since 1 to maximum 4 h) compared with 48 to 72 h for warfarin and up to 5 to 7 days to reach steady state [36,37]. In a very interesting random-effects meta-analysis performed by Brunetti et al. [38], a total of 8564 patients undergoing both electrical and pharmacologic cardioversions for NVAF were included observing, one more time, the effectiveness and safety of DOACs in patients undergoing NVAF.

Unfortunately, today, head-to-head studies do not exist and direct comparisons between DOACs are not possible. Even though other studies concerning DOACs in the context of AF are ongoing (for example, the RE-LATED AF-AFNET 7 trial [33]) and further real-life data are needed, DOACs therapy is an effective and safe strategy in the context of atrial fibrillation patients scheduled for cardioversion.

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Review

# Diagnosis and Management of Left Atrium Appendage Thrombosis in Atrial Fibrillation Patients Undergoing Cardioversion

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**Abstract:** Atrial fibrillation is the most common cardiac arrhythmia and is associated with an increased risk of stroke and thromboembolic complications. A rhythm control strategy with both electrical and pharmacological cardioversion is recommended for patients with symptomatic atrial fibrillation. Anticoagulant therapy for 3–4 weeks prior to cardioversion is recommended in order to avoid thromboembolic events deriving from restoring sinus rhythm. Transesophageal echocardiography has a pivotal role in this setting, excluding the presence of left atrial appendage thrombus before cardioversion. The aim of this review is to discuss the epidemiology and risk factors for left atrial appendage thrombosis, the role of echocardiography in the decision making before cardioversion, and the efficacy of different anticoagulant regimens on the detection and treatment of left atrial appendage thrombosis.

**Keywords:** atrial fibrillation; cardioversion; oral anticoagulation therapy; left atrial appendage thrombosis; transesophageal echocardiography

## 1. Introduction

Atrial fibrillation (AF) is the most common sustained arrhythmia, with a prevalence of 0.4% in the general population and 9% in octogenarian patients [1]. Patients with AF have a higher risk of cardiovascular complications, including a 3–5-fold increase of stroke [2]. A 4–5 fold risk of systemic embolism (SE) [3] and a higher risk of heart failure (HF) development [4]. Without prior adequate anticoagulation, cardioversion (CV) (both electric and pharmacological) in patients with AF is associated with a non-negligible risk of thromboembolic events [5]. Consequently, for patients with AF >48 h onset, the current guidelines recommend anticoagulant therapy for at least three weeks before and four weeks after CV [6]. The transesophageal echocardiogram (TOE) is a diagnostic method that allows a detailed evaluation of the anatomy and function of the left atrial appendage (LAA), and is considered the gold standard for identifying or excluding left atrium (LA) and LAA thrombosis [6]. Vitamin K antagonists (VKAs) have traditionally been considered the gold standard for thromboembolic prophylaxis before CV; however, novel oral anticoagulants (NOACs) have also been studied, and are increasingly employed in this setting [7–9]. The aim of this review is to discuss the risk factors and diagnostic modalities of LAA thrombosis in AF patients undergoing CV, and to provide a summary and update of the therapeutic strategies to prevent and resolve LAA thrombosis.



## 2. Risk Factors of Left Atrial Appendage Thrombosis

LAA is the most prominent site of LA thrombus formation, with more than 90% of thrombi generating within this anatomical structure [10]. Extra-appendage thrombosis is a very rare finding in non-valvular AF and, when present, an LAA thrombus is usually concomitant [11]. The CHA<sub>2</sub>DS<sub>2</sub>-VASc score incorporates the more common stroke risk factors seen in everyday clinical practice, and is recommended to guide anticoagulant therapy in AF patients. CHA<sub>2</sub>DS<sub>2</sub>-VASc and older CHADS<sub>2</sub> scoring systems are also good predictors of LAA thrombosis. CHA<sub>2</sub>DS<sub>2</sub>-VASc showed a higher sensibility and specificity for LAA thrombus detection, and severe impairment of left ventricle systolic function is a powerful predictor of LAA thrombosis [12–14]. Moreover, the addition of the AF type (persistent AF) and renal function to the CHA<sub>2</sub>DS<sub>2</sub>-VASc score may better stratify thromboembolic risk and could identify patients who do not need preprocedural TOE [15]. In AF patients with low thromboembolic risk, the CHA<sub>2</sub>DS<sub>2</sub>-VASc score seems more able to identify low-risk individuals with a low probability of LAA thrombus, as seen in two retrospective studies totaling 1100 AF patients where no LAA thrombi were identified in individuals with a CHA<sub>2</sub>DS<sub>2</sub>-VASc score <2 [16,17]. Conversely, a low CHADS<sub>2</sub> score is less reliable in predicting the risk of LAA thrombus formation [18].

Moreover, the addition of biomarkers such as brain natriuretic peptide can improve the risk stratification of CHADS<sub>2</sub> and CHA<sub>2</sub>DS<sub>2</sub>-VASc scores for LAA thrombus [19,20].

## 3. The Role of Echocardiography before Cardioversion

### 3.1. Transthoracic Echocardiography

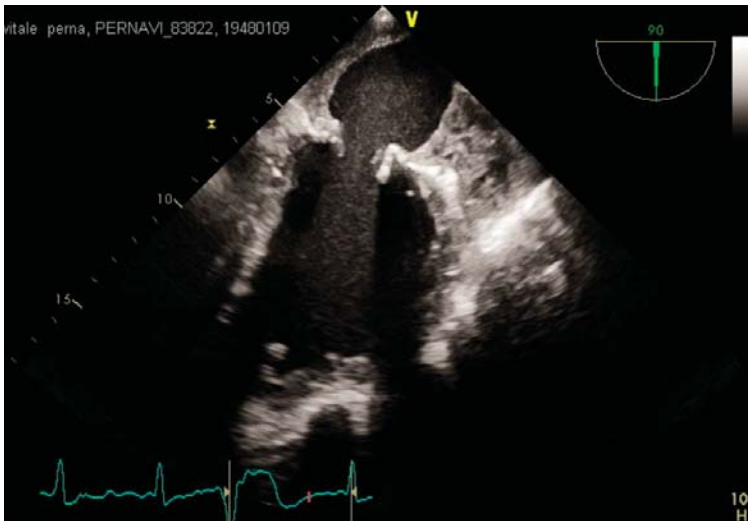
Transthoracic echocardiography (TTE) should be performed for the clinical evaluation of every AF patient. TTE provides a comprehensive evaluation of cardiac anatomy and function that can help to define the type of AF and to identify patients with high risk of LAA thrombosis. Firstly, echocardiographic assessment is necessary to diagnose valvular AF, defined by the presence of moderate–severe mitral stenosis or a prosthetic valve, which is necessarily treated with VKAs anticoagulant therapy [6]. TTE provides an overall assessment of left ventricle ejection fraction (LVEF), a risk marker of both stroke and LAA thrombus presence before CV [21]. An LVEF < 40% is considered an equivalent of the congestive HF criterion in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score, while a normal LVEF has been associated with a low prevalence of LAA thrombosis in AF patients undergoing TOE [22]. Evaluation of LA dimension is fundamental in assessing risk of LAA thrombosis and the probability of successful rhythm control [23]. The measurement of antero-posterior LA diameter has been traditionally considered the gold standard for LA dimension assessment. However, growing evidence suggests that the LA volume index (LAVI) is a more powerful predictor of LAA thrombus. [22]. Furthermore, a combination of LVEF-to-LAVI ratio <1.5 showed a 100% sensitivity in predicting the presence of LAA thrombus, therefore identifying a low-risk population before CV [24].

TTE provides markers to predict the probability of successful rhythm control before CV. LAVI, LVEF, diastolic function, E/e' wave ratio, and LV hypertrophy can influence the outcome of rhythm control strategy [25,26]. The HATCH score (which stands for hypertension, age 75 years, thromboembolic event, pulmonary disease, and HF) summarizes the main markers affecting the likelihood of a successful CV [27].

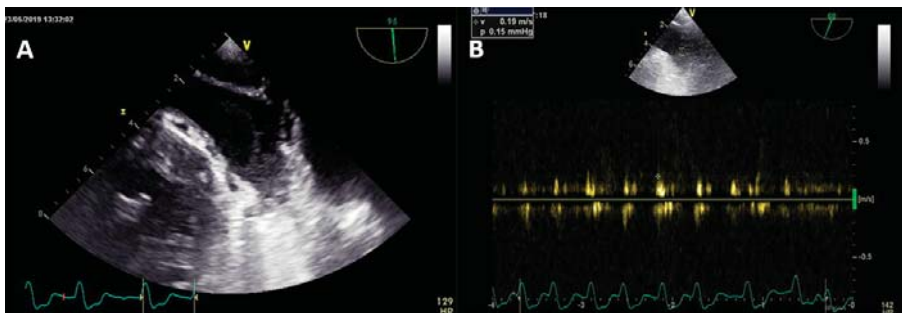
The assessment of LA function with 2D speckle tracking echocardiography (STE) is a promising tool in the clinical evaluation of AF patients. Normal LA strain analysis with STE has three phases: active filling phase (reservoir), passive emptying phase (conduit), and booster pump phase (pump), which corresponds to LA contraction at the end of the ventricular diastole. In AF patients, the booster pump phase is missing, and the most reliable parameter is the peak systolic reservoir strain. STE deformation analysis is highly correlated with the amount of LA interstitial fibrosis and remodeling process occurring in AF patients [28]. A reduced peak positive strain has been associated with lower LAA emptying velocities, with an LA prothrombotic state, and with higher incidence of LAA thrombosis [29,30].

### 3.2. Transesophageal Echocardiography and Intracardiac Echocardiography

TOE is considered the gold standard modality for diagnosis of LAA thrombi with a sensitivity and specificity of 95%–100% [31]. Current guidelines recommend TOE as an alternative to periprocedural anticoagulation in patients with >48 h AF duration or when the exact duration and onset of AF cannot be determined [6]. Moreover, in patients where thrombosis is identified, a repeat TOE after 3–4 weeks of anticoagulation should be considered before CV [6]. Modern multiplane TOE enables a visual assessment of LAA thrombi (Figure 1) or other potential intracardiac sources of embolism. TOE allows visual diagnosis of spontaneous echo contrast (SEC), also called “smoke” (Figure 2B), and “sludge” (Figure 2A), a dense and marked SEC, which is a precursor of thrombus formation and has a greater prognostic significance than smoke alone [32]. LAA mechanical function can be assessed from TOE with pulsed wave Doppler sample volume placed 1 cm below LAA ostium. LAA emptying velocities <20 cm/s are associated with a higher prevalence of SEC and LAA thrombosis [33] (Figure 2B). A combined use of color and pulsed-wave Doppler with contrast echocardiography can provide incremental information in aiding the diagnosis of LAA thrombosis in patients with doubtful diagnosis [34].



**Figure 1.** Transesophageal echocardiogram (TOE) intercommissural view showing massive left atrium (LA) and left atrial appendage (LAA) thrombosis.



**Figure 2.** Detection of sludge in LAA with swirling effect (A) and associated low LAA emptying velocities (B).

However, despite the high sensitivity for thrombus detection, there are some potential limitations of the traditional bidimensional TOE. TOE may misdiagnose thrombi <2 mm, which have high embolic potential, especially in the setting of complex multilobed LAA anatomy [35]. Moreover, the LAA has a complex and highly variable three-dimensional morphology, which can render its assessment difficult using 2D TOE alone. In particular, the presence of pectinate muscles, multilobed appendage morphology, SEC, or acoustic shadowing from the Coumadin ridge might be misinterpreted as thrombi, and could prevent the accurate evaluation of the LAA with traditional 2D imaging [36]. 3D TOE improves the evaluation of LAA anatomy, overcoming some limitations associated with 2D imaging. 3D TOE enables a multiplanar reconstruction that provides a more extensive evaluation of the LAA (especially of complex multilobe morphologies), and a better depiction of the surrounding anatomical landmarks [37] (Figure 3). There is a lack of evidence regarding the sensitivity and specificity of 3D TOE for detecting LAA thrombosis. However, a recent report suggests that 3D TOE should be suggested when the diagnosis of LAA thrombosis remains equivocal after a detailed 2D analysis [36]. Moreover, with the widespread diffusion of LAA percutaneous closure techniques and increasing operator experience in 3D imaging, it is reasonable that 3D TOE will have a growing role in the diagnosis of LAA thrombosis.

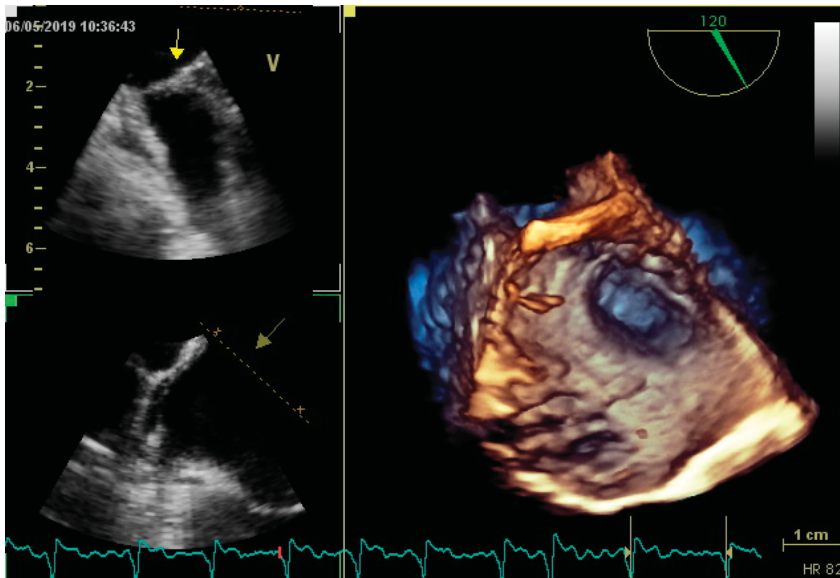


Figure 3. A three-dimensional TOE imaging of LAA.

Finally, intracardiac echocardiography (ICE) is an alternative imaging method of the LAA, usually indicated when TOE is contraindicated or not obtainable. ICE is performed with an 8–10 Fr catheter introduced through femoral venous access and advanced in right heart chambers under fluoroscopic guidance [38]. In the absence of interatrial transseptal crossing, the LAA can be displayed indirectly through the right ventricle outflow tract and the pulmonary artery, considering their close anatomical relationship [39]. Although ICE is less sensitive than TOE for thrombus detection [40], it can serve as a complementary method—especially when equivocal TOE findings require further evaluation. However, considering its invasive nature, in practice ICE is mainly performed in the catheterization laboratory during planned interventional cardiac procedures and when TOE is contraindicated.

#### 4. Prevention and Treatment of Left Atrial Appendage Thrombosis

CV is associated with an increased risk of thromboembolic events and strokes. For patients with AF >48 h onset, current guidelines recommend anticoagulant therapy for at least three weeks before and four weeks after CV [6]. The reason for three weeks of anticoagulation before electrical CV derives from a study suggesting that at least 14 days are needed for fibroblastic infiltration and organization of an LAA thrombus [41]. The four weeks of anticoagulation after CV are due to postprocedural LA stunning, with marked impairment of Doppler-derived indexes of LA contraction that contribute to a higher risk of thromboembolic stroke [5,42].

VKAs are considered the gold standard for thromboembolic prophylaxis before CV, and are the only recommended treatment in patients with valvular AF [6]. Previous studies suggest that the incidence of LA/LAA thrombosis under treatment with VKAs ranges between 0.6% and 7%, depending on population study and sample size [43–45]. The narrow therapeutic interval and difficulties in keeping a target time in therapeutic range are considered the main limitations of VKA therapy.

NOACs are safe and effective alternatives to VKA therapy [46–49], and are currently considered as first-line therapy for long-term stroke prevention in patients with nonvalvular AF [6]. The overall safety and efficacy profile of NOACs have been confirmed in different clinical scenarios [50–58]. The clinical performance of NOACs in the setting of acute and elective CV has been addressed by three prospective randomized trials. In the X-VerT trial, 1504 patients with AF of either >48 h or unknown duration undergoing CV were randomized to once-daily rivaroxaban or VKA [7]. The composite endpoint of stroke or systemic embolism after CV occurred in 1.02% of patients on VKAs and in 0.51% of patients on rivaroxaban. More recently, the ENSURE-AF trial randomized 2199 patients with AF >48 h and <1 year duration undergoing electrical cardioversion to 60 mg edoxaban once daily or warfarin with enoxaparin bridging [8]. The primary efficacy composite endpoint of stroke, systemic embolic event, myocardial infarction, and cardiovascular mortality at 28 days post CV occurred in 1.0% of patients of both arms. The EMANATE trial randomized 1500 patients with AF of ≤48 h onset to apixaban or heparin/VKA [9]. The trial showed a significant reduction with apixaban in strokes (0% vs. 0.8%) and in major bleeding (0.4% vs. 0.8%) at 30 days compared to warfarin. The favorable clinical profile of NOACs in patients undergoing CV has also been confirmed in a recent meta-analysis [59,60] and in real-world studies [61–66].

Probably as a result of this evidence, a recent multicentric European registry addressing NOAC strategies before CV showed a trend towards an increasing use of NOACs and a significant decrease of VKA use [67]. However, in this registry 68.5% of patients received VKA anticoagulant therapy before CV and clinicians appeared to hesitate to embrace NOAC usage before CV [67].

In a real-world clinical scenario, the average time to CV was shorter with NOACs compared to warfarin [62]. Moreover, a budget impact analysis showed that the potential use of an early rivaroxaban strategy before direct-current CV could lead to a significant saving of costs related to procedure [68]. Therefore, considering these positive points and the effective clinical profile versus warfarin, it is reasonable that the use of the NOAC anticoagulation strategy before CV could increase in coming years.

Although randomized trials have addressed the efficacy and clinical profile of NOACs versus warfarin before CV, the prevalence of LA/LAA thrombus after adequate anticoagulation with NOACs remains a relatively unaddressed issue. In the X-VerT study, a relatively high occurrence of LAA thrombi (18.2%) was observed in the 33 patients enrolled in the trial who underwent TOE before elective CV [7]. However, only about 10% of patients scheduled for elective CV in the X-VerT trial underwent TOE, and these data could explain the high percentage of LAA thrombosis. In the ENSURE-AF trial, 47 patients (8%) in the edoxaban arm and 42 patients (7.1%) in the enoxaparin-warfarin arm had LAA thrombosis on pre-CV TOE [8]. In the EMANATE trial, LA/LAA thrombus was detected in 61 patients (4%), 30 in the apixaban group, and 31 in the heparin/VKA group, in over 829 patients who underwent TOE before CV [9].

There is a paucity of data on the prevalence of LAA thrombosis on NOAC therapy before CV in a real-life setting. A multicenter real-world study performed in AF patients undergoing TOE 12 h

before CV or catheter ablation reported LAA thrombus in 3.6% of patients (15/414) with no significant difference between dabigatran, rivaroxaban, and apixaban [69]. Another recent real-world study showed LAA thrombosis in 7/127 patients (5.5%) and SEC in 24/127 (18.9%) [70].

Therefore, these data firstly suggest that LAA thrombosis is not a negligible event despite adequate anticoagulation, and that—although not universally accepted—a TOE-guided CV strategy is mandatory in order to reduce the burden of thromboembolic periprocedural events and to reduce bleeding events [71].

Once an LAA thrombus is identified, effective anticoagulation is recommended for at least three weeks or until LAA thrombus resolution is detected on follow-up TOE [6]. In this setting, VKA therapy for four weeks with repeat TOE showed resolution of thrombi in 80%–89% patients who were not previously anticoagulated [72,73]. If LAA thrombus occurs despite therapeutic anticoagulation, different strategies can be pursued, including switching to NOACs. Data are lacking on LAA resolution after NOACs therapy, and principally comprise case reports, where NOACs were initiated after failure of VKAs therapy or low time in therapeutic range [74–76]. The X-TRA multicenter prospective trial explored the use of rivaroxaban for the treatment of firstly-diagnosed LAA thrombus in 53 patients with available baseline and follow-up TOE [77]. About 75% of the patients had no prior anticoagulant therapy, while approximately one-quarter were treated with subtherapeutic VKA therapy. After six weeks of treatment, repeat TOE found a resolution of LAA thrombi in 41.5% of patients, 19% had LAA thrombi reduced in size, while 17% were unchanged and 22.5% had an increase in thrombi size [77].

In a recent retrospective study, among the 1485 patients with AF undergoing TOE, LAA thrombus or sludge was detected in 117 patients (7.8%) [78]. Of these, 39 (33%) were prescribed an NOAC, with rivaroxaban being the most frequently prescribed (54%). On repeat TOE, LAA thrombus resolution was seen in 37 patients (58.7%) with higher resolution rates, although not statistically significant, with NOAC therapy. A recent report on TOE showed 4.7% of LA/LAA thrombosis in 864 AF patients [79]. Follow-up TOE was performed in 22 patients, and 19 of them had LA/LAA thrombus resolution. In this real-world study, the preferred anticoagulant strategy was an uptitration of NOAC dosages and keeping higher INR values for warfarin therapy. However, a reduced NOAC dosage was most frequently associated with LA/LAA thrombi detection [79].

In conclusion, there is still a lack of solid evidence on the efficacy and safety of NOACs in LAA thrombus resolution. Current ongoing randomized trials comparing NOACs with VKAs in LA/LAA thrombosis resolution (rivaroxaban NCT03792152; dabigatran NCT02256683) will provide further evidence in this clinical scenario.

## 5. Conclusions

- The incidence of LAA thrombosis in AF patients undergoing CV is not a negligible event despite adequate anticoagulant therapy.
- A TOE-guided CV is a mandatory strategy in order to reduce the burden of periprocedural thromboembolic events.
- Although VKAs have been historically considered the cornerstone anticoagulant therapy before CV, growing evidence show that NOACs are safe and effective alternatives in this setting.
- Further and extended data are needed to assess the efficacy and safety profile of NOACs for the treatment of LAA thrombosis.

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Review

# “A Tale of Two Cities”: Anticoagulation Management in Patients with Atrial Fibrillation and Prosthetic Valves in the Era of Direct Oral Anticoagulants

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**Abstract:** Valvular heart disease and atrial fibrillation often coexist. Oral vitamin K antagonists have represented the main anticoagulation management for antithrombotic prevention in this setting for decades. Novel direct oral anticoagulants (DOACs) are a new class of drugs and currently, due to their well-established efficacy and security, they represent the main therapeutic option in non-valvular atrial fibrillation. Some new evidences are exploring the role of DOACs in patients with valvular atrial fibrillation (mechanical and biological prosthetic valves). In this review we explore the data available in the medical literature to establish the actual role of DOACs in patients with valvular heart disease and atrial fibrillation.

**Keywords:** novel oral anticoagulants; prosthetic valve replacement; atrial fibrillation

## 1. Prologue

In 1859 Charles Dickens wrote “*A tale of two cities*”, a historical novel set in London and Paris during the French Revolution, a transition period from the monarchical ancient regime to a new form of government. In medicine, now as then, with the introduction into the clinical practice of new therapeutic options for anticoagulation management, a new era is rising, but contrasts are still present. Even in fields of application in which new anticoagulants have proved to be superior to the old molecules (thrombosis prevention in atrial fibrillation and systemic thromboembolism), a sense of comfortability, given by decades of clinical experience of historical anticoagulant drugs, is still contrasting the potential widespread use of new therapeutic option, encouraged by their favorable outcome in terms of efficacy and security.

Moreover, the ancient regime of oral vitamin K antagonists (VKAs) is still dominating the anticoagulation management in prosthetic valve replacement. However, some new evidence seems able to promote a possible revolution in this setting.

## 2. Introduction

Prosthetic valve replacement represents a historical and effective therapeutic approach for symptoms and outcome improvement in patients with valvular heart disease (VHD) [1]. However, its effectiveness is counterbalanced by complications, whose frequency and severity depend upon valve type and position, as well as other patient-specific risk factors. Thromboembolic events are among those potential prosthesis-related complications, especially early after valve implantation [2].

Biological prosthetic valves, mechanical prosthetic valves, and more recently transcatheter biological prosthetic valve represent the options available in case of natively diseased or damaged heart valves. The decision about the use of one of these prosthetic valves depends upon patient’s age, a punctual balance between thromboembolic and bleeding factors, and patient’s decision [3].

Long-term anticoagulation therapy has been based historically on oral VKAs [4]. Those agents have been used for some time, accumulating through these decades robust data and clinical experience. For these reasons, despite numerous important limitations, physicians are still confident with their use. Novel direct oral anticoagulants are target-selective agents, including direct thrombin, or factor IIa (dabigatran), and factor Xa inhibitors (apixaban, rivaroxaban, edoxaban). In meta-analysis, including patients across all registration trials, those agents have shown superiority to warfarin (the main VKA agent) for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation [5,6]. DOACs have several pharmacokinetic advantages compared to VKAs: A fixed dose, which avoids the necessity for drug monitoring, rapid onset of action and a short-half life, which limits their action during a short time, few interactions with food and drugs, which makes their use easier and safer. Those characteristics make the DOACs an attractive to VKAs in long-term anticoagulation management of patients with prosthetic valves. However, currently, data showing a net benefit of DOACs in anticoagulation management of prosthetic valve are still lacking.

Recently, in a European Heart Rhythm Association (EHRA) position paper [7] about antithrombotic therapy in atrial fibrillation (AF), a new categorization of VHD in relation to the type of oral anticoagulation use has been proposed. Considering the terms “valvular” and “non-valvular” AF as outdated, the functional EHRA (evaluated heart valves rheumatic or artificial) categorization proposes a distinction in type 1 form, which refers to AF patients with VHD needing therapy with VKAs (moderate-to-severe mitral stenosis of rheumatic origin), and type 2 form, which refers to AF patients with VHD needing therapy with VKAs or DOACs (heart valve regurgitation, aortic stenosis, tricuspid stenosis, pulmonic stenosis, mild mitral stenosis, mitral valve repair, transaortic valve intervention, and bioprosthetic valve replacement). However, this categorization is in contrast with the purpose of the review, namely exploring the possible use of DOACs even in the EHRA type 1 forms, in which these agents are currently contraindicated.

DOACs in AF have showed to be safe and effective in different scenarios: in the elderly [8], in cancer patients [9,10], and in real-life experiences [11,12]. Moreover, DOACs have showed to be well tolerated, with low rates of discontinuation, in real-life [13] as in pivotal trials. Periprocedural and long-time anticoagulation therapy management in patients with AF undergoing interventional procedures represents one of the great chapters related to the use of anticoagulants. Numerous clinical trials have investigated the use of individual drugs in various scenarios and have been translated in recent joint consensus documents among various scientific societies (antithrombotic management in transcatheter valve replacement or repairment [14], percutaneous coronary interventions [15,16], electrophysiological procedures [17], and AF cardioversion [18]). Recent data, analyzing the clinical performance of DOACs in real-world patients who underwent interventional procedures, are emerging. DOACs have shown to be, also in real-world data, both effective and safe in many scenarios (for example, in electrical AF cardioversion [19], also in a population at a high thromboembolic and hemorrhagic risk [20]), confirming the data emerged from dedicated trials. Conversely, real-world data about anticoagulation therapy management in patients undergoing surgical or percutaneous valvular interventions are still missing.

### 3. Discussion

#### 3.1. Anticoagulation Therapy in Prosthetic Valves

##### 3.1.1. Anticoagulation Therapy in Mechanical Prosthetic Valves

Mechanical prosthetic valves (MPV) are often chosen in younger patients for their intrinsic high durability and low incidence of valve failure. However, these advantages are counterbalanced by a significant increase in thromboembolic events, especially shortly after valve implantation. Multiple thrombotic risk factors are concomitantly present in the vast majority of patients (older age, hypercoagulable state, a history of congestive heart failure, chronic kidney disease or atrial fibrillation,

etc.) and for these reasons, long-term anticoagulation is mandatory for MPV and the VKAs are the current standard of care in these patients [3,21].

### 3.1.2. Anticoagulation Therapy in Biological Prosthetic Valves

Biological prosthetic valves (BPV) are considered less thrombogenic than MPV. However, valve thrombosis in the absence of anticoagulation therapy should not be underestimated, especially in the presence of known risk factors, such as low cardiac output state and structural valve deterioration [2]. Therefore, in patients in sinus rhythm with BPV, following current ACC/AHA guidelines recommendation [22], short-term anticoagulation and antithrombotic management with VKA and low-dose aspirin should be co-administrated for the three to six months after valve implantation. On the other side, ESC/EACTS 2017 guidelines recommend only a short-term (three months) anticoagulation management with VKA after mitral bioprosthetic implantation or surgical valvuloplasty. However, as bioprosthetic aortic valves are considered less thrombogenic than mitral ones [14], short-term antithrombotic management with low-dose aspirin is preferred to anticoagulation therapy. On the other hand, in patients with AF and BPV, long-term anticoagulation with VKA is mandatory, and the general increase in life expectancy is leading to a more frequent association between these two. The thromboembolic risk, in this setting, may be related to both BPV and to AF. However, the incidence of thromboembolic events is similar to those of age-matched patients with chronic AF only [23].

### 3.1.3. Anticoagulation Therapy After Transcatheter Aortic Valve Implantation

Transcatheter bioprosthetic aortic implantation (TAVI) represents a new therapeutic option for patients with symptomatic severe aortic valve stenosis considered at moderate-to-high risk of surgical replacement. The ESC/EACTS guidelines [3] suggest a dual antiplatelet therapy for the first three to six months after TAVI, followed by lifelong single antiplatelet therapy. In case of high bleeding risk, the dual antiplatelet therapy should be avoided, and the lifelong antithrombotic management should be based on a single antiplatelet therapy. However, new evidence has shown that those valves determine a higher risk of subclinical leaflet thrombosis than surgical prostheses, without significant differences in terms of incidence of stroke [24]. Considering this, current ACC/AHA guidelines [21] have suggested anticoagulation management (non-fractionated heparin for the time interval needed to achieve a 2.5 target INR with VKA) for at least three-months after TAVI, in the absence of a high bleeding risk.

## 3.2. Role of Direct Oral Anticoagulants in Prosthetic Valves

### 3.2.1. DOACs in Patients with Atrial Fibrillation and Biological Prosthetic Valves

In AF alone, DOACs represent an effective and safe alternative to VKA. Due to their attractive pharmacokinetic profile, their use has been recently extended to patients with MPV and AF despite the lack of prospective controlled data. Indeed, DOACs have only been restricted for cases with “non-valvular” AF in the currently available trials, and only very few patients with mitral bioprosthesis have been enrolled on the ARISTOTLE [25] and ENGAGE-AF-TIMI48 trials [26].

Guimaraes et al. [27] have recently explored the efficacy and safety of apixaban versus warfarin in patients with AF and prior BPV replacement or valve repair, analyzing the data obtained from patients enrolled in the apixaban pivotal trial (ARISTOTLE). Of more than 18,000 patients enrolled, only 0.6% (104 patients, n = 76 aortic, n = 23 mitral and n = 5 aortic and mitral) had a history of BPV replacement: 55 were randomized to apixaban and 49 to warfarin. Moreover, about 0.3% had a history of valve repair (52 pts, n = 50 mitral and n = 2 aortic): 32 were randomized to apixaban and 20 to warfarin. Efficacy outcomes included stroke or systemic embolism, all-cause stroke, ischemic stroke, myocardial infarction, all-cause death, and cardiovascular death. Safety outcomes included major bleeding, major or clinically evident non-major bleeding, intracranial hemorrhage, gastrointestinal bleeding, and any bleeding. In this subgroup analysis, no significant differences were found between

the groups for any of the characteristics analyzed, showing that apixaban is safe and effective also in patients with AF and prior BPV replacement or valve repair. Those results were consistent with results shown in the main ARISTOTLE pivotal trial.

In the edoxaban pivotal ENGAGE AF-TIMI 48 trial patients with left-sided valvular heart disease were enrolled, including those with a history of aortic or mitral valve surgical or transcatheter implantation more than 30 days before randomization [28]. Of more than 21,000 patients enrolled, 0.9% had a previous BPV replacement (191 pts, n = 131 mitral, n = 60 aortic), and among them, 70 patients were randomized to warfarin, 63 patients to high-dose of edoxaban (60 mg daily) and 58 to low-dose of edoxaban (30 mg daily). Primary endpoints included stroke and systemic embolic events, major bleeding, and the primary net clinical outcome. Secondary composite endpoints included ischemic stroke, major adverse cardiac events (myocardial infarction, stroke, or cardiovascular death), and the composite of stroke, all-cause mortality, and life-threatening bleeding. In a subgroup analysis, patients with BPV treated with higher dose edoxaban had similar rates of stroke and major bleeding and lower rates of cardiovascular events (myocardial infarction, cardiovascular death) and primary net clinical outcome compared with warfarin. Patients treated with lower dose edoxaban had similar rates of stroke but lower rates of major bleeding and of the primary net clinical outcome compared with warfarin. In this analysis, edoxaban appears to be a reasonable alternative to warfarin in patients with AF and previous BPV implantation.

However, both the sub-analyses of DOAC pivotal trials have important limitations, including a small sample size and low number of events. Then, to definitively establish the role for alternative anticoagulation to VKA in this setting, larger dedicated controlled trials are needed to definitively assess the safety and efficacy of DOACs.

Russo et al. [29] have proposed in 2018 a multicenter observational study to investigate the efficacy and safety of DOACs in AF patients with BPV or prior surgical valve repair. A total of 122 patients were enrolled. In 92% of cases, warfarin was replaced due to lack of compliance and subtherapeutic INR range. The study population included 24 patients (19.6%) with mitral BPV, 52 patients (43%) with aortic BPV, 41 patients (33.6%) with previous surgical mitral repair, and 5 patients (4%) with a previous surgical aortic repair. Of the total study population, 28.6% were taking apixaban 5 mg twice daily, 24.5% apixaban 2.5 mg twice daily, 18% dabigatran 150 mg twice daily, 13% dabigatran 110 mg twice daily, 9.8% rivaroxaban 20 mg daily, and 5.7% rivaroxaban 15 mg daily. All patients were evaluated for thromboembolic events (ischemic stroke, transient ischemic attack, systemic embolism) as well as major bleeding events during the follow-up period and showed a low mean annual incidence of thromboembolism (0.8%) and major bleeding (1.3%). According to this data, DOAC therapy seems to be an effective and safe treatment alternative for AF patients with BPV or prior surgical valve repair. However, this study is limited by small sample size, a retrospective design, heterogeneous anticoagulation management and lack of VKA control group.

At present, the use of DOACs for the management of concomitant AF following BPV replacement may be considered a valid therapeutic option, with the exception of biological mitral prosthesis implanted in the setting of rheumatic mitral stenosis [30]. However, dedicated double-blinded trials confronting DOACs to VKA in this setting are necessary to evaluate the actual efficacy and safety of recommending the DOACs in patients with bioprosthetic valves.

### 3.2.2. DOACs in Patients with Atrial Fibrillation and Mechanical Prosthetic Valves

The only published trial investigating the use of a DOACs in mechanical prosthetic valves is the RE-ALIGN Trial [31]. The study made a comparison between dabigatran and warfarin in patients with aortic valve replacement with a mechanical prosthesis for the prophylaxis of thromboembolic events. The study was stopped early after enrollment of only 252 patients due to a significant increase in both thromboembolic (5% in dabigatran group vs. 0% in warfarin group) and bleeding (4% in dabigatran group vs. 2% in warfarin group) events in patients treated with dabigatran compared to conventional therapy with warfarin. Therefore, the use of DOACs in this particular subset of

patients appeared of no benefit and excessively harmful, so that the trial was prematurely discontinued. Different mechanisms of action of dabigatran and warfarin can partially explain these findings. In patients with mechanical prosthesis, thrombus formation can derive from contact pathway of coagulation, triggered by exposure of blood to the artificial elements of the valve (ring, struts, leaflets) and from direct release of prothrombotic tissue factor from damaged tissues during surgery. Therefore, VKAs are more effective than dabigatran in this setting by stopping both tissue factor and contact pathway induced coagulation [32].

Despite discouraging results from the RE-ALIGN Trial, Durães and coworkers [33] designed a pilot study to investigate the potential role of rivaroxaban as an alternative to VKA in patients with mechanical prosthetic valves. Their rationale [34,35] was that clotting on the mechanical valves is triggered by the contact and that dabigatran administered in the RE-ALIGN Trial was insufficient to inhibit thrombus formation in this scenario. On the other hand, rivaroxaban is a direct inhibitor of Factor Xa with potential to reduce significantly the generation of thrombin on mechanical prostheses. Accordingly, seven patients with mechanical mitral prosthesis received rivaroxaban 15 mg twice daily and were followed-up for 90 days. At the end of the study, no patients experienced neither thromboembolic nor bleeding adverse events. These findings opened the way to a subsequent randomized controlled trial, whose enrolling phase is expected to end in December 2019.

### 3.2.3. DOACs After Transcatheter Aortic Valve Implantation in Atrial Fibrillation Patients

The use of DOACs after TAVI has been investigated in the GALILEO trial [36]. In the study, rivaroxaban (10 mg once daily) plus short-term (three months) antiplatelet therapy with low dose aspirin (75 to 100 mg once daily) has been compared to short-term dual antiplatelet therapy management (clopidogrel 75 mg plus aspirin 75 to 100 mg once daily for three months), followed by long-term single antiplatelet management with aspirin alone for thromboembolic prevention after TAVI. The primary efficacy endpoint of the trial is a composite of all-cause death, stroke, systemic embolism, MI, pulmonary embolism, deep vein thrombosis, or symptomatic valve thrombosis. The primary safety endpoint is a composite of life-threatening or disabling bleeding or major bleeding. The trial has been halted precociously: From preliminary data released by Bayer, the rivaroxaban-based antithrombotic strategy has shown an increase in the rates of death or first thromboembolic event (11.4% vs. 8.8%), all-cause death (6.8% vs. 3.3%), and primary bleeding (4.2% vs. 2.4%) compared to antiplatelet-based therapy. Therefore, this confirmed that the use of DOACs is contraindicated after TAVI.

A summary of the main clinical trials and subgroup analysis is reported in Table 1.

**Table 1.** Summary of the main clinical trials and subgroup analysis assessing the clinical performance of novel oral anticoagulants in patients with bioprosthetic or mechanical heart valve.

| Clinical Trial    | Prosthetic Valve | N. Patients                         | Anticoagulant Regimen   | Primary Efficacy Endpoint   | Safety Endpoint  |
|-------------------|------------------|-------------------------------------|---|---|--|
| ARISTOTLE         | Biological       | 104 bioprosthetic valve             | Apixaban (n = 55)<br>Warfarin (n = 49)                                  | No significant difference   | No significant difference  |
| ENGAGE AF-TIMI 48 | Biological       | 191 bioprosthetic valve             | Edoxaban 60 mg (n = 63)<br>Edoxaban 30 mg (n = 58)<br>Warfarin (n = 70) | No significant difference for stroke/systemic embolic events for edoxaban 60 mg (P = 0.15) and edoxaban 30 mg (P = 0.31) vs. warfarin. Lower rates of primary net clinical outcome with edoxaban 60 mg (P = 0.03) and edoxaban 30 mg (P = 0.03) | No significant difference between high dose edoxaban and warfarin (P = 0.26)<br>Lower major bleeding events with edoxaban 30 mg (P = 0.045) vs. warfarin |
| RE-ALIGN          | Mechanical       | 252 (trial was prematurely stopped) | Dabigatran (150–220–300 mg based on kidney function)<br>Warfarin        | 9 stroke events (5%) in the dabigatran group<br>No stroke event in the warfarin group   | 7 major bleeding events (4%) in the dabigatran group<br>2 major bleeding events (%) in the warfarin group  |



Table 1. Cont.

| Clinical Trial | Prosthetic Valve                       | N. Patients                          | Anticoagulant Regimen   | Primary Efficacy Endpoint  | Safety Endpoint   |
|----------------|--|--------------------------------------|---|--|---|
| GALILEO        | Transcatheter aortic valve replacement | 1644 (trial was prematurely stopped) | Rivaroxaban 10 mg + Aspirin 100 for 90 days after TAVR<br>Clopidogrel 75 mg + Aspirin 100 mg for 90 days after TAVR | Death and first thromboembolic events: 11.4% rivaroxaban group vs. 8.8% in antiplatelet group.<br>All-cause death: 6.6% in rivaroxaban group vs. 3.3% in antiplatelet group. | Primary bleeding: 4.2% in rivaroxaban group vs. 2.4% in antiplatelet group. |

#### 4. Conclusions

As for all huge transformations occurring in the human history, there always exists a contrast between the forces of changes, which promise to revolutionize the previous status quo, and the forces of reaction, which react against them with the certainties accumulated over the years.

The revolution promised by the novel direct oral anticoagulants in the management of anticoagulant therapy in patients undergoing valve replacement is likely to remain inconclusive: The few clinical trials comparing DOACs to warfarin have been shown to increase the risk of all-cause of mortality, thromboembolic events, and bleeding in patients with MPV. Moreover, a single clinical trial with a single DOAC does not represent robust and clear evidence for dismissing a therapeutic strategy. Furthermore, we should consider that not all DOACs are equal in terms of effectiveness for different indications. Therefore, long-term anticoagulation therapy with VKAs is still mandatory in the setting of mechanical valve replacement.

Even after transcatheter aortic valve replacement, DOACs did not show an advantage over warfarin in terms of thromboembolic bleeding risk reduction. However, the concomitant presence of both thromboembolic and hemorrhagic risk factors, and the lack of robust data, make it difficult to establish the best antithrombotic strategy in this setting.

In patients with BPV, some observations obtained by sub-analysis of pivotal trials data are encouraging. However, in the absence of dedicated double-blinded trials confronting DOACs to VKA in terms of efficacy and safety, there is little evidence of treatment with DOACs in clinical practice in patients with bioprosthetic valves.

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Article

# Role of Biological Markers for Cerebral Bleeding Risk STRATification in Patients with Atrial Fibrillation on Oral Anticoagulants for Primary or Secondary Prevention of Ischemic Stroke (Strat-AF Study): Study Design and Methodology

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**Abstract:** *Background and Objectives:* In anticoagulated atrial fibrillation (AF) patients, the validity of models recommended for the stratification of the risk ratio between benefits and hemorrhage risk is limited. Cerebral small vessel disease (SVD) represents the pathologic substrate for primary intracerebral hemorrhage and ischemic stroke. We hypothesize that biological markers—both circulating and imaging-based—and their possible interaction, might improve the prediction of bleeding risk in AF patients under treatment with any type of oral anticoagulant. *Materials and Methods:* The Strat-AF study is an observational, prospective, single-center hospital-based study enrolling patients with AF, aged 65 years or older, and with no contraindications to magnetic resonance imaging (MRI), referring to Center of Thrombosis outpatient clinic of our University Hospital for the management of oral anticoagulation therapy. Recruited patients are evaluated by means of a comprehensive protocol, with clinical, cerebral MRI, and circulating biomarkers assessment at baseline and after 18 months. The main outcome is SVD progression—particularly microbleeds—as a selective surrogate marker of hemorrhagic complication. Stroke occurrence (ischemic or hemorrhagic) and the progression of functional, cognitive, and motor status will be evaluated as secondary outcomes. Circulating biomarkers may further improve predictive potentials. *Results:* Starting from September 2017, 194 patients (mean age  $78.1 \pm 6.7$ , range 65–97; 61% males) were enrolled. The type of AF was paroxysmal in 93 patients (48%), and persistent or permanent in the remaining patients. Concerning

the type of oral anticoagulant, 57 patients (29%) were on vitamin K antagonists, and 137 (71%) were on direct oral anticoagulants. Follow-up clinical evaluation and brain MRI are ongoing. *Conclusions:* The Strat-AF study may be an essential step towards the exploration of the role of a combined clinical biomarker or multiple biomarker models in predicting stroke risk in AF, and might sustain the incorporation of such new markers in the existing stroke prediction schemes by the demonstration of a greater incremental value in predicting stroke risk and improvement in clinical outcomes in a cost-effective fashion.

**Keywords:** atrial fibrillation; anticoagulation; stroke; intracerebral hemorrhage; cerebral small vessel disease; brain MRI; circulating biomarkers

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## 1. Introduction

Thromboprophylaxis with oral anticoagulation effectively reduces stroke risk in patients with atrial fibrillation (AF). Benefits must be balanced against the risk of bleeding, with intracranial hemorrhage being the most feared. Stroke and bleeding risk stratification schemes are aimed at identifying patients who may benefit most from different types of oral anticoagulation (vitamin K antagonists vs. direct oral anticoagulants). Currently, such schemes (e.g., CHADS<sub>2</sub>VASC<sub>2</sub> and HASBLED scores) rely only on clinical information, the validity of which remains controversial and needs to be improved. In AF patients, advanced imaging technology such as magnetic resonance imaging (MRI), has led to the increased detection of asymptomatic brain changes, mainly those related to small vessel disease (SVD), which is the pathologic substrate for primary intracerebral hemorrhage (ICH) [1–6]. These changes have also been proven to strongly predict stroke risk [2,5]. Such imaging findings, obtained both at baseline and in terms of lesion progression over time, could be used as additional markers for risk stratification [3,7]. Furthermore, markers of coagulation activation, including prothrombin fragment 1+2, thrombin–antithrombin complex, D-dimer, time in therapeutic range for warfarin, and drug dosage for new anticoagulants, may be also studied as cofactors. Preliminary data suggest that circulating biomarkers of endothelial dysfunction, hypercoagulable state, and inflammation may further enhance risk prediction [4].

The validity of the currently recommended models for the stratification of risk ratio between benefits and hemorrhagic risk in anticoagulated AF patients is limited. These models do not specifically take intracranial hemorrhage into account, which is indeed the most severe hemorrhagic complication [8]. Our hypothesis is that biological markers—both circulating and imaging-based, and their possible interaction—might improve the prediction of bleeding risk in AF patients treated with any type of oral anticoagulant. Neuroimaging biomarkers of SVD—particularly microbleeds—may serve as a selective surrogate marker of hemorrhagic complications. Circulating biomarkers assessed together with imaging may further improve predictive potentials.

In this scenario, we set up the prospective observational Strat-AF study, primarily aimed at investigating circulating biomarkers and MRI markers (baseline and progression) of SVD as surrogate markers for the prediction of cerebral bleeding in a cohort of patients with AF on oral anticoagulants. Secondary outcomes included stroke occurrence (either ischemic or hemorrhagic) and the progression of functional, cognitive, and motor status.

## 2. Materials and Methods

Stratification of Cerebral Bleeding Risk in AF, Strat-AF, Strat-AF is an observational, prospective, single-center hospital-based study enrolling patients with AF, referring to the Center of Thrombosis outpatient clinic of our University Hospital for the management of oral anticoagulation therapy.

### 2.1. Inclusion Criteria

- Diagnosis of AF and ongoing oral anticoagulation therapy;
- Aged  $\geq$  65 years;
- No contraindications to MRI.

### 2.2. Exclusion Criteria

- Inability or refusal to undergo cerebral MRI;
- Inability to give an informed consent.

All subjects gave their informed consent for inclusion before they participated in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Ethics Committee of the Careggi University Hospital (Project identification code 16RFAP, approved on March 2017).

Sample size was estimated based on a feasibility criterion (i.e., the real flow of patients to the Thrombosis outpatient clinic of Careggi Hospital). Yearly, approximately 600 patients with AF on oral anticoagulation refer to the outpatient clinic. Considering a foreseeable rate of ineligible patients and refusals, we originally estimated to contact approximately 300 patients in one year fulfilling the inclusion criteria. Starting from September 2017, consecutive eligible patients were invited to participate in the study. The initial foreseen period for enrollment was 12 months, but in order to augment the number of included patients, we extended the enrollment period to 18 months.

### 2.3. Clinical Assessment

All enrolled patients were assessed at baseline by means of a standard clinical/functional protocol collecting information on vascular risk factors (particularly hypertension and diabetes), dietary habits, previous cerebrovascular events, general neurological and functional status, cognitive performances, mood and gait disorders, and general neurological examination.

In detail, clinical data were collected about social and medical history; a standard cardiovascular and neurological examination, including office blood pressure measurement, were performed. Functional status was assessed using the Activities of Daily Living scale and the Instrumental Activities of Daily Living scale [9,10]; mood assessment using the Geriatric Depression Scale [11]; motor performance using the Short Physical Performance Battery [12]; daytime sleepiness using the Epworth Sleepiness Scale [13]; and quality of life using the EuroQol Visual Analog Scale [14]. Dietary habits were assessed by means of the questionnaire on the adherence to the Mediterranean diet [15].

A comprehensive multi-domain cognitive assessment, including global functioning, orientation, memory, attention, executive functions, language, speed, and motor control was administered to each included patient.

The cognitive domains assessed by means of the extensive battery of tests were as follows:

- Global cognitive efficiency, by means of the Montreal Cognitive Assessment (MoCA): it is a 10-minute cognitive screening tool created to detect mild cognitive impairment (MCI), suggested from the harmonization standards of the National Institute of Neurological Disorders and Stroke—Canadian Stroke Network (NINDS-CSN) and thought to be specifically sensitive to frontal, attention, and executive deficits [16–18]. It covers eight cognitive domains: short-term and delayed verbal memory; visuospatial abilities; executive functions; attention; concentration; working memory; language; and orientation (score range 0–30)
- Verbal memory, by means of the Rey Auditory-Verbal Learning Test (RAVLT) and the Short Story Recall Test [19,20]. The RAVLT and Short Story Recall Test measure several components of verbal memory, such as immediate free recall, verbal learning, and retention of information after a certain period of time. Two scores are obtained from the RAVLT: immediate free recall (range 0–75) and delayed free recall (range 0–15). The Short Story Recall Test has a total score obtained by the



mean number of elements correctly remembered on the immediate and delayed recalls (score range 0–28).

- Attention, by means of the Visual Search test [21]. This is a number cancellation task that requires visual selectivity at fast speed, and assesses the capacity for sustained attention and accuracy of visual scanning (score range 0–60). The Colour Word Stroop test was also used [22]. It is a measure of concentration effectiveness and deals with response inhibition and selective attention. The activity required by this test is a selective processing of only one visual feature while continuously blocking out the processing of others. The execution time and the errors committed are recorded.
- Language, by means of:
  - i. Semantic verbal fluency test: a test allowing the semantic evaluation of lexical access [23]. Three categories were tested: car brands, fruits, and animals. The total score was given by the sum of the number of words produced for each category in one minute.
  - ii. Sentence construction test: a test used to evaluate the verbal ability to construct a meaningful sentence starting from a set of two or three words (score range 0–25) [19].

All raw test scores were demographically corrected according to Italian population normative data, and adjusted scores were then recoded as normal, borderline, or abnormal according to equivalent scores (ES) methodology [24]. ES methodology is a non-parametric norming method based on percentiles and is independent from the distribution form. ES is an ordinal 5-point scale (ranging from 0 to 4), and the main point of ES methodology is to fix the outer tolerance limit of the left queue of the adjusted scores so that it is possible to assess, with a known risk of error (<5%), the cut-off splitting the bottom 5% of the population and representing pathological performance (ES = 0). At the other end of the scale, ES = 4 indicates an optimal performance (equal to or better than the median). ES = 1 indicates a borderline performance (an adjusted score between the outer and inner confidence limits for the fifth centile of the normal population), while the remaining ES scores of 2 and 3 represent normal performances.

The diagnosis of MCI requires at least one altered score (ES = 0) plus one borderline score (ES = 1) in any cognitive test included in the neuropsychological battery.

#### 2.4. Cerebral Magnetic Resonance Imaging Assessment

Cerebral MRI scans were performed at baseline, and again 18 months after enrollment. The brain imaging protocol was planned and set up by imaging personnel with different expertise and skills, as suggested by current guidelines [25].

Baseline and follow-up MRI examinations are performed on an Ingenia 1.5-Tesla MRI unit (Philips Healthcare, Eindhoven, The Netherlands). Our standardized MRI protocol consisted of the following sequences: sagittal T1-weighted spin-echo (repetition time (TR) = 547 ms; echo time (TE) = 12 ms; slice thickness = 5 mm; interslice spacing = 0.5 mm; matrix size = 320 × 250; field of view (FOV) = 23 cm × 23 cm; number of signals averaged (NSA) = 1), coronal T2-weighted fast spin-echo (TR = 3347 ms; TE = 110 ms; slice thickness = 5 mm; interslice spacing = 0.5 mm; matrix size = 512 × 322; FOV = 22 cm × 22 cm; NSA = 2); axial fluid-attenuated inversion recovery (FLAIR) (TR = 11,000 ms; TE = 125 ms; inversion time (TI) = 2800 ms; slice thickness = 5 mm; interslice spacing = 0.5 mm; matrix size = 384 × 204; FOV = 23 cm × 23 cm; NSA = 2); axial gradient-echo T2\* (GRE) (TR = 534 ms; TE = 23 ms; flip angle (FA) = 18; slice thickness = 5 mm; interslice spacing = 0.5 mm; matrix size = 256 × 185; FOV = 23 cm × 23 cm; NSA = 1); axial diffusion-weighted imaging (DWI) (TR = 3891 ms; TE = 75 ms; slice thickness = 5 mm; interslice spacing = 0.5 mm; matrix size = 164 × 162; FOV = 23 cm × 23 cm; NSA = 2); gradient-echo 3D T1-weighted (TR = 7.5 ms; TE = 3.4 ms; TI = 950, slice thickness = 1 mm; matrix size = 256 × 241; FOV = 25.6 cm × 25.6 cm; NSA = 1) followed by multiplanar reconstruction (MPR) in axial, coronal, and sagittal planes. DWI images were obtained by single-shot echo-planar spin-echo sequences according to the Stejskal–Tanner method. The diffusion

gradients were applied in three orthogonal directions ( $x, y, z$ ) with two b-values (0 and 1000 s/mm<sup>2</sup>) to form the isotropic DWI images at b 1000 s/mm<sup>2</sup>. Apparent diffusion coefficient (ADC) maps were generated automatically by the software provided by the manufacturer from isotropic DWI images and concurrent images with a b value of 0 s/mm<sup>2</sup> by using the following equation:  $ADC = -\ln [S(b)/S(0)]/b$ , where b indicates the b value and S(b) and S(0) are the signal intensities of images with b values equal to 1000 and 0, respectively.

Each MRI scan was evaluated by an expert neuroradiologist, and a written medical report was provided to patients. Neurologists involved in the project revised the report before returning it to patients, so that any incidental findings could be handled according to individual needs.

Qualitative and quantitative analyses of SVD-related features on MRI are under way.

The following features related to SVD will be assessed: i) lacunar infarcts, either silent or not; ii). white matter hyperintensities; iii) microbleeds; iv) dilated perivascular spaces; v) cortical and subcortical atrophy; vi) superficial siderosis [5].

Non-lacunar infarcts will be visually assessed in terms of number and location of lesions.

### 2.5. Circulating Biomarker Assessment

Venous blood samples were collected after enrollment and placed at -80 °C for long-term storage.

Besides routine parameters (complete blood count (CBC), prothrombin time (PT), activated partial thromboplastin time (APTT), D-dimer, fibrinogen, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglycerides, glucose, creatinine, glomerular filtration rate (GFR), alanine aminotransferase, C-reactive protein (CRP), N Terminal pro B-type natriuretic peptide, Lp(a), troponin), several circulating biomarkers will be evaluated:

- Endothelial function biomarkers;
- Pro- and anti-inflammatory molecules;
- Metalloproteinases and their inhibitors;
- Markers of renal function;
- Markers of blood clotting activation and of fibrinolytic system of coagulation activation, including prothrombin fragment 1+2, thrombin–antithrombin complex, D-dimer, and endogenous thrombin potentials;
- Genetic polymorphisms that may influence the effect of anticoagulants and plasmatic microRNA profile.

The list of biomarkers under investigation is detailed in Table 1. The biological material (serum, plasma, DNA) is properly conserved to allow the evaluation of further biomarkers by specific or global assessment strategies (e.g., metabolomics profiling, targeted or whole-exome sequencing).

Proteomic and genetic biomarkers will be evaluated with high-multiplex immunoassays or high-throughput technologies such as Bio-Plex Multiplex Immunoassay System (BioRad), Proximity Extension Assay (Olink) technology, H-nuclear magnetic resonance spectroscopy (Bruker BioSpin), real-time PCR (Life Technologies), droplet digital PCR (BioRad), and high-throughput sequencing (Illumina).

Biosamples were processed using standard and harmonized operating procedures.

Clinical data are registered electronically in the web-based registry (<http://www.strat-af.it/>). Quality controls are done on a weekly basis. Imaging data are instantly checked for protocol conformity.

The same clinical/functional assessment and brain MRI will be repeated 18 months after enrollment. An interim telephone follow-up interview will be scheduled approximately three months before the final clinical assessment.

**Table 1.** Circulating biomarkers under investigation in the Strat-AF study.

| Category                                     | Biomarkers Name   |
|--|---|
| Markers of endothelial function              | - von Willebrand Factor (vWF)   |
|  | - Tissue Factor Pathway Inhibitor (TFPI)                                  |
| Pro- and anti-inflammatory molecules         | - Chemokine (C-C motif) ligand 3 (CCL3)                                   |
|  | - Interleukin (IL)-1 $\beta$ (IL-1 $\beta$ ),                             |
|  | - IL-1 Receptor antagonist (IL-1RA)                                       |
|  | - IL-2  |
|  | - IL-6  |
|  | - IL-8  |
|  | - IL-10   |
|  | - IL-12 P40   |
|  | - Tumor Necrosis Factor Alpha (TNF- $\alpha$ )                            |
|  | - Intercellular Adhesion Molecule-1 (ICAM-1)                              |
| Metalloproteinases                           | - Vascular cell adhesion molecule-1 (VCAM-1)                              |
|  | - Vascular Endothelial Factor (VEGF)                                      |
| Markers of coagulation activation            | - Matrix metalloproteinase (MMP)-2, MMP-8, MMP-9, MMP-12                  |
|  | - Tissue Inhibitor of Metalloproteinases (TIMP)-1, TIMP-2, TIMP-3, TIMP-4 |
|  | - Endogenous thrombin potential (ETP)                                     |
|  | - Plasminogen activator inhibitor-1 (PAI-1) antigen                       |
|  | - Prothrombin fragment 1+2 (F1+2)   |
|  | - Thrombin antithrombin complexes (TAT)                                   |
| Genetic polymorphisms and plasmatic miRNA    | - Tissue factor   |
|  | - Plasminogen Activator Inhibitor-1 (PAI-1) antigen                       |
|  | - Clot lysis time (CLT)   |
|  | - CES1 rs2244613  |
|  | - CES1 rs8192935  |
|  | - ABCB1 rs148738  |
|  | - VKORC1 G3673A or -1639G>A rs9923231                                     |
|  | - CYP2C9*2 rs1799853  |
|  | - CYP2C9*3 rs1057910  |
|  | - CYP2C9*5 rs28371686   |
|  | - CYP2C9*6 rs9332131  |
| - CYP4F2 V433M rs2108622 C>T                 |   |
| - GGCX rs11676382                            |   |
| - Plasmatic miRNA profiling by real-time PCR |   |

## 2.6. Primary Endpoint

The primary study endpoint will be SVD progression, evaluated by means of the control MRI performed 18 months after enrollment. The progression of lacunar infarcts and microbleeds will be evaluated as the appearance of at least one new lesion, respectively. White matter hyperintensities progression will be rated by means of the visual Rotterdam Progression Scale (score range from 0 to 9) [26]. Absence or presence of progression (0 or 1, respectively) will be rated in three periventricular regions (frontal caps, occipital caps, bands), four subcortical white matter regions (frontal, parietal, occipital, temporal), basal ganglia, and the infratentorial region. Post-processing and ratings will be centralized and performed by expert and reliable observers, blinded to clinical data.

## 2.7. Secondary Endpoints

Secondary endpoints will be:

1. Stroke occurrence (ischemic or hemorrhagic).
2. Considering data from medical history and available laboratory and imaging exams, new major cerebrovascular events will be recorded as ischemic or hemorrhagic strokes. Ischemic strokes will

be further categorized in subtypes according to the TOAST classification system [27]. Hemorrhagic strokes will be classified according to lesion type and location.

3. Progression of global functioning, cognitive, and motor performances.
4. Progression in cognitive status will be determined by the occurrence of a diagnosis of MCI or dementia, and defined according to performances on the comprehensive neuropsychological test battery (evaluated as normal or abnormal by means of national normative data), and functional status.
5. The change in global functional status will be based on the Activities of Daily Living and Instrumental Activities of Daily Living scales, and the worsened condition will be defined as the loss of at least one item (i.e., the patient became dependent for an item function that was preserved at baseline evaluation).
6. Motor status will be evaluated by means of the Short Physical Performance Battery. Based on the total score (range 0–12), at each visit individuals will be categorized as having normal (SPPB  $\geq$  11) or impaired mobility (SPPB  $\leq$  10), and variations in performance categories over time (baseline vs. 18 months) will be evaluated for each patient.

### 2.8. Statistical Analyses

Multivariate regression analyses will be performed in order to identify independent predictors of SVD and its progression. Among the variables of interest, apart from the clinical ones and those assessed by means of conventional MRI, special attention will be paid to the relationship with advanced neuroimaging features and circulating biological markers.

Cerebral SVD and its progression—particularly microbleeds, which are considered the main expression of a bleeding-prone state—will be studied as outcome variables in multivariate regression models, considering the independent effect of all relevant markers, including major vascular risk factors and anticoagulant treatment with different types of anticoagulants (vitamin K antagonists vs. direct thrombin antagonists or factor Xa antagonists), and circulating biomarkers.

Interactions of circulating biomarkers with imaging markers, and types of oral anticoagulants will also be analyzed. Bonferroni correction will be applied in multivariate models to counteract the problem of multiple comparisons.

The multivariable prediction of the risk of SVD progression in this cohort of AF patients on oral anticoagulants will be studied as the methodological background for clinical research in the setting of stroke prevention in patients with AF (i.e., for designing and sample sizing studies potentially adopting the above indicated biomarkers as surrogate markers of the clinical outcomes).

## 3. Results

Starting from September 2017 until March 2019, 617 patients referring to the outpatient clinic of the Center of Thrombosis for oral anticoagulants therapy control were screened for inclusion in the study. As shown in Figure 1, 423 patients (68%) were excluded because of MRI contraindications ( $n = 227$ ) or refusal ( $n = 196$ ). The remaining 194 patients were enrolled. Demographic and clinical characteristics of the baseline sample are shown in Table 2: mean age was  $78.1 \pm 6.7$  (range 65–97) years, 118 (61%) were males, and mean education was  $9.1 \pm 4.3$  (range 2–19) years. The type of AF was paroxysmal in 93 patients (48%), and persistent or permanent in the remaining patients. Concerning the type of oral anticoagulant, 57 patients (29%) were on vitamin K antagonists, and 137 (71%) were on direct oral anticoagulants. Follow-up clinical evaluation and brain MR are ongoing.

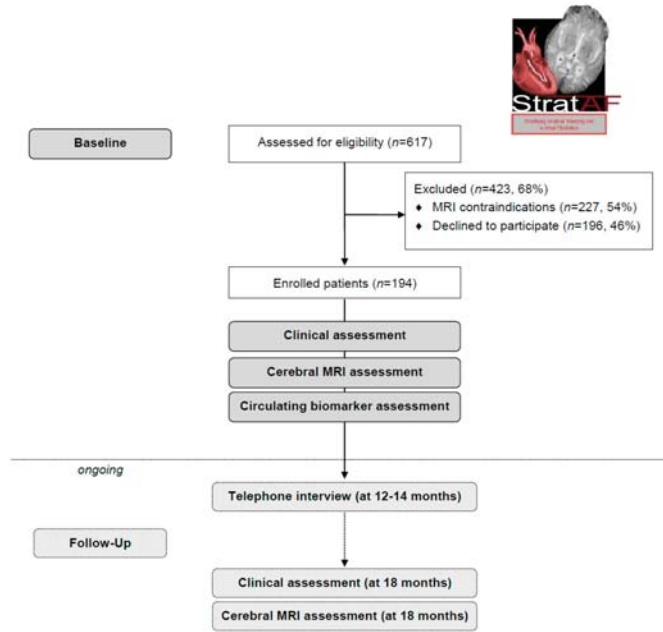


Figure 1. Strat-AF flow diagram.

Table 2. Baseline sample demographic and clinical characteristics.

|                            | Min–Max | Baseline Sample n = 194 |
|----------------------------|---------|-------------------------|
| Age, years (mean ± SD)     | 65–97   | 78.1 ± 6.7              |
| Years of education         | 2–19    | 9.1 ± 4.3               |
| Sex (% males)              | -       | 61% (n = 118)           |
| Hypertension               | -       | 82% (n = 159)           |
| Hypercholesterolemia       | -       | 48% (n = 94)            |
| Diabetes                   | -       | 13% (n = 25)            |
| Smoking habits             | -       | 61% (n = 119)           |
| History of stroke          | -       | 22% (n = 42)            |
| Alcohol consumption        | -       | 51% (n = 100)           |
| Paroxysmal AF              | -       | 48% (n = 93)            |
| Type of oral anticoagulant |         |                         |
| Vitamin K antagonists      | -       | 29% (n = 57)            |
| Direct oral anticoagulants | -       | 71% (n = 137)           |

#### 4. Discussion

The Strat-AF study is an ongoing, single-center, longitudinal observation study evaluating elderly patients with AF on oral anticoagulation for primary or secondary prevention of stroke. The project foresees, in consecutive elderly patients with AF attending the Center for Thrombosis outpatient clinic of Careggi University Hospital for management of oral anticoagulation therapy, the implementation of a comprehensive neurological, neuropsychological, and functional evaluation together with blood sample collection for the determination of circulating biological markers (in relation to the hemorrhagic risk profile) and brain MRI for the determination of brain parenchyma lesions as surrogate markers of a bleeding-prone state. The Strat-AF cohort will allow the evaluation of the possible role of biological markers, including clinical, circulating, and neuroimaging-based, and their interaction, on the prediction of bleeding risk in AF patients under treatment with any type of oral anticoagulant.

Neuroimaging biomarkers of SVD, particularly microbleeds, will be tested as a selective surrogate marker of such complication. Circulating biomarkers assessed together with imaging might further improve the predictive potentials. Active enrollment started from September 2017 and ended in March 2019. The baseline study cohort included 194 elderly patients. Follow-up assessments are now ongoing.

One first major comment arises from the fact that in order to reach the number of enrolled patients, more than 600 patients had to be screened. Of these, more than half were excluded. Main reasons for exclusion were refusal (46%) and MRI contraindications (54%). Thus, the method under evaluation (i.e., brain MRI) will not be feasible for all AF patients, but just for those without contraindication. According to our experience, about one-quarter of patients would not be included in such a new stratification risk schema.

Overall, the study protocol seems feasible, and nearly all included patients completed the evaluation.

Our results will provide a unique opportunity to achieve preliminary data about SVD progression as a surrogate marker of the effect of antithrombotic treatments used for stroke prevention in patients with AF. The longitudinal design of the study may also provide clues about the possible association of SVD and its progression with clinical endpoints. Thrombo-embolic and bleeding risk will be assessed using the clinical risk scores CHADS<sub>2</sub>VASC<sub>2</sub> and HAS-BLED respectively. Such predictive models will be completed studying the effect of neuroimaging features, particularly those related to SVD, and circulating biological markers, in order to provide preliminary knowledge about the incremental value of such markers.

Conclusive evidence about the predictive value of these markers in single patients can only come from adequately powered large prospective follow-up studies, and few efforts are already under way. Prospective multicenter studies such as the CROMIS 2 (clinical relevance of microbleeds in stroke; [ClinicalTrials.gov](#) Identifier NCT02513316), ICH because of oral anticoagulants: prediction of the risk by MRI (HERO, Hirulog Early Reperfusion/Occlusion Trial; [ClinicalTrials.gov](#) Identifier NCT02238470), and CMB-NOW (CMBs during NOACs or warfarin therapy in non-valvular AF patients with acute ischemic stroke; [ClinicalTrials.gov](#) Identifier NCT02356432) are ongoing. Main results from CROMIS-2 have been recently published: among the 1490 patients with AF enrolled after their ischemic stroke, the presence of CMBs significantly increased the risk of symptomatic ICH (adjusted hazard ratio 3.67, 95% CI 1.27–10.60), confirming that CMBs are independently associated with symptomatic ICH risk, and could be used to inform anti-coagulation decisions. In this study, after 24 months of follow-up, 14 patients had an intracerebral hemorrhage. The very low number of events did not allow the establishment of whether a CMBs threshold exists. Moreover, the study does not foresee a control MRI, so no information is available concerning the possible role of CMBs progression. A recent meta-analysis assessed the association between CMBs and future ICH risk in ischemic stroke patients with AF taking oral anticoagulants. The authors concluded that the presence of CMBs on MRI and the dichotomized cutoff of  $\geq 5$  CMBs might identify subgroups of patients with high ICH risk [28], but these data need to be confirmed before they can be used in clinical practice.

## 5. Conclusions

Long-term oral anticoagulation is the mainstay therapy for ischemic stroke prevention in patients with AF. Available stroke and bleeding risk stratification schemes are aimed at identifying patients who may benefit most from oral anticoagulation [29]. Such schemes (e.g., CHADS<sub>2</sub>VASC<sub>2</sub>, HAS-BLED scores) currently rely only on clinical information, the validity of which remains controversial and needs to be improved. Attempts have been made to refine the risk stratification scores by the addition of various biomarkers (blood, urine, cardiac, and cerebral imaging), but data are still inconclusive as to whether the costs are justified [30].

The Strat-AF study may be an essential step towards the exploration of the role of a combined clinical biomarker or multiple biomarker models in predicting stroke risk in AF, and might sustain the incorporation of such new markers in the existing stroke prediction schemes by the demonstration

of a greater incremental value in predicting stroke risk and improvement in clinical outcomes in a cost-effective fashion.

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Article

# Physicians' Perceptions of Their Patients' Attitude and Knowledge of Long-Term Oral Anticoagulant Therapy in Bulgaria

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**Abstract:** *Background and Objectives:* Oral anticoagulation (OAC) is widely used in daily clinical practice worldwide for various indications. We aimed to explore the perception of Bulgarian clinicians about their patients' attitude and knowledge of long-term OAC, prescribed for atrial fibrillation (AF) and/or known deep venous thrombosis (DVT)/pulmonary embolism (PE). *Materials and Methods:* We performed a cross-sectional study that involved 226 specialists: 187 (82.7%) cardiologists, 23 (10.2%) neurologists, and 16 (7.1%) vascular surgeons. They filled in a questionnaire, specially designed for our study, answering various questions regarding OAC treatment in their daily clinical practice. *Results:* The mean prescription rate of OACs in AF patients was 80.3% and in DVT/PE—88.6%. One hundred and eighty-seven (82.7%) of the participants stated they see their patients on OAC at least once per month. According to more than one-third of the inquired clinicians, the patients did not understand well enough the provided information concerning net clinical benefit of OAC treatment. About 68% of the clinicians declared that their patients would prefer a “mutual” approach, discussing with the physician the OAC options and taking together the final decision, whereas according to 43 (19.0%), the patients preferred the physician to take a decision for them. Patients' OAC treatment had been interrupted at least once within the last year due to a physician's decision by 178 (78.8%) of the participants and the most common reason was elective surgery. The most influential factors for a patient's choice of OAC were the need of a specific diet to be kept, intake frequency, and possible adverse reactions. *Conclusions:* Our results suggest that a clinician's continuous medical education, shared decision-making, and appropriate local strategies for improved awareness of AF/DVT/PE patients are key factors for improvement of OAC management.

**Keywords:** atrial; fibrillation; venous; thrombosis; anticoagulation; perception

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## 1. Introduction

Oral anticoagulation (OAC) is widely used in contemporary clinical practice for preventive and therapeutic indications [1–3]. Until recently, the OAC treatment choice was restricted to the vitamin K antagonists (VKAs) and patients' preferences were less commonly encountered [2–4]. Even after the introduction of new direct oral anticoagulants (DOACs) to clinical use and the large volume of data from clinical trials comparing VKAs' and DOACs' efficacy and safety, the patients' awareness of the treatment choices, benefits, and risks with long-term OAC remains unclear [3–7]. Moreover, their role in the decision-making process is frequently neglected thus affecting the treatment adherence and persistence [5,7].

To date, there are no large-scale, population-based studies or national registries in Bulgaria evaluating the prescription rate of OACs and/or the prevalence of atrial fibrillation (AF), deep venous thrombosis (DVT)/pulmonary embolism (PE)—some of the most common diseases requiring OAC. A single center cross-sectional study, including 1027 patients, hospitalized for different diseases in the largest Bulgarian internal clinic showed that ~62% of all patients suffered at least one episode of AF [8]. Of these patients, ~14% had undergone ischemic stroke and OAC was prescribed to ~86% [8].

These data gave us grounds to perform the present study, aiming to explore the practicing clinicians' perceptions of their patients' attitude and knowledge of long-term OAC.

## 2. Materials and Methods

A cross-sectional questionnaire-based study involved 226 clinical specialists from 20 cities in Bulgaria. Of these, 187 (82.7%) were cardiologists, 23 (10.2%) neurologists, and 16 (7.1%) vascular surgeons. For the purposes of the study, a structured questionnaire with 12 questions was formulated, as shown in Appendix A.

The study was conducted from 1 July to 30 September 2017. The inclusion criteria were: (1) clinical experience for at least 5 years, and (2) regular prescription of OAC for atrial fibrillation (AF) and/or deep venous thrombosis (DVT)/pulmonary embolism (PE). The regular OAC prescription was defined as at least two prescriptions per week of a VKA or a DOAC. Exclusion criteria: (1) clinicians with other clinical specialties, (2) prescription of anticoagulants for indications other than those in the inclusion criteria, and (3) inability to fill in the study questionnaire for any reason.

As this is a non-trial activity (NTA) for health care providers (no involvement of patients at all in the study), an internal approval only has been done according to Boehringer Ingelheim requirements and standards (NTA tracking no. 170432).

### *Statistical Analysis*

Categorical variables were shown as counts and percentages, and continuous variables as mean values and standard deviation (SD). Where normal distribution was not confirmed using the Shapiro–Wilk test, the median value and interquartile range (IQR) were used for variables with skewed distribution. Categorical variables were compared using the independent samples Chi-square test. Analysis of variance (ANOVA) was used for comparison of parametric data and the Mann–Whitney U test for non-parametric data. A two-sided *p*-value of <0.05 was considered statistically significant. The statistical analysis was performed by SPSS statistical package, version 19.0 (SPSS Inc., Chicago, IL, USA).

## 3. Results

The answers of the questions 1 to 7 are provided in Tables 1 and 2. The vast majority of 226 participating physicians (210, 92.9%) reported that they treated patients with AF. The highest average monthly number of patients with AF was seen by cardiologists (46, 60.5%), whereas those with known DVT/PE by vascular surgeons (21, 60.0%). The physicians stated they had assigned an OAC to 80.3% of their AF patients for stroke prevention and to 88.6% of the patients with known DVT/PE for secondary prevention. One hundred and eighty-seven (82.7%) of the participants in our study declared they see their patients on OAC at least once per month, 28 (12.4%)—at least twice and 11 (4.9%)—three or more times per month (without significant difference between the specialties), as shown in Table 1.

According to 168 physicians (74.3%), the patients were satisfied with the provided general information about OAC treatment before its initiation, 42 (18.6%) answered their patients were very satisfied, and 16 (7.1%)—the patients were neither satisfied nor unsatisfied (no statistically significant difference between cardiologists, neurologists, and vascular surgeons). However, only 64.2% of the surveyed physicians answered that their patients understand well enough the discussed information about OAC, as shown in Table 1.

**Table 1.** Questions 1 to 7 and the clinicians' answers.

| Question and Answers   | All N (%)   | Cardiologists N (%) | Neurologists N (%) | Vascular Surgeons N (%) | <i>p</i> Value   |
|--|-------------|---------------------|--------------------|-------------------------|------------------|
| 1. What is the average monthly number of patients with the following diagnoses in your practice?   |             |                     |                    |                         |                  |
| AF   | 76 (100%)   | 46 (60.5%)          | 16 (21.1%)         | 14 (18.4%)              | <i>p</i> < 0.001 |
| Known DVT/PE   | 35 (100%)   | 10 (28.6%)          | 4 (11.4%)          | 21 (60.0%)              | <i>p</i> < 0.001 |
| 2. What is the approximate proportion of your patients with: AF treated with OAC for stroke prevention (%) or known deep vein thrombosis (DVT) with or without pulmonary embolism (PE) on OAC (%)? |             |                     |                    |                         |                  |
| AF   | 61 (80.3%)  | 41 (67.2%)          | 11 (18.0%)         | 9 (14.8%)               | <i>p</i> < 0.001 |
| Known DVT/PE   | 31 (88.6%)  | 8 (25.8%)           | 2 (6.5%)           | 21 (67.7%)              | <i>p</i> < 0.001 |
| 3. How often do you see your patients on OAC per month?  |             |                     |                    |                         |                  |
| At least once  | 187 (82.7%) | 155 (82.9%)         | 19 (82.6%)         | 13 (81.3%)              | NS               |
| At least twice   | 28 (12.4%)  | 23 (12.3%)          | 3 (13.0%)          | 2 (12.5%)               | NS               |
| 3 or more times  | 11 (4.9%)   | 9 (4.8%)            | 1 (4.3%)           | 1 (6.3%)                | NS               |
| 4. In your opinion, how satisfied are your patients with the information about the OAC treatment they receive before its initiation?   |             |                     |                    |                         |                  |
| Satisfied  | 168 (74.3%) | 139 (74.3%)         | 17 (73.9%)         | 12 (75.0%)              | NS               |
| Very satisfied   | 42 (18.6%)  | 35 (18.7%)          | 4 (17.4%)          | 3 (18.75%)              | NS               |
| Neither satisfied nor unsatisfied  | 16 (7.1%)   | 13 (7.0%)           | 2 (8.7%)           | 1 (6.25%)               | NS               |
| 5. How do you rate your patients' understanding of the provided information about OAC?   |             |                     |                    |                         |                  |
| Very good  | 101 (44.7%) | 84 (44.9%)          | 10 (43.5%)         | 7 (43.8%)               | NS               |
| Good   | 44 (19.5%)  | 36 (19.3%)          | 5 (21.7%)          | 3 (18.8%)               | NS               |
| Inadequate   | 81 (35.8%)  | 67 (35.8%)          | 8 (34.8%)          | 6 (37.5%)               | NS               |

AF—atrial fibrillation, DVT—deep venous thrombosis, PE—pulmonary embolism, OAC—oral anticoagulation, NS—non-significant; the *p* value refers to the inter-physicians' answers.

**Table 2.** Questions 6 and 7, and the clinicians' answers.

|  |             |             |            |            |                  |
|--|-------------|-------------|------------|------------|------------------|
| 6. In your opinion, to what extent would your patients like to be involved in the choice of OAC?                                     |             |             |            |            |                  |
| They prefer to discuss with the physician, then make the decision together.  | 153 (67.7%) | 135 (72.2%) | 8 (34.8%)  | 10 (62.5%) | <i>p</i> = 0.02  |
| They prefer to discuss with the physician, then make the decision by themselves.   | 30 (13.3%)  | 25 (13.4%)  | 2 (8.7%)   | 3 (18.75%) | <i>p</i> < 0.001 |
| They prefer the physician to make the decision.  | 43 (19.0%)  | 27 (14.4%)  | 13 (56.5%) | 3 (18.75%) | <i>p</i> < 0.001 |
| 7. Did you have to stop the current OAC in any of your patients within the past 12 months due to a planned surgery and/or emergency? |             |             |            |            |                  |
| Yes, I had to stop OAC   | 178 (78.8%) | 151 (80.7%) | 14 (60.9%) | 13 (81.3%) | <i>p</i> < 0.001 |
| Due to a planned surgery   | 167 (93.8%) | 146 (96.7%) | 8 (57.1%)  | 13 (100%)  | <i>p</i> = 0.02  |
| Because of an emergency  | 11 (6.2%)   | 5 (3.3%)    | 6 (42.9%)  | 0          | <i>p</i> < 0.01  |

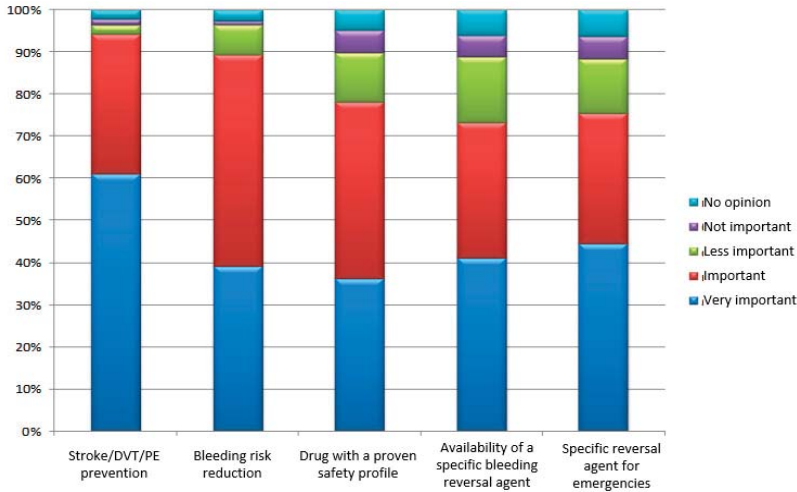
OAC—oral anticoagulation; the *p* value refers to the inter-physicians' answers.

In terms of the patients' role in the decision-making process concerning OAC, 153 (67.7%) of the participants stated that their patients preferred to discuss with the physician all possible treatment options (advantages and disadvantages) and then make a decision together (equal role of both sides), 43 (19.0%)—the patients preferred the physician to take a decision for them (with or without prior

discussion, whereas 30 (13.3%) reported the patients would make their therapeutic choice alone irrespective of the physician’s opinion during the discussion, as shown in Table 2.

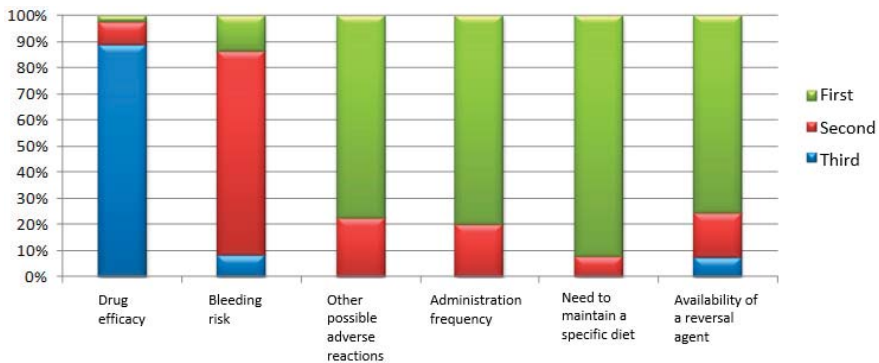
Patients’ OAC therapy had been interrupted at least once within the last 12 months due to a physician’s decision by 178 (78.8%). This occurred significantly more often with cardiologists and vascular surgeons and more rarely with neurologists. The most common reasons for interruption of OAC was the elective surgery—reported by 167 (93.8%), followed by an emergency—by 11 (6.2%) physicians, as shown in Table 2.

The physicians’ answers of the question “In your opinion, how do your patients rate the importance of treatment outcomes and attributes of OAC?” are shown in Figure 1.



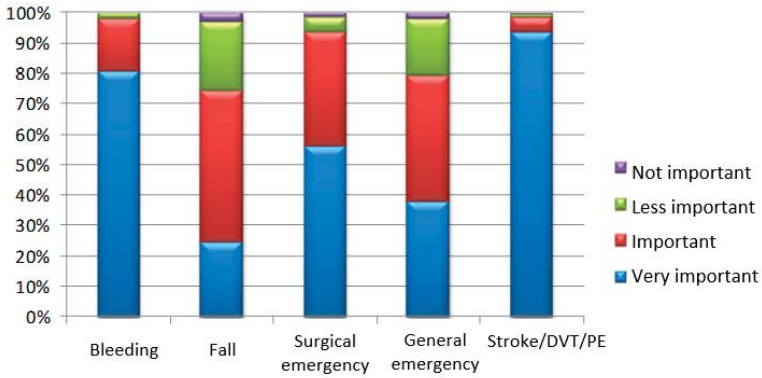
**Figure 1.** Some basic characteristics of the OAC treatment according to the patients (the information was provided by their physicians); DVT—deep venous thrombosis; PE—pulmonary embolism.

The responders were asked to rank up to three factors (out of a total of six) which their patients would consider the most important in their choice of OAC. The drug’s efficacy was most commonly rated as the third important factor, whereas the need a specific diet to be kept, intake frequency, and possible adverse reactions were considered the most influential factors by the majority of the physicians, as shown in Figure 2.

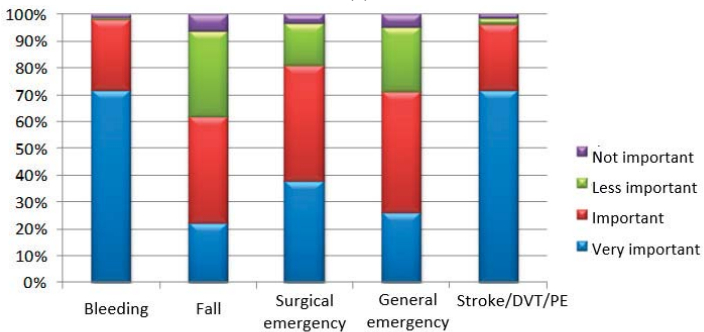


**Figure 2.** Rankings of factors of the surveyed physicians based on their responses to the question “If you had to discuss with your patients the OAC to be prescribed, which three factors they would consider the most important in your opinion?” (absolute number; relative share).

The physicians were asked to rate five complications by importance and then to report how they evaluate their patients' opinion about those complications. There was a close similarity between physicians' answers and their opinions about what would the patients say when they chose an OAC. The complication the physicians rated the highest was stroke/DVT/PE, followed by bleeding, and then surgical emergencies, as shown in Figure 3a,b.



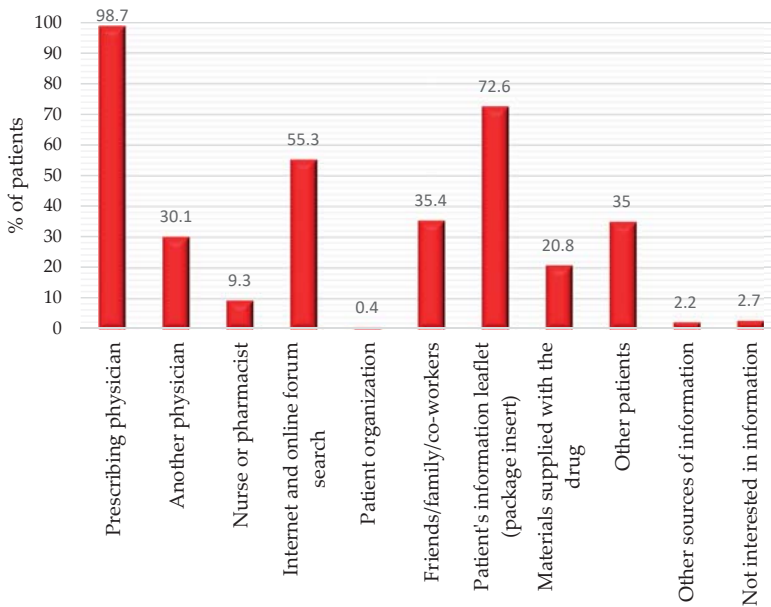
(a)



(b)

**Figure 3.** (a) Importance of five basic complications according to the physicians, when choosing an OAC. (b) Importance of five basic complications according to the patients, when choosing an OAC (the information was provided by their physicians); DVT—deep venous thrombosis; PE—pulmonary embolism.

Most commonly, the information about the assigned OAC was provided to patients by the prescribing physician (223 physicians, 98.7%), followed by the printed leaflet inserted into the drug package (164, 72.6%), internet and online forums (125, 55.3%), friends/family (80, 35.4%), other patients (79, 35.0%), another physician (68, 30.1%), other materials supplied together with the drugs (47, 20.8%), and nurse/pharmacist (21, 9.3%), as shown in Figure 4.



**Figure 4.** Sources of information from the surveyed physicians based on their responses to the question “What sources, in your opinion, do patients use to get information about the OAC they are taking?”.

#### 4. Discussion

This is a cross-sectional questionnaire-based study, conducted among 226 physicians in 20 towns of Bulgaria, the vast majority of which 82.7% were cardiologists, 10.2% were neurologists, and 7.1% were vascular surgeons. They answered specific questions in order to evaluate the attitude, knowledge, and preferences of their patients with AF and/or DVT/PE concerning the long-term OAC treatment.

The prescription rate of oral anticoagulants in our study was relatively high compared the published data of other authors—80.3% of the physicians dealing with AF (mostly cardiologists) stated their patients had been treated with an OAC (VKA or DOAC) for prevention of embolic events [1–4]. Atrial fibrillation was the most common indication for prescription of OAC [7–14]. This could be explained by the high prevalence of this arrhythmia in the general population (25% long-life risk for at least one episode of AF in people aged >40 years) and probably by the significantly improved awareness of the cardiologists and other health specialists for the last two decades about the cardio-embolic risk of AF [11,12,15–17]. In developed countries, 65% to 80% of the patients diagnosed with AF and a CHADS<sub>2</sub> or CHA<sub>2</sub>DS<sub>2</sub>VASc risk score higher than 2, receive long-term oral anticoagulation [2,3,15]. Data from the USA IMS Health’s National Disease and Therapeutic Index revealed that OAC prescription rates in AF patients with high thromboembolic risk varied from 20% to 80% [2]. Interestingly, ~15% of all AF patients in these studies did not receive any antithrombotic treatment because of various concomitant conditions (active bleeding, patient refusal, severe comorbid illnesses, pregnancy, etc.) [3,16–19]. In our study, the percentage of non-anticoagulated AF patients was around 20%. In contrast to other studies, we found similar (~67%) prescription rates of OAC (VKA or DOAC) for AF (most often by cardiologists) and DVT/PE (by vascular surgeons). Other authors reported a higher use of oral anticoagulants for DVT and/or PE, than in the case of AF—85–88% versus 60–80%, respectively [1–5]. It should be pointed out, the level of education and patients’ knowledge had a direct influence on the OAC management for embolic stroke prevention in AF [9,18–21].

Most of the physicians (~83%) of all specialties enrolled in our study stated they had visits with their patients on OAC therapy at least once per month. According to the guidelines, patients on DOACs

should be seen at least once per year and if their kidney function was impaired (creatinine clearance <60 mL/min), the annual frequency of clinical visits could be calculated dividing the creatinine clearance by 10 [1,2].

The vast majority of our participants considered their patients were satisfied or very satisfied with the provided information about OACs. Since no patients were included in our study we could not discuss if the physician's opinion about the patient's level of satisfaction was really true. According to other studies, patients' satisfaction varies widely from 42% to 97% [18,22,23].

The patient's proper understanding of the provided information regarding the OAC treatment could influence the decision-making process, adherence to therapy, and the immediate and long-term prognosis, respectively [1,3]. In addition, there was frequently a discrepancy between the level of patient satisfaction from the medical information and the real understanding of this information [4,5]. According to only 64.2% of the inquired physicians in our study, their patients understood well enough the discussed information. In the study of Nadar et al., conducted in the United Kingdom, between 18% and 45% of all patients (depending on the ethnic group) had difficulties with the proper understanding about any aspect of the antithrombotic treatment [16].

Regarding the decision-making process, about 68% of our participants stated their patients would prefer a "mutual" approach, discussing with the physician the treatment options and taking together the final decision. Only 13% of the physicians answered the patients would prefer to decide themselves irrespective of the physician's opinion. These data were supported by other studies, which confirmed that shared decision-making would improve patients' adherence and persistence to OAC treatment [13,24,25].

An alarming finding of our study was that at least ~79% of all patients had stopped their OAC therapy at least once per year. These results were similar to other published data [2,5]. Our participants reported elective surgery as the most frequent cause for treatment cessation. According to other studies, gastrointestinal procedures and surgery with biopsy were the most frequent reason for temporary OAC discontinuation [1,3]. These findings were important from a clinical point of view—previous studies had shown that major thromboembolic complications, especially ischemic stroke, occurred in approximately 1% of the patients who underwent temporary discontinuation of OAC before an invasive procedure [2,3].

Intriguing answers were given by the participants concerning the most important characteristics of OAC medication according to their patients—the highest role of stroke/DVT/PE prevention, followed by the availability of a reversal agent in case of bleeding or emergencies. Obviously, the presence of a specific inhibitor of the OAC action make the patients more confident and trustworthy during a discussion of their anticoagulation management. This is particularly relevant for Dabigatran use in daily clinical practice [23].

In our study the most important factors for a patient's choice about OAC therapy were the necessity to keep a specific diet, the intake frequency, and the possible adverse reactions. They were reported as "first three factors" exerting influence on the therapeutic decision by the majority of the participants. Surprisingly, the efficacy of the OAC drugs was classified most frequently as the third important factor by many of them. This finding could be related to patients' misperception of OAC risks and benefits, which might be overcome by a well-structured patient education program [13]. However, in our study, the physicians' answers and their opinions about the patients' judgment of the complications, concerning the choice of OAC, were very similar—the highest importance was attributed to stroke/DVT/PE, followed by bleeding and surgical emergencies. Perhaps, the communication gap in this population had not been so large as expected based on the previously published data [20,25].

Nowadays, concerns about the patients' awareness, choices, and preferences are becoming more important for the complex therapeutic approach, including antithrombotic treatment. Patients want to participate actively in the decision-making about the proposed procedures or treatments and to know all their alternatives [4,5]. The environment in which patients consume medical and health information has changed dramatically during the past decades worldwide [9,10]. The rapid diffusion of Internet



technologies within the public sphere has placed an unprecedented amount of health information within reach of general consumers [6]. Nevertheless, according to our data, the prescribing physician continues to be a principal trusted resource for information about the OAC in spite of the variety of new sources of health information. Direct communication between physicians and patients is still an influential factor for the patient's awareness and decisions. The second and third most used sources of information in our study—the printed leaflet (provided together with the box of the medication in Bulgaria) and internet/online forums—could exert positive but also negative influence (particularly the last source) on the patient's attitude and therapeutic choice. We have the impression from our own clinical practice that the reading of the printed leaflet of the drugs (short product characteristics) might discourage the patients. Internet sites are not always reliable for the information they provide, and many could mislead the patients to an inappropriate decision. A study conducted in the USA among Hispanic adult patients with different diseases revealed that common health information sources were doctors (71%), television (68%), family and friends (63%), newspapers and magazines (51%), and radio (40%) [25]. In Europe, the Electrophysiology Wire Survey showed that considerable amount of time and resources were used to inform AF patients about their risk profile and appropriate management. However, a diversity of strategies across the European hospitals was reported [13].

*Study limitations:* (1) Disproportion of cardiologists, neurologists, and vascular surgeons in our study with the much larger number of the first ones. Patients with AF would attend a cardiologist for examinations and treatment (those without a cerebrovascular or peripheral arterial embolic event would not be referred to neurologist or a vascular surgeon). Patients with DVT were likely to visit a vascular surgeon for evaluation and treatment (a much fewer number in our study) and were less likely to be registered/followed up by a cardiologist or a neurologist unless another condition requiring OAC (AF, prosthetic valve disease, post-stroke, etc.) was present. (2) Our study did not include patients of the inquired physicians to answer the same questions, so we could not compare the answers of both sides. (3) The number of participants was not large enough for our results to be extrapolated nationwide.

## 5. Conclusions

This questionnaire-based study, conducted among Bulgarian cardiologists, neurologists, and vascular surgeons, shows that patients' attitude and knowledge about OAC depends on their direct communication with the doctor rather than on drug leaflets or internet/online sources. Our patients prefer to discuss thoroughly with the physician the therapeutic options and then to take together the final decision. However, more than one-third of the physicians report their patients do not understand well enough the provided information concerning net clinical benefit of OAC. Moreover, the discontinuation of OAC remains an important issue in our population. These data suggest that physicians' continuous medical education, shared decision-making, and appropriate local strategies for better informing AF/DVT/PE patients are the crucial factors for improvement of OAC management.

**Author Contributions:** Conceptualization: N.R., T.P., and A.V.; Methodology: N.R., T.P., S.N., and G.G.; Software: S.N. and A.V.; Validation: T.P., G.G., and E.M.; Formal Analysis: N.R., S.N., and E.M.; Investigation: A.V., G.G., and E.M.; Resources: S.N., A.V., and G.G.; Data Curation: N.R., T.P., S.N., and E.M.; Writing-Original Draft Preparation: N.R. and S.N.; Writing-Review & Editing: N.R., T.P., S.N., and E.M.; Visualization: A.V., G.G., and E.M.; Supervision: N.R., T.P., and E.M.; Project Administration: A.V. and G.G.

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**Conflicts of Interest:** Nikolay Runev has received research contracts and honoraria for lectures from Boehringer Ingelheim; Tatjana Potpara declares no conflict of interest; Stefan Naydenov has received honoraria for lectures from Boehringer Ingelheim; Emil Manov declares no conflict of interest; A.V. and Gergana Georgieva are full-time employees of Boehringer Ingelheim; Boehringer Ingelheim supported technically the conductance of the current study without financial funding; Nikolay Runev, Stefan Naydenov, Tatjana Potpara, Emil Manov, and the participants in the study received no financial support/reward for conductance of the study.

## Appendix A. Questions: Included in the Study Questionnaire

1. What is the average monthly number of patients with the following diagnoses in your practice: atrial fibrillation (AF) or known deep vein thrombosis (DVT) with or without pulmonary embolism (PE)?
2. What is the approximate proportion of your patients with: AF treated with OAC for stroke prevention (%) or known DVT with or without PE on OAC (%)?
3. How often do you see your patients on OAC per month?
4. In your opinion, how satisfied are your patients with the information about the OAC treatment they receive before its initiation?
5. How do you rate your patients' understanding of the provided information about OAC?
6. In your opinion, to what extent would your patients like to be involved in the choice of OAC:
  - They prefer the physician to make the decision
  - They prefer to discuss with the physician, then make the decision by themselves
  - They prefer to discuss with the physician, then make the decision together
7. Did you have to stop the current OAC medication in any of your patients within the past 12 months?
8. In your opinion, how do your patients rate the importance of treatment outcomes and attributes of OAC medication?
9. If you had to discuss with your patients the OAC to be prescribed, which three factors from the ones listed below they would consider the most important in your opinion: drug efficacy; risk of bleeding; other possible adverse reactions; administration frequency of the medication; having to follow a specific diet while on medication; availability of a reversal agent?
10. As a specialist how would you rate the importance of the following complications when choosing an OAC medication: bleeding, fall, surgical emergency, general emergency situations, strokes/DVT/PE?
11. How would your patients rate the importance of the following complications: bleeding, fall, surgical emergency, general emergency situations, stroke/DVT/PE?
12. What sources, in your opinion, do patients use to get information about the OAC they are taking (multiple answers allowed)?

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Article

# Polymorphism of Interleukin 1B May Modulate the Risk of Ischemic Stroke in Polish Patients

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**Abstract:** *Background and Objectives:* Inflammation plays a crucial role in the pathophysiology of ischemic stroke (IS). Interleukin-1B and interleukin-1 receptor antagonists are key factors in inflammatory processes. *Aims:* The aims of our study were to evaluate the relationship between genetic variation in interleukin-1B (*IL1B*) rs1143627 and interleukin-1 receptor antagonist (*IL1RN*) variable-number-tandem-repeats (VNTR), and overall IS and subtype prevalence rates. *Materials and Methods:* The analysis included 147 hospitalized Polish patients with IS diagnosed using conventional criteria. The control group consisted of 119 healthy subjects. Genotypes were determined by polymerase chain reaction. *Results:* A significant association between rs1143627 and stroke was found. The -31C *IL1B* polymorphism showed an association with overall IS, OR = 2.30 (1.36–3.87)  $p = 0.020$ . An association was also detected for LVI (large vessel infarction) subtypes of stroke. After risk factor adjustment (age, diabetes mellitus, dyslipidemia), the C allele was found to be an independent risk factor for LVI, OR = 1.99 (1.05–3.79)  $p = 0.036$ . Significant association was not observed between *IL1RN* alleles and IS. *Conclusions:* Our results suggest that the C allele of *IL1B* rs1143627 may be associated with susceptibility to overall IS and LVI subtypes of stroke in the Polish population.

**Keywords:** *IL1B*; *IL1RN*; polymorphism; stroke; inflammation

## 1. Introduction

Ischemic stroke (IS) is a multifactor disease, resulting from classical and genetic risk factors and their interactions. Accumulating evidence supports a critical role of inflammation in the pathogenesis of IS. Interleukin-1 (IL1) is one of the key pro-inflammatory cytokines which plays a key role in this inflammatory process. The IL1 family consists of IL1A, IL1B and one antagonist cytokine, the IL1 receptor antagonist (IL1RA) [1,2]. IL1A and IL1B are inflammatory factors produced by different cell types in response to various stimuli. They affect the endothelial cells, including the induction of adhesion molecules and prothrombotic effects, while the naturally occurring competitive IL1RA may antagonize the immune response. Disturbed balance in the action of IL1A, IL1B and IL1RA leads to the development and progression of atherosclerosis. In fact, earlier studies have shown that increased levels of inflammatory cytokines are associated with vascular ischemic disease [3–5].

The IL1 gene cluster, with loci on chromosome 2, encompasses the *IL1A*, *IL1B*, and *IL1RN* genes. The polymorphisms in this *IL1* gene cluster, including *IL1B* and *IL1RN* (interleukin-1 receptor antagonist, encoding IL1RA), have been commonly studied and appeared to be associated with plasma levels of IL1B and IL1RA [6,7].

In experimental studies, several independent groups have reported an early increase in IL1 expression in response to cerebral ischemia in rodents [8,9]. It has also been demonstrated in wild-type (WT) and knock-out IL1RI (IL1RI KO) mice that IL1 may exacerbate ischemic brain injury independently of IL1RI, which suggests the existence of an additional IL1 receptor or receptors in the brain [10]. Currently, IL1 polymorphism is considered to be an independent risk factor for IS development, although some studies have not confirmed this relationship.

The polymorphism in intron 2 of the interleukin receptor antagonist gene (*IL1RN*) is caused by the variable copy number of an 86-bp sequence. The most common allele, allele 1 (*IL1RN\*1*), contains two repeats. The alleles 2, 3, 4, and 5 have two, five, three, and six repeats, respectively [11]. The *IL1RN\*2* allele of the variable number tandem repeat (VNTR) of *IL1RN* has been reported to be associated with increased ILRA production, which naturally downregulates the immune response [12]. However, some studies have shown that *IL1RN\*2* is associated with decreased IL1RA production. IL1B influences the endothelium, including the induction of adhesion molecules and procoagulant activity. Thus, the IL1/IL1RA balance may modulate inflammation processes which may contribute to the pathogenesis of ischemic stroke. A pro-inflammatory profile comprising SNPs in gene encoding regions of *IL1B* and *IL1RN* was further reported to confer an increased risk of atherosclerosis development [13–15] and some studies have reported that *IL1B* and *IL1RN* polymorphisms are associated with genetic risk of IS [16]. However, other studies on different populations did not confirm this and the association remains controversial [17,18].

Ischemic stroke is a disease with devastating consequences, which is why we are still looking for markers enabling early diagnosis. Currently, many risk factors are known for the development of stroke. However, our knowledge concerning the genes which promote the development of stroke is still limited. Our study attempts to explain the role of the genetic variants of *IL1B* (C(-31)T) and *IL1RN*, considered to be key factors regulating inflammatory processes in the development of ischemic stroke. Therefore, we have investigated the possible association between genetic variation in *IL1B* rs1143627 and *IL1RN* VNTR with overall IS and subtypes of IS classified by TOAST (see Materials and Methods) in the Polish population.

## 2. Materials and Methods

### 2.1. The Study Group

A total of 147 unrelated patients (80 males and 67 females) were admitted to hospital because of acute brain ischemic stroke (IS): Diagnosed using conventional criteria, including rapidly developed focal or global disturbance of cerebral function lasting more than 24 h, without CT signs of a hemorrhagic lesion in the brain. The study group was from a homogeneous Polish population. All 147 patients underwent clinical scrutiny, investigation of medical history and family anamnesis, evaluation of vascular risk factors, general physical and neurological examinations, routine biochemical analyses, ECG (electrocardiography), and computed tomography (CT) of the brain, within two days of onset.

Data from risk factors were recorded, including arterial hypertension (HT, defined as systolic blood pressure exceeding 140 mmHg or diastolic blood pressure greater than 90 mmHg or previous diagnosis), body mass index (BMI, calculated as weight/height<sup>2</sup>), and diabetes (DM, previously diagnosed or a fasting plasma glucose concentration > 7.8 mL/L). Patients were classified as “current smokers” if they reported smoking more than five cigarettes per day. Routine biochemical analyses were done including fasting blood glucose, total cholesterol, HDL cholesterol and triglycerides, liver, and kidney function tests.

The study population was divided according to the TOAST classification [19], which identified five causes of ischemic cerebral infarction: (1) Large artery atherosclerosis (LVI—large-vessel infarction) in 71 patients (46.7%), (2) small-vessel occlusion (SVI—small vessel infarction) in 40 patients (26.3%), (3) cardioembolism (CEI—cardioembolic infarction) in 24 patients (15.8%), (4) stroke of other determined

etiology (e.g., non-atherosclerotic artery disease) in no patients, and (5) stroke of unknown etiology in 17 patients (11.2%).

The control group consisted of 119 subjects (65 men, 52 women) who reported non-specific chest complaints and were diagnosed in regard to CAD. They underwent coronary angiography which detected no lesions in coronary arteries. A medical examination ruled out IS and other atherosclerotic diseases as well as a history of ischemic, hemorrhagic, and other brain diseases. The protocol of the study was approved by the Pomeranian Medical University Ethics Committee (nr BN-001/119/03/16.03.2003), with formal informed consent signed by all participants.

## 2.2. Genotyping

Genomic DNA was isolated from peripheral blood leukocytes using a commercial kit (QIAamp DNA Mini Kit; Qiagen, Hilden, Germany).

For the analysis of C(-31)T *IL1B* gene polymorphism (rs1143627) a polymerase chain reaction/restriction fragments length polymorphism (PCR/RFLP) method was applied with the following primer pair: Forward: 5' AgA AgC TTC CAC CAA TAC TC, and reverse: 5' AgC ACC TAg TTg TAA ggA Ag (TIB MOL BIOL, Poznań, Poland). Amplification was performed in volumes of 10 µL containing 40 ng genomic DNA, 0.1 µL of each primer, 5 µL 2xPCR Master Mix (Fermentas, Vilnius, Lithuania). The reactions were run under the following conditions: Denaturation (94 °C, 5 min), annealing (56 °C, 40 s), and extension (72 °C, 8 min). Thirty-five cycles were performed using a Mastercycler gradient machine (Eppendorf, Hamburg, Germany). The resulting product (234 bp) was digested with the Alu I restriction enzyme (MBI Fermentas, Vilnius, Lithuania), and the digestion products were separated in 4% agarose gels. The polymorphic region within intron 2 of the *IL1RN* gene was amplified using polymerase chain reaction (PCR). Genomic DNA (20 ng) served as a template in the 10 µL PCR reaction. This reaction contained the following components: 0.1 µL of each forward primer: 5' CCC CTC AgC AAC ACT CC, and reverse primer: 5' ggT CAg AAg ggC AgA gA (TIB MOL BIOL, Berlin, Germany); 5 µL 2xPCR Master Mix (Fermentas, Vilnius, Lithuania) the reaction was performed using standard settings: Denaturation (94 °C, 5 min), annealing (58 °C, 1 min) and extension (72 °C, 8 min), 36 cycles performed using a Mastercycler gradient machine (Eppendorf, Germany). The sizes of amplified products were determined by electrophoresis on 3% agarose gels.

## 2.3. Statistical Analysis

Statistical analysis was conducted with the R statistical platform (<http://cran.r-project.org>) using the package SNPAssoc (SNPs-based whole-genome association studies. R package version 1.9-2. <https://CRAN.R-project.org/package=SNPAssoc>). In the analysis of single SNPs, multiple inheritance models were used: Co-dominant, dominant, and recessive. Analysis of gene–gene interactions was carried out for the dominant and recessive models. Inheritance models were created with respect to minor alleles. The significance of interactions was calculated by comparing two models with and without the interaction term, using likelihood ratio tests.  $p < 0.05$  was considered statistically significant.

## 3. Results

Demographic characteristics of the IS and control groups, risk factors and TOAST classifications in stroke cases are shown in Table 1. All characteristics did not differ between the two groups except for age ( $66.9 \pm 12.1$  vs.  $56.8 \pm 9.8$ ,  $p < 0.0001$ ) and the frequencies of diabetes mellitus (27% vs. 13%,  $p = 0.004$ ) and dyslipidemia (16%/84% vs. 76%/24%,  $p < 0.0001$ ).

**Table 1.** Demographic and risk factors of stroke characteristics.

| Characteristic               | Cases (n = 147) | Control (n = 117) | p       |
|------------------------------|-----------------|-------------------|---------|
| Age (years)                  | 66.9 ± 12.1     | 56.8 ± 9.8        | <0.0001 |
| BMI (kg/m <sup>2</sup> )     | 27.6 ± 4.8      | 26.9 ± 4.2        | 0.286   |
| Sex (Males)                  | 54% (80)        | 56% (65)          | 0.854   |
| Smoking                      | 32% (47)        | 24% (28)          | 0.150   |
| Diabetes mellitus            | 27% (40)        | 13% (15)          | 0.004   |
| Hypertension                 | 60% (88)        | 51% (60)          | 0.163   |
| Dyslipidemia                 | 16% (23)        | 76% (89)          | <0.0001 |
| <b>TOAST</b>                 |                 |                   |         |
| Large-vessel atherosclerosis | 46% (68)        |                   |         |
| Cardioembolism               | 17% (25)        |                   |         |
| Small-vessel                 | 26% (38)        |                   |         |
| Others                       | 11% (16)        |                   |         |

3.1. Association between Overall IS and Genetic Variation in *IL1B* and *IL1RN*

The genotype distributions were in Hardy–Weinberg equilibrium for *IL1B* (all individuals  $p = 0.081$ , cases  $p = 0.741$ , control group  $p = 0.073$ ) and *IL1RN* (all individuals  $p = 0.794$ , cases  $p = 0.867$ , control group  $p = 0.675$ ). Observed genotype frequencies for the *IL-1B:C(-31)T* polymorphism (rs1143627) were: 33.3% T/T ( $n = 88$ ), 43.9% C/T ( $n = 116$ ), 22.7% C/C ( $n = 60$ ) and for alleles: 55.3% T and 44.7% C. The genotype frequencies for the *IL1RN* were 39.0% 1/1 ( $n = 103$ ), 46.2% 1/2 ( $n = 122$ ), 14.8% 2/2 ( $n = 39$ ) and for alleles: 62.1% 1 and 37.9% 2. The *IL1RN* alleles 3 and 4 were rare and their frequencies did not significantly differ between the IS patients and the control group (1.9% vs. 1.6%,  $p = 0.765$  for allele 3 and 0.3% vs. 1.2%,  $p = 0.122$  for allele 4). Baseline characteristics of the study group are shown in Table 1. The results of tests of association of the *IL1RN* and *IL1B* polymorphisms with stroke are summarized in Tables 2 and 3.

**Table 2.** An association of the *IL1RN* polymorphism with stroke under codominant, dominant, and recessive model.

| Model             | Control (n = 117) | %    | Cases (n = 147) | %    | OR   | 95% CI    | p       |
|-------------------|-------------------|------|-----------------|------|------|-----------|---------|
| <b>Codominant</b> |                   |      |                 |      |      |           |         |
| 1/1               | 54                | 46.2 | 49              | 33.3 | 1.00 |           |         |
| 1/2               | 49                | 41.9 | 73              | 49.7 | 1.64 | 0.97 2.79 | 0.647 * |
| 2/2               | 14                | 12.0 | 25              | 17.0 | 1.97 | 0.92 4.21 |         |
| <b>Dominant</b>   |                   |      |                 |      |      |           |         |
| 1/1               | 54                | 46.2 | 49              | 33.3 | 1.00 |           |         |
| 1/2–2/2           | 63                | 53.8 | 98              | 66.7 | 1.71 | 1.04 2.83 | 0.358 * |
| <b>Recessive</b>  |                   |      |                 |      |      |           |         |
| 1/1–1/2           | 103               | 88.0 | 122             | 83.0 | 1.00 |           |         |
| 2/2               | 14                | 12.0 | 25              | 17.0 | 1.51 | 0.75 3.05 | 0.650 * |

\* Adjusted by: age, diabetes mellitus, dyslipidemia.

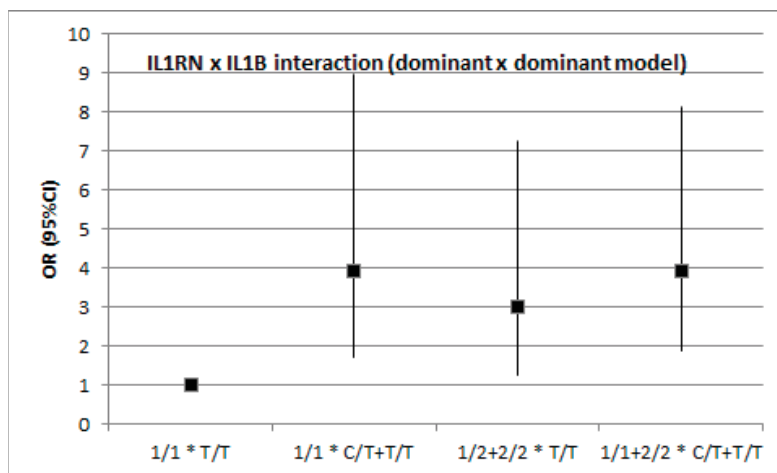
The results of tests for association of the *IL1RN* and *IL1B* polymorphisms with stroke are summarized in Tables 2 and 3. In multivariable modeling, including covariates (age, diabetes mellitus, dyslipidemia), the association of the *ILRN* with stroke was insignificant (Table 2). For the *IL1B* polymorphism, the association under codominant and recessive models was insignificant after adjustment for covariates (age, diabetes mellitus, dyslipidemia), however with the dominant model, the risk of stroke with CT-CC was 2.3 higher than for TT homozygotes (2.30 (1.36–3.87);  $p = 0.020$ ) (Table 3).

**Table 3.** An association of the *IL-1B* polymorphism with stroke under codominant, dominant, and recessive model.

| Model      | Control (n = 117) | %    | Cases (n = 147) | %    | OR   | 95% CI |      | p *     |
|------------|-------------------|------|-----------------|------|------|--------|------|---------|
| Codominant |                   |      |                 |      |      |        |      |         |
| T/T        | 51                | 43.6 | 37              | 25.2 | 1.00 |        |      |         |
| C/T        | 45                | 38.5 | 71              | 48.3 | 2.17 | 1.24   | 3.82 | 0.065 * |
| C/C        | 21                | 17.9 | 39              | 26.5 | 2.56 | 1.30   | 5.05 |         |
| Dominant   |                   |      |                 |      |      |        |      |         |
| T/T        | 51                | 43.6 | 37              | 25.2 | 1.00 |        |      |         |
| C/T-C/C    | 66                | 56.4 | 110             | 74.8 | 2.30 | 1.36   | 3.87 | 0.020 * |
| Recessive  |                   |      |                 |      |      |        |      |         |
| T/T-C/T    | 96                | 82.1 | 108             | 73.5 | 1.00 |        |      |         |
| C/C        | 21                | 17.9 | 39              | 26.5 | 1.65 | 0.91   | 3.00 | 0.322 * |

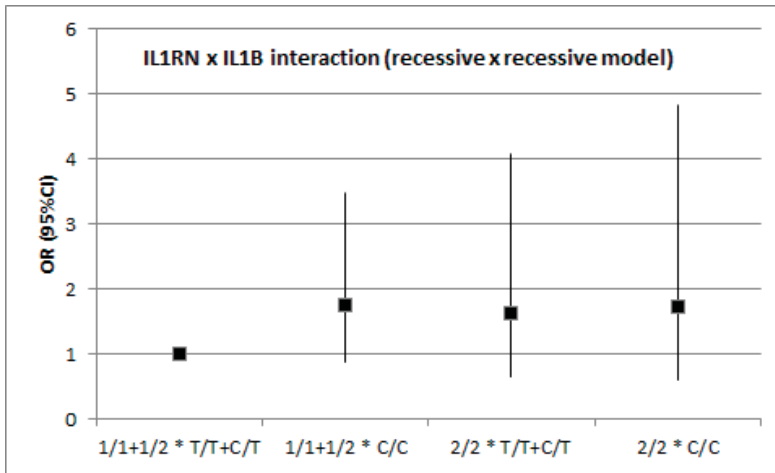
\* Adjusted by: Age, diabetes mellitus, dyslipidemia.

In addition to single-locus analyses, we investigated whether the two genes interacted with respect to the modification of stroke risk (Figures 1 and 2). The analysis was conducted with the assumption of dominant or recessive models for each polymorphism and no evidence was found of gene–gene interaction with respect to IS risk. Although the raw *p* value for the dominant x dominant model was 0.046, it turned out to be non-significant after adjustment for covariates.



**Figure 1.** *IL1RN* × *IL1B* interaction (dominant × dominant model). Raw *p* = 0.046, adjusted *p* = 0.232 (age, diabetes mellitus, dyslipidemia status).





**Figure 2.** *IL1RN* × *IL1B* interaction (recessive × recessive model). Raw  $p = 0.502$ , adjusted  $p = 0.910$  (age, diabetes mellitus, dyslipidemia status).

### 3.2. Association between IS and Genetic Variation in *IL1B* and *IL1RN* by Stroke Subtype (TOAST)

Each stroke subtype, i.e., CEI, SVI, LVI of the TOAST classification, was compared with control subjects (Tables 4 and 5). No significant associations were found between *IL1RN* and stroke under codominant, dominant, and recessive models by stroke subtype according to TOAST classification (Table 4). For the *IL1B* gene, the carriers of the C allele were significantly overrepresented in LVI subtypes compared with controls with (1.99 (1.05–3.79),  $p = 0.036$ ) (Table 5). For the other subtypes, we did not find any significant correlations (Table 5).

**Table 4.** An association of the *IL1RN* polymorphism with stroke under codominant, dominant, and recessive models by stroke subtype (TOAST classification).

| Model      | Control (n = 117) | CEI (n = 25) | OR (95% CI)       | p *   | SVI (n = 38) | OR (95% CI)      | p *   | LVI (n = 68) | OR (95% CI)      | p *   |
|------------|-------------------|--------------|-------------------|-------|--------------|------------------|-------|--------------|------------------|-------|
| Codominant |                   |              |                   |       |              |                  |       |              |                  |       |
| 1/1        | 54 (46.2)         | 6 (24.0)     | 1.00              |       | 13 (34.2)    | 1.00             |       | 25 (36.8)    | 1.00             |       |
| 1/2        | 49 (41.9)         | 14 (56.0)    | 2.57 (0.92–7.21)  |       | 19 (50.0)    | 1.61 (0.72–3.60) |       | 34 (50.0)    | 1.50 (0.79–2.86) |       |
| 2/2        | 14 (12.0)         | 5 (20.0)     | 3.21 (0.85–12.09) | 0.388 | 6 (15.8)     | 1.78 (0.57–5.52) | 0.947 | 9 (13.2)     | 1.39 (0.53–3.63) | 0.974 |
| Dominant   |                   |              |                   |       |              |                  |       |              |                  |       |
| 1/1        | 54 (46.2)         | 6 (24.0)     | 1.00              |       | 13 (34.2)    | 1.00             |       | 25 (36.8)    | 1.00             |       |
| 1/2–2/2    | 63 (53.8)         | 19 (76.0)    | 2.71 (1.01–7.28)  | 0.261 | 25 (65.8)    | 1.65 (0.77–3.53) | 0.854 | 43 (63.2)    | 1.47 (0.80–2.72) | 0.982 |
| Recessive  |                   |              |                   |       |              |                  |       |              |                  |       |
| 1/1–1/2    | 103 (88.0)        | 20 (80.0)    | 1.00              |       | 32 (84.2)    | 1.00             |       | 59 (86.8)    | 1.00             |       |
| 2/2        | 14 (12.0)         | 5 (20.0)     | 1.84 (0.60–5.68)  | 0.695 | 6 (15.8)     | 1.38 (0.49–3.88) | 0.752 | 9 (13.2)     | 1.12 (0.46–2.75) | 0.823 |

\* Adjusted by: Age, diabetes mellitus, dyslipidemia.

**Table 5.** An association of the *IL1B* polymorphism with stroke under codominant, dominant, and recessive models by stroke subtype (TOAST classification).

| Model      | Control (n = 117) | CEI (n = 25) | OR (95% CI)       | p *   | SVI (n = 38) | OR (95% CI)      | p *   | LVI (n = 68) | OR (95% CI)      | p *   |
|------------|-------------------|--------------|-------------------|-------|--------------|------------------|-------|--------------|------------------|-------|
| Codominant |                   |              |                   |       |              |                  |       |              |                  |       |
| T/T        | 51 (43.6)         | 5 (20.0)     | 1.00              |       | 8 (21.1)     | 1.00             |       | 19 (27.9)    | 1.00             |       |
| C/T        | 45 (38.5)         | 14 (56.0)    | 3.17 (1.06–9.50)  |       | 19 (50.0)    | 2.69 (1.07–6.74) |       | 33 (48.5)    | 1.97 (0.99–3.93) |       |
| C/C        | 21 (17.9)         | 6 (24.0)     | 2.91 (0.80–10.60) | 0.074 | 11 (28.9)    | 3.34 (1.18–9.48) | 0.236 | 16 (23.5)    | 2.05 (0.89–4.72) | 0.069 |
| Dominant   |                   |              |                   |       |              |                  |       |              |                  |       |
| T/T        | 51 (43.6)         | 5 (20.0)     | 1.00              |       | 8 (21.1)     | 1.00             |       | 19 (27.9)    | 1.00             |       |
| C/T–C/C    | 66 (56.4)         | 20 (80.0)    | 3.09 (1.09–8.80)  | 0.305 | 30 (78.9)    | 2.90 (1.22–6.86) | 0.106 | 49 (72.1)    | 1.99 (1.05–3.79) | 0.036 |
| Recessive  |                   |              |                   |       |              |                  |       |              |                  |       |
| T/T–C/T    | 96 (82.1)         | 19 (76.0)    | 1.00              |       | 27 (71.1)    | 1.00             |       | 52 (76.5)    | 1.00             |       |
| C/C        | 21 (17.9)         | 6 (24.0)     | 1.44 (0.51–4.05)  | 0.225 | 11 (28.9)    | 1.86 (0.80–4.34) | 0.874 | 16 (23.5)    | 1.41 (0.68–2.93) | 0.993 |

\* Adjusted by: Age, diabetes mellitus, dyslipidemia.

#### 4. Discussion

Ischemic stroke is a disease of complex etiology, and it is generally accepted that both environmental and genetic factors play a crucial role in the development of the disease. Although there are many studies which have indicated that inflammatory cytokines and their genetic polymorphisms play an important role in the pathogenesis of IS, the results are still controversial. In this study, two important polymorphisms of the IL1 cluster were investigated for their association with stroke. We have not shown any connection between genetic variants of *ILRN* VNTR with overall stroke or subtypes. This is in line with previous studies on IS [20]. In contrast some studies, have reported an association of the *ILRN* with stroke [21]. This inconsistency could be explained with the rather relatively small size of study groups than differences between populations. However, we have shown that the *IL1B*:T(-31)C polymorphism is independently associated with overall IS and subtype of IS in the homogeneous Polish population.

For the *IL1B*:C(-31)T polymorphism, we found that carriers of the C allele were associated with a higher risk of overall stroke. Moreover, we found that CT/CC genotypes can increase the risk of subtypes of IS. The relationship of *IL1B* polymorphism and stroke has been examined in several previous studies and our results remain in line with those presented so far. Extensive studies on the *IL1B* polymorphism at position -511 have indicated that *IL1B*:511T carriers had higher levels of IL1B than *IL1B*:511C and were associated with increased risk of IS [22]. It is also worth mentioning the study by Iacoviello et al. [23] which is the main source of research heterogeneity because this study reported that TT homozygotes of *IL1B*:511 are associated with a decreased risk of IS. However, patients in this study were relatively young. Thus, the association between *IL1B* polymorphism and IL1B production still remains controversial. A recent study has documented that IL1B mRNA was increased in the TT genotype [24] whereas Hall et al. [25] showed a 2–3-fold increase in IL1B protein secretion in subjects with the T allele at -511 and the C allele at -31.

We found no interaction between *ILRN* and *IL1B* concerning IS risk assuming the dominant x dominant and recessive x recessive models. The gene–gene interaction was analyzed using a linear model in which only two (and the same) inheritance patterns for each locus were considered. This approach could possibly have less power as compared with a non-parametric and model-free multifactor dimensionality reduction method that has been shown to have reasonable power to detect epistasis [26].

The polymorphism of *IL1B* at -31 is tightly linked with the polymorphism at -511. However, it is unclear whether the C or T allele of *IL1B* -31 is associated with high expression. We have not measured the plasma IL1B and IL1RA levels and this can be considered as a limitation of our study. It is worth emphasizing that genetic variations of *IL1B* -31 and von Willebrand factor are associated with the recanalization rate of fibrinolysis with tissue-type plasminogen activator, and thus with treatment efficacy [27]. As the authors report, the mechanisms by which these SNPs modulate recanalization could be related to homeostasis modulation by modification of coagulation factor activities. Manso et al. [28] also tested the inflammatory genes *IL1B*, interleukin 6 (*IL6*), myeloperoxidase (*MPO*), and *TNF* with stroke susceptibility, and demonstrated that only two SNPs of *IL6* and one *MPO* single-nucleotide polymorphism were significantly associated with stroke risk in their sample. Probably, an observed lesser genetic influence is related to widespread classical risk factors, or lifestyle. Some studies have reported that *IL1B*:C(-31)T and *ILRN*:VNTR polymorphisms are significantly correlated with the development of CAD, and thus atherosclerosis process [3,29]. However, other studies conducted in different populations have not confirmed this and these associations still remain controversial. In our previous study we showed no association between polymorphisms of *IL1B*:C(-31)T/*ILRN* (VNTR) or their haplotypes and CAD in the Polish population [30], which may suggest lesser importance of genetic factors in the development of atherosclerotic diseases in our population.

Nevertheless, IL1B is a potent pro-inflammatory cytokine and plays a major role in the development of both inflammation processes and thrombosis. It is hypothesized that in IS development, IL1B is involved in thrombus formation rather than in atherosclerosis progression because IL1

induces tissue factor and plasminogen activator inhibitor type 1 gene expression [31]. However, this cytokine can induce complex biological effects by the regulation of gene expression of multiple cell types [32]. Therefore, more mechanisms should be considered in the development of IS, although both inflammatory and prothrombotic mechanisms seem to play a fundamental role. The formation of a thrombus leading to occlusion of a vessel is the endpoint which is influenced by many factors (genes, hypertension, hyperlipidemia, diabetes mellitus, etc.), and the gene–environment interaction can be of great importance. Thus, the *IL1B* C allele may not be associated directly with IS per se, but could be modulating cytokines in the inflammatory processes that affect the development of atherosclerosis resulting in IS. It has been shown that genetic variants of *IL1B* that predict higher inflammatory phenotypes modify the risk of Lp(a) in mediating long-term cardiovascular events [33]. These results indicate that *IL1B* can modify many pathways involved in the development of atherosclerosis and thus, cardiovascular events. Additionally, some studies have also reported that the risk of stroke increases with the number of high-risk genotypes in proinflammatory gene polymorphisms carried by an individual, thus suggesting that such polymorphisms may act synergistically [34]. We have evaluated genetic variants of only two genes which are crucial in inflammation. IS is a very complicated and extremely complex disease and its pathomechanism is still not fully explained. It is not yet known how many risk factors in the development of atherosclerosis could be modulated by the genetic variants of *IL1B*, which acts as a key regulator in inflammatory processes.

In different populations with varying intensity of classical risk factors, the impact of genetics may be found to have a variable extent. Previous studies have reported that ethnicity or regional locations are very important in the determination of environmental risk factors [35]. One of advantages of the present study is that it included a well-characterized and homogeneous patients' group (from the northwest region of Poland), but it should be emphasized that our society has strongly expressed classical risk factors for IS. It should be noted that observed differences between the study group and the controls could interfere with the assessment of the role for the *IL1RN* polymorphism in the development of IS. Diabetes, which is a widely recognized risk factor for the development of atherosclerosis, has been more frequent in IS patients, while dyslipidemia has been less frequent. However, the IS patients had been already treated (b-blocker, statin, etc.) which could have downregulated to some extent the inflammatory process agents, while the control group comprised subjects without treatment for this. Moreover, the control group was slightly younger than the IS group, which may have had some impact on the obtained results, and could be considered another limitation of our study. The population included in the study was homogeneous (monoethnic, Polish) and, therefore, our data need to be confirmed in different ethnic groups.

## 5. Conclusions

The complex interplay between genetic backgrounds, clinical and lifestyle factors, and the environment may ultimately lead to the development of stroke. In the present study, we present supporting evidence for a role of the *IL1B* inflammatory gene in stroke susceptibility. Our findings confirm previous genetic observations, highlighting the need for further functional studies, particularly in view of the possible utility of *IL1B* as a diagnostic biomarker for stroke.

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Article

# Detrimental Impact of Chronic Obstructive Pulmonary Disease in Atrial Fibrillation: New Insights from Umbria Atrial Fibrillation Registry

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**Abstract:** *Background and objectives:* Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide. Among extra-pulmonary manifestations of COPD, atrial fibrillation (AF) is commonly observed in clinical practice. The coexistence of COPD and AF significantly affects the risk of cardiovascular morbidity and mortality. Nonetheless, the mechanisms explaining the increased risk of vascular events and death associated to the presence of COPD in AF are complex and not completely understood. We analyzed data from an Italian network database to identify markers and mediators of increased vascular risk among subjects with AF and COPD. *Materials and Methods:* Cross-sectional analysis of the Umbria Atrial Fibrillation (Umbria-FA) Registry, a multicenter, observational, prospective on-going registry of patients with non-valvular AF. Of the 2205 patients actually recruited, 2159 had complete clinical data and were included in the analysis. *Results:* the proportion of patients with COPD was 15.6%. COPD patients had a larger proportion of permanent AF when compared to the control group (49.1% vs. 34.6%,  $p < 0.0001$ ) and were more likely to be obese and current smokers. Other cardiovascular risk factors including chronic kidney disease (CKD), peripheral artery disease and subclinical atherosclerosis were more prevalent in COPD patients (all  $p < 0.0001$ ). COPD was also significantly associated with higher prevalence of previous vascular events and a history of anemia (all  $p < 0.0001$ ). The thromboembolic and bleeding risk, as reflected by the CHA<sub>2</sub>DS<sub>2</sub>-VASc and HAS-BLED scores, were higher in patients with COPD. Patients with COPD were also more likely to have left ventricular (LV) hypertrophy at standard ECG than individuals forming the cohort without COPD ( $p = 0.018$ ). *Conclusions:* AF patients with COPD have a higher risk of vascular complications than AF patients without this lung disease. Our analysis identified markers and mediators of increased risk that can be easily measured in clinical practice, including LV hypertrophy, CKD, anemia, and atherosclerosis of large arteries.

**Keywords:** chronic obstructive pulmonary disease; atrial fibrillation; cardiovascular risk; outcome; prognosis

## 1. Introduction

Chronic obstructive pulmonary disease (COPD) is a major global public health problem, being a leading cause of morbidity and mortality worldwide [1,2]. It is currently rated the fourth most common cause of death and predicted to be the third in the next ten years [2].



Among extra-pulmonary manifestations of COPD, atrial fibrillation (AF) is commonly observed in clinical practice [3,4]. An accumulating body of evidence suggests that COPD is independently associated with this type of arrhythmia [5] and the presence of COPD in AF patients significantly affects outcomes and risk of all-cause mortality [6–10]. In the modern era of anticoagulation therapy, some post-hoc analyses of clinical trials demonstrated that COPD is strongly associated with cardiovascular and non-cardiovascular mortality in AF: data from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial [9] demonstrated that, after multivariable adjustment for confounders, COPD was associated with a higher risk of all-cause mortality (adjusted hazard ratio [HR]: 1.60, 95% confidence interval [CI]: 1.36 to 1.88,  $p < 0.001$ ) and both cardiovascular and non-cardiovascular mortality. Similarly, the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET AF) [10] showed that COPD was independently associated with higher mortality, suggesting that optimal prevention and treatment of COPD may improve survival.

Nonetheless, the pathophysiological mechanisms underlying the increased risk of vascular events and death associated to the presence of COPD in AF are complex and not completely understood [7]. There is also a paucity of information on risk factors and mediators of vascular events in patients with COPD and AF in most studies [5].

To this purpose, we performed a cross-sectional analysis on a large cohort of AF patients to investigate the interplays between these two conditions. Specifically, we used the unique features of our Italian network database (see methods) to further elucidate and identify markers and mediators of increased vascular risk among subjects with AF and COPD.

## 2. Materials and Methods

### 2.1. Population

We performed a cross-sectional analysis of the Umbria Atrial Fibrillation (Umbria-FA) Registry approved by CEAS-Umbria on date 20 September 2012—Number 1976/12, a multicenter, observational, prospective on-going registry of patients with non-valvular AF (see Appendix A).

Details of this Registry have been reported elsewhere [11]. Enrollment is being performed in 22 Hospitals or out-patient facilities in the setting of the Italian Health System, beginning in January 2013. All patients sign a written informed consent and the study is conducted in accordance with the EU Note for Guidance on Good Clinical Practice CPMP/ECH/135/95 and the Declaration of Helsinki. Each participating centre (see Appendix A) obtained the approval by the Ethics Committees at regional-local levels.

For enrollment, patients must be affected by AF at entry into the Registry or, in case of paroxysmal or persistent AF currently in sinus rhythm, by evidence of AF within one year before entry (standard ECG, ECG-Holter monitoring, or pacemaker diagnostics are also accepted for diagnosis of AF) [11].

Our Italian Network database on AF has the potential to evaluate in detail the key features of AF patients and major gaps in the Guidelines [12,13] implementation in clinical practice, when compared to other registries. Indeed, the initial evaluation of Umbria-FA Registry include a detailed clinical examination, 12-lead electrocardiogram (ECG), laboratory tests and, when feasible, an echocardiographic study.

Based on characteristics of AF episodes, five types of AF are distinguished: first diagnosed, paroxysmal, persistent, long-standing persistent, and permanent AF [12,13]. Standard 12-lead ECG is recorded during brief end-expiratory apnea and left ventricular (LV) hypertrophy at ECG is diagnosed using the BMI-corrected Perugia criterion [14].

The presence of COPD was defined according to documented medical history, as collected by physicians at study site-level. This assessment was performed by any physician during the clinical interview with the patient and by searching through medical records [1]. As for other risk factors, Investigators were asked to follow international guidelines to define COPD [1].

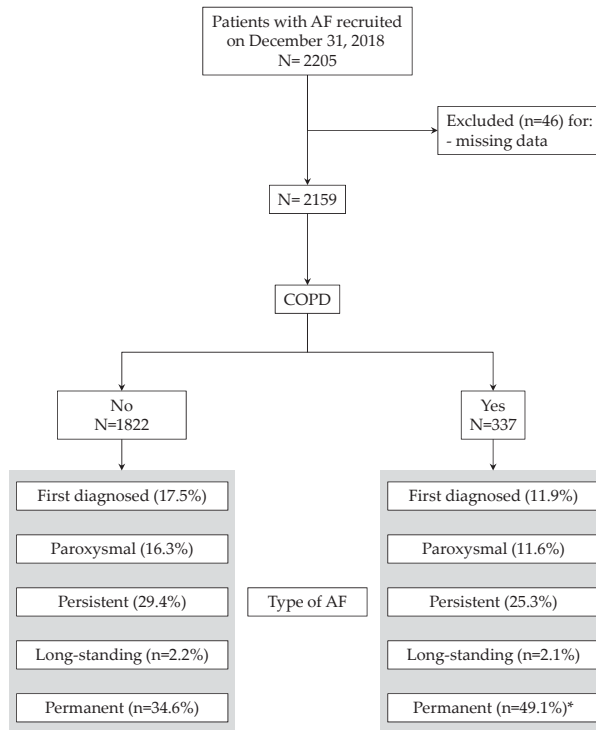
2.2. Statistical Analysis

We used STATA 14 (StataCorp, College Station, TX, USA) and R software version 3 (R Foundation for Statistical Computing, Vienna, Austria). Data are presented as mean ± standard deviation (SD) for continuous variables and proportions for categorical variables. Differences in proportions between groups were analyzed using the  $\chi^2$  test. Mean values of variables were compared by independent sample t-test. In 2-tailed tests,  $p$  values < 0.05 were considered statistically significant.

3. Results

Of the 2205 patients recruited on 31 October 2018 in the Umbria-AF Registry, 2159 had complete clinical data (Figure 1) and were included in the final analysis. The proportion of patients with COPD was 15.6% with a mean age equal to  $79.2 \pm 8.4$  (median: 77). Figure 1 also summarizes the types of AF in the two groups: as depicted, COPD patients had a larger proportion of permanent AF (49.1% vs. 34.6%,  $p < 0.0001$ ). The main characteristics of recruited patients (including risk factors, comorbid conditions and previous vascular events in the two groups) are shown in Table 1.

Patients with COPD were more likely to be obese and current smokers. While hypertension showed a similar prevalence among the two groups, other cardiovascular risk factors (including diabetes and chronic kidney disease (CKD)) were more prevalent in COPD patients (all  $p < 0.0001$ ). Prevalence of patients with established peripheral artery disease (PAD) was 13.9% in the COPD group and 4.7% in the control group ( $p < 0.0001$ ). Subclinical atherosclerosis of large arteries was present in 15% of patients with COPD and 8% in the control group ( $p < 0.0001$ ).



**Figure 1.** Flow chart of patients through the study. Types of atrial fibrillation are also depicted. \*  $p < 0.0001$  vs. patients without chronic obstructive pulmonary disease (COPD).

**Table 1.** Baseline characteristics of patients included in the analysis.

| Variable                             | Overall<br>(n = 2159) | COPD        |                | p       |
|--------------------------------------|-----------------------|-------------|----------------|---------|
|                                      |                       | No (1822)   | Yes (n = 3 37) |         |
| Age (years)                          | 75.6 ± 11.2           | 74.9 ± 11.5 | 79.2 ± 8.4     | <0.0001 |
| Sex (female, %)                      | 44.5                  | 46.3        | 34.7           | 0.0001  |
| BMI (Kg/m <sup>2</sup> )             | 26.8 ± 13.7           | 26.5 ± 11.9 | 28.5 ± 20.9    | 0.0153  |
| Systolic BP (mmHg)                   | 130 ± 18              | 131 ± 18    | 127 ± 16       | 0.0016  |
| Diastolic BP (mmHg)                  | 77 ± 11               | 77 ± 11     | 75 ± 11        | 0.0008  |
| Pulse pressure (mmHg)                | 53 ± 15               | 53 ± 15     | 52 ± 15        | 0.1960  |
| Heart rate (b.p.m.)                  | 78 ± 22               | 77 ± 21     | 82 ± 23        | 0.0037  |
| Risk factors and comorbid conditions |                       |             |                |         |
| Current smoker (%)                   | 6.7                   | 5.8         | 11.6           | <0.0001 |
| Hypertension (%)                     | 80.9                  | 81.2        | 79.8           | 0.561   |
| Diabetes (%)                         | 19.7                  | 18.4        | 26.7           | <0.0001 |
| Chronic kidney disease (%) *         | 29.6                  | 28.1        | 38.0           | <0.0001 |
| Peripheral artery disease (%)        | 6.1                   | 4.7         | 13.9           | <0.0001 |
| Previous vascular events             |                       |             |                |         |
| Coronary artery disease (%)          | 17.8                  | 16.6        | 24.6           | <0.0001 |
| Acute coronary syndrome (%)          | 14.2                  | 13.5        | 17.8           | 0.037   |
| Heart failure (%)                    | 21.1                  | 17.4        | 40.9           | <0.0001 |
| Stroke/Transient ischemic attack (%) | 18.1                  | 17.3        | 22.3           | 0.029   |
| Pulmonary embolism (%)               | 1.5                   | 1.5         | 1.2            | 0.625   |

**Legend:** BMI = body mass index; BP = blood pressure; \* eGFR < 60 mL/min/1.73m<sup>2</sup>.

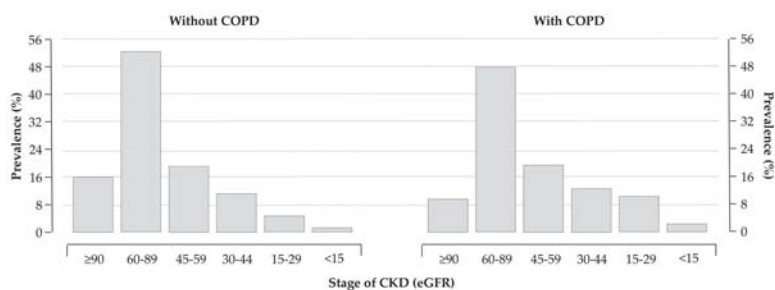
Similar results were obtained for history of previous vascular events: COPD was significantly associated with a higher prevalence of acute coronary syndrome, stroke/transient ischemic attack, and heart failure (HF, all *p* < 0.05). Of note, COPD patients showed an impressive 2.5-fold increase in the frequency of prior HF requiring hospitalization when compared to AF patients without COPD (40.9% vs. 17.4%, *p* < 0.0001). Such different distributions of HF among the two groups translated in lower BP values measured in COPD patients due to LV systolic dysfunction. Indeed, after exclusion of patients with HF from both groups (COPD and non-COPD), none of blood pressure (BP) components showed statistically significant differences between the groups (all *p* ≥ 0.05).

Routine laboratory data are reported in Table 2. As expected, COPD patients had a lower estimated glomerular filtration rate (eGFR, computed using the CKD-EPI formulas [15]) compared to patients without COPD. Distributions of eGFR classes in the two groups are depicted in Figure 2.

**Table 2.** Laboratory data of patients included in the analysis.

| Variable                          | Overall<br>(n = 2159) | COPD        |               | p       |
|-----------------------------------|-----------------------|-------------|---------------|---------|
|                                   |                       | No (1822)   | Yes (n = 337) |         |
| Haemoglobin (g/dL)                | 13.4 ± 4.3            | 13.5 ± 4.6  | 12.9 ± 2.0    | 0.0179  |
| Total cholesterol (mg/dL)         | 170 ± 43              | 172 ± 43    | 162 ± 42      | 0.0013  |
| LDL cholesterol (mg/dL)           | 100 ± 35              | 101 ± 35    | 93 ± 33       | 0.0024  |
| Serum glucose (mg/dL)             | 109 ± 34              | 108 ± 32    | 115 ± 43      | 0.0023  |
| Creatinine (mg/dL)                | 1.08 ± 0.61           | 1.06 ± 0.58 | 1.20 ± 0.76   | 0.0003  |
| BUN (mg/dL)                       | 52 ± 27               | 50 ± 26     | 60 ± 34       | <0.0001 |
| eGFR (mL/min/1.73m <sup>2</sup> ) | 67 ± 22               | 68 ± 22     | 62 ± 23       | 0.0001  |
| Uric acid (mg/dL)                 | 6.7 ± 5.3             | 6.7 ± 5.7   | 6.8 ± 2.8     | 0.7657  |

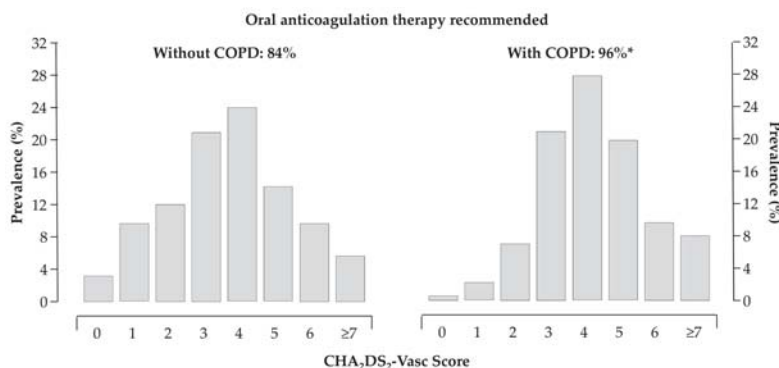
**Legend:** LDL=low density lipoprotein; BUN=blood urea nitrogen; eGFR=glomerular filtration rate estimated by Cockcroft-Gault equation.



**Figure 2.** Distribution of chronic kidney disease (CKD) stages in patients without (left panel) and with (right panel) COPD; 28% and 38% of patients without and with COPD had an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73 m<sup>2</sup>, respectively ( $p < 0.0001$ ).

Of note, COPD influenced the history of previous anemia (24% for COPD patients vs. 14% for patients without COPD,  $p < 0.0001$ ) with mean values of hemoglobin of 12.9 g/dL and 13.5 g/dL for patients with and without COPD at the baseline examination (Table 2), respectively.

The thromboembolic and bleeding risk, as reflected by the CHA<sub>2</sub>DS<sub>2</sub>VASc [16] ( $4.3 \pm 0.09$  vs.  $3.6 \pm 0.04$ ,  $p < 0.0001$ ) and HAS-BLED [17] ( $1.9 \pm 0.06$  vs.  $1.5 \pm 0.02$ ,  $p < 0.0001$ ) scores, were higher in patients with COPD. About 96% of patients with COPD had the recommendation to be treated with oral anticoagulants according to current Guidelines [12,13] (Figure 3).



**Figure 3.** Distribution of CHA<sub>2</sub>DS<sub>2</sub>VASc score in patients without (left panel) and with (right panel) COPD; 84% and 96% of patients without and with COPD had the recommendation to be treated with oral anticoagulants, respectively; \*  $p < 0.05$  vs. patients without COPD.

Among ECG characteristics, 71% of patients with COPD had AF at entry-ECG with a mean heart rate equal to  $82 \pm 23$  b.p.m. In the control group of patients without COPD, 57% showed AF at baseline with a mean heart rate of  $77 \pm 21$  b.p.m. ( $p = 0.0037$  vs. patients with COPD). Interestingly, patients with COPD were more likely to have LV hypertrophy at standard ECG than individuals forming the cohort without COPD (45% vs. 38%,  $p = 0.018$ ).

#### 4. Discussion

COPD is a major cause of morbidity and mortality and its prevalence is steadily rising resulting in a significant economic and social burden [2]. Although COPD is a predominantly respiratory disease, it has been recently recognized as a systemic disease with significant clinical extra-pulmonary effects and manifestations, leading to a worsening cardiovascular prognosis [7].

A recent study conducted in 7441 patients (mean age 64, 49% women, 92% Caucasian) demonstrated that COPD is an independent predictor of AF onset and progression [3,18]. More specifically, the increased likelihood of AF associated to the presence of COPD remained significant ( $p < 0.0001$ ) after adjusting for several confounders including age, gender, tobacco use, obesity, hypertension, coronary artery disease, HF, diabetes, anemia, cancer, CKD, and rate/rhythm control medications [3].

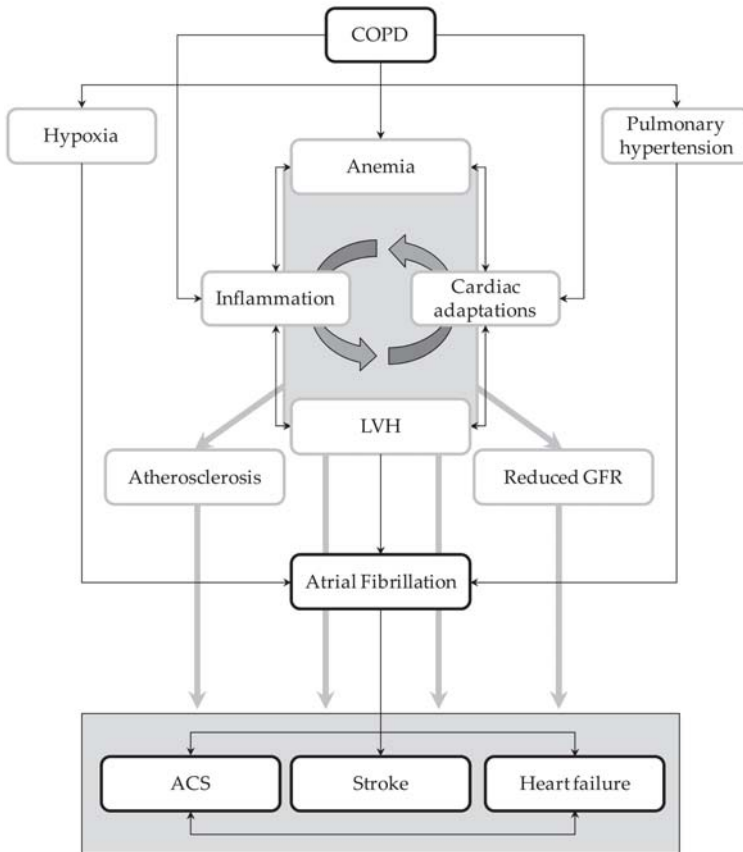
A wide variety of mechanisms for arrhythmias in COPD seems to exist. In particular, experimental models showed that COPD-related inflammatory responses and hypoxia are implicated in AF development and perpetuation as well [19–21]. Furthermore, the coexistence of AF and COPD is a stronger predictor of vascular events than AF only or COPD only [5,7–10]. Huang et al. reported that the presence of COPD in patients with AF is an independent risk factor for one-year all-cause and cardiovascular mortality [22]; similarly, in the EURObservational Research Programme-Atrial Fibrillation General Registry Pilot Phase (EORP-AF Pilot), COPD was highly prevalent in European AF patients, and was associated with higher rates of cardiovascular death, all-cause death, and the composite outcome of any thromboembolic event/bleeding/cardiovascular death [23]. Furthermore, The Atrial Fibrillation in the Emergency Room (AFTER) Study, derived and validated a complex and a simplified model for the prediction of mortality in the emergency department patients with AF. Of note, both the models that included COPD as a risk variable have been shown to predict mortality after an emergency visit for AF [24].

Nonetheless, the relationships between these two disorders and how they simultaneously act in increasing the risk of vascular events are not completely understood. Taking advantage of the unique features of Umbria-AF registry [11], we tried to elucidate in a large cohort of AF patients the potential mechanisms explaining the increased vascular risk related to COPD. Results of our cross-sectional analysis highlighted the notion that AF patients with COPD have a higher risk of cardio- and cerebro-vascular complications than AF patients without this lung disease. Moreover, our analysis identified potential markers and mediators of high vascular risk that can be easily measured in clinical practice. They include LV hypertrophy, reduced renal function, anemia, and atherosclerosis of large arteries. As summarized below, all these conditions play a central part in the prediction and development of vascular complications (Figure 4).

LV hypertrophy is a powerful and independent predictor of all-cause mortality and major cardiac and cerebrovascular events [25,26]. Experimental evidence is accumulating that several factors, which promote progression of atherosclerosis through plaque growth and destabilization can also induce LV hypertrophy by acting on myocyte and interstitium [25,27]. LV hypertrophy may also be a causative factor for myocardial ischemia and reduced pumping performance and arrhythmias [25,28]. In other words, LV hypertrophy is a marker of cardiovascular risk because it reflects and integrates the long-term level of activity of factors inducing progression of atherosclerosis.

In this context, it is worth mentioning that atherosclerosis of large arteries, as reflected by a wide pulse pressure is significantly related to the risk of major cardiovascular events [29–31] and a progressive stiffening of large elastic arteries have been observed in early stages of renal dysfunction [32]. Various studies showed a strong association between the markers of CKD (typically the reduced eGFR) and cardiovascular morbidity and mortality [33–35]; more specifically, eGFR is indirectly related to the elevated probability of death and cardiovascular disease [33–35]. A recent meta-analysis of clinical studies including 7 million participants reported an increased risk of vascular events and all-cause mortality by 20–30% with a 30% decrease in eGFR [34]. It also suggested that around 20% of vascular events among those over 70 years is attributable to renal dysfunction [34]. Importantly, the complex association of CKD with cardiovascular disease is due to clustering of several cardiovascular risk factors, including “traditional risk factors” (i.e., advanced age, hypertension, diabetes mellitus, and dyslipidemia) and “nontraditional risk factors” that are specific to CKD (i.e., volume overload and anemia). Of note, the presence of anemia may lead to adverse cardiovascular consequences. In the Atherosclerosis Risk in Communities study (ARIC), anemia was associated with cardiovascular outcomes [36], and a significant interaction between anemia and the presence of CKD was documented [37,38]. From a

pathophysiological point of view, chronic anemia may increase preload, reduce afterload, and lead to increased cardiac output. In the long term, this may also exacerbate cardiac ischemia as a result of decreased supply or increased demand for oxygen, such as in patients with underlying coronary disease or those with LV hypertrophy, respectively [39].



**Figure 4.** Graphical representation of the potential interplays between atrial fibrillation (AF) and COPD. LVH = left ventricular hypertrophy; ACS = acute coronary syndrome; GFR = glomerular filtration rate.

Taken together, these observations suggest that implications of our results are obvious but clinically relevant at the same time. The elucidation of underlying mechanisms affecting the risk of adverse outcome of AF patients with COPD offers the possibility for better therapeutic options and surveillance strategies. Treatment of AF patients with concomitant COPD should not be the same as those without COPD and physicians need to increase monitoring and early intervention for COPD patients to treat AF.

Our cross-sectional analysis has some limitations. Since white subjects were 99%, caution is needed in extrapolating results to different ethnic groups. Presence or absence of COPD was acknowledged into the electronic case report form reporting the presence/absence of the condition, but with no further details on its severity and lung function testing parameters. The absence of any further details about clinical and severity of COPD is a major limitation. Finally, markers of inflammation are not routinely collected in our Registry. Thus, we are unable to explore the relationships between a pro-inflammatory state and COPD.

## 5. Conclusions

COPD is one of the leading causes of mortality and morbidity worldwide. COPD is an independent risk factor for AF. The coexistence of COPD and AF significantly affects the risk of mortality and vascular events. Thus, it is important to understand the relationship between these two disorders and appropriately manage both these co-morbidities for improved outcomes.

Our cross-sectional analysis produced several findings. First, we highlighted the point that the estimated risk of cardiovascular complications is markedly higher in AF patients with COPD than in those without COPD. Second, we identified markers and mediators of high vascular risk that can be easily measured in clinical practice. Finally, our analysis suggests that specific surveillance strategies and early intervention for COPD patients with AF should be urgently implemented.

**Author Contributions:** Conceptualization, F.A., G.R., M.T. and P.V.; Data curation, F.A., G.R., M.T., A.A. and P.V.; Formal analysis, F.A., G.R., M.T. and P.V.; Funding acquisition, P.V.; Investigation, F.A., G.R., M.T., A.A., G.A. and P.V.; Methodology, F.A., G.R., M.T. and P.V.; Project administration, F.A., G.R. and P.V.; Supervision, F.A., G.R. and P.V.; Writing—Original draft, F.A., G.R., M.T. and P.V.; Writing—Review & Editing, F.A., G.R., M.T. and P.V.

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**Conflicts of Interest:** The authors declare no conflict of interest.

## Appendix A

### Umbria-Atrial fibrillation study group ([www.umbriafa.it](http://www.umbriafa.it))

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**No-profit Sponsor:** Fondazione Umbra Cuore e Ipertensione—ONLUS.

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Article

# Left Atrial Function after Atrial Fibrillation Cryoablation Concomitant to Minimally Invasive Mitral Valve Repair: A Pilot Study on Long-Term Results and Clinical Implications

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**Abstract:** *Background and Objectives:* Surgical atrial fibrillation (AF) ablation concomitant to minimally invasive mitral valve repair has been proven to offer improved short- and long-term sinus rhythm (SR) maintenance compared to mitral valve surgery only. The objective of the present study was to explore, by thorough echocardiographic assessment, long-term morphological and functional left atrial (LA) outcomes after this combined surgical procedure. *Materials and Methods:* From October 2006 to November 2015, 48 patients underwent minimally invasive mitral valve repair and concomitant surgical AF cryoablation. *Results:* After  $3.8 \pm 2.2$  years, 30 (71.4%) of those completing the follow-up ( $n = 42$ , 87.5%) presented SR. During follow-up, four (9.5%) patients suffered from cerebrovascular accidents and two of these subjects had a long-standing persistent AF relapse and were in AF at the time of the event, while the other two were in SR. An echocardiographic study focused on LA characteristics was performed in 29 patients (69.0%). Atrial morphology and function (e.g., maximal LA volume indexed to body surface area and total LA emptying fraction derived from volumes) in patients with stable SR ( $60.6 \pm 13.1$  mL/mq and  $25.1 \pm 7.3\%$ ) were significantly better than in those with AF relapses ( $76.8 \pm 16.2$  mL/mq and  $17.5 \pm 7.4\%$ ; respectively,  $p = 0.008$  and  $p = 0.015$ ). At follow-up, patients who suffered from ischemic cerebral events had maximal LA volume indexed to body surface area  $61 \pm 17.8$  mL/mq, with total LA emptying fraction derived from volumes  $23.6 \pm 13.7\%$ ; patients with strokes in SR showed very enlarged LA volume ( $>70$  mL/mq). *Conclusions:* AF cryoablation concomitant with minimally invasive mitral valve repair provides a high rate of SR maintenance and this relates to improved long-term morphological and functional LA outcomes. Further prospective studies are needed to define the cut-off values determining an increase in the risk for thromboembolic complications in patients with restored stable SR.

**Keywords:** atrial fibrillation; surgical cryoablation; left atrial function; minimally invasive mitral valve repair; echocardiography; ischemic cerebral events

## 1. Introduction

Atrial fibrillation (AF) prevalence in patients with indication for mitral valve surgery is about 30–54% [1], it has a strong impact on hemodynamics [2], and it has been demonstrated to significantly affect the mortality rate [3,4].

Concomitant surgical AF ablation to video-assisted minimally invasive mitral valve surgery (MIMVS) [5–7] has been proven to offer improved short- and long-term sinus rhythm (SR) maintenance compared to patients undergoing mitral valve surgery only (73% versus 43% of SR maintenance at 12 months' follow-up) [8] without increasing complications [9,10].

Therefore, SR maintenance seems achievable, but does this reflect in an improved atrial function? It has been demonstrated that SR maintenance is related to reduced left atrial volumes [11], but little is known about left atrial (LA) functional properties in this clinical setting. In fact, an organized atrial activity is not always accompanied by an effective mechanical atrial contraction [12].

In patients with underlying mitral valve diseases, atrial remodeling is remarkable: longstanding volume overload to the LA results in chronic stretching and atrophy of atrial myocytes, interstitial fibrosis, overall thinning, and dilatation of the LA wall, which may relate to functional alterations despite the underlying electrical activity.

To date, however, it remains unknown to which degree “the residual atrial function” after a successful AF ablation predicts clinical outcome. For example, which level of contractility is required to avoid the increased thromboembolic risk of a “static” LA, despite SR?

The aim of the present study was therefore to describe, by a thorough echocardiographic assessment, long term LA morphology and function in patients submitted to surgical ablation of persistent/long-term persistent AF concomitant to MIMVS.

## 2. Materials and Methods

### 2.1. Surgical Procedure

According to current guidelines, patients referred to our Cardiac Surgery Division for mitral valve disease and AF resistant to antiarrhythmic therapy, when technically feasible, were proposed video-assisted MIMVS via right mini-thoracotomy through the fourth intercostal space and concomitant left sided AF cryoablation. All enrolled patients were retrospectively identified, starting since October 2006. Patients that had already performed a cardiac surgical procedure or a previous transcatheter AF ablation were not included in this series. Each patient in our study signed a written informed consent for inclusion. The study was conducted in accordance with the Declaration of Helsinki, was observational and retrospective, did not add treatment or modify conventional surgical procedure for the specific clinical indication and was approved by the local Institutional Review Board (Project Identification “CryoMIMS—Concomitant Cryoablation to Video-assisted Minimally INvasive Mitral Valve Surgery”, code 9718; date of approval 1 February 2016).

Surgical technique has already been described [13].

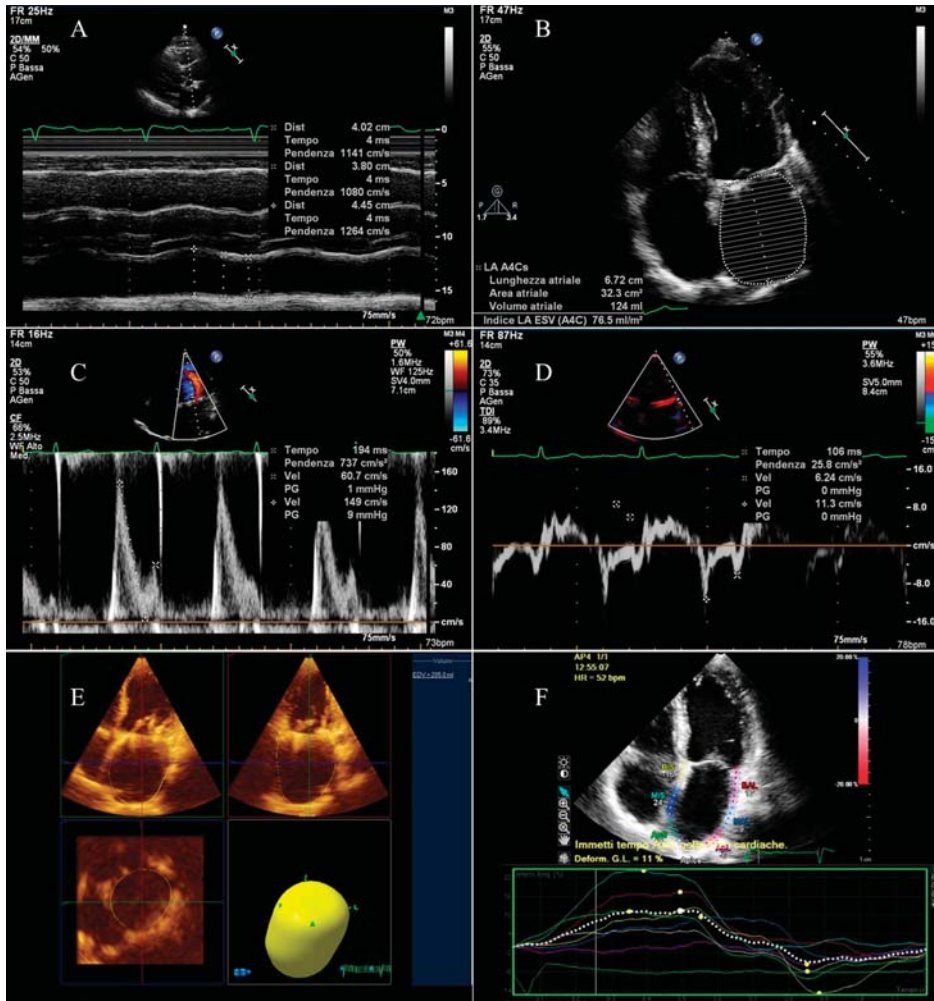
Concomitant left sided AF cryoablation (Argon based Cryomaze, Cryoflex Medtronic, Minneapolis, MN, USA) consisted of isolation of the pulmonary veins (PVs) and of the posterior LA wall between the veins by a “U” encircling cryolesion connected to the surgical paraseptal LA incision performed for mitral exposure, eventually creating the so-called “box lesion”. In addition, a linear cryolesion was performed from the previously created box lesion to the mitral valve annulus to block conduction across the left atrial isthmus (“mitral line”) [6,14]. The surgical procedure performed was the same in every patient included in the study.

### 2.2. Echocardiographic Analysis

Complete echocardiographic assessment was performed in patients undergoing mitral valve repair by the MIMVS approach and concomitant left sided AF cryoablation. The echocardiographic assessment was performed at  $4.0 \pm 2.1$  years after the surgical procedure. Subjects who underwent

mitral valve replacement with biological or mechanical prosthesis were excluded due to distortions related to the presence of the prosthetic scaffold.

Echocardiographic scans were performed by a Philips ultrasound system (iE33 xMATRIX, Andover, MA, USA) with S5-1 sector array probe and X3-1 3D probe. All the examinations were carried out by the same operator. Standard measurements were computed based on the American Society of Echocardiography guidelines. Maximum left atrial diameter (LAD max), minimum (LAD min) and at the beginning of atrial contraction (LAD pre-A) antero-posterior diameters were measured in the parasternal long axis view by either B-mode or M-mode technique (Figure 1A).



**Figure 1.** Echocardiographic evaluation of left atrial function: (A) measurement of antero-posterior diameters; (B) evaluations of areas and volumes and measurement of maximum supero-inferior diameter; (C) measurement of transmitral peak velocity of the late filling wave (A wave); (D) measurement of lateral mitral annulus peak velocity related to atrial contraction (a' wave) and evaluation of atrial conduction delay; (E) calculation of maximum 3D volume; (F) evaluation of global longitudinal atrial strain.

The apical four chamber view was used to measure maximum left atrial supero-inferior diameter (Figure 1B).

The left atrial volumes were evaluated by modified Simpson's method using the apical four chamber view at the tele-systolic frame preceding the mitral valve opening (maximum volume, LAV max), at the tele-diastolic frame preceding mitral valve closure (minimum volume, LAV min), and at the beginning of the P wave for the subjects not in AF at the moment of the exam (pre A volume, LAV pre-A) (Figure 1B).

Volumes were subsequently indexed on the body surface area.

From the above-mentioned linear measurements and volumes, the following parameters defining different components of LA function were calculated:

- Left atrial active emptying fraction, related to the LA booster pump function;
- Left atrial passive emptying fraction, describing the LA conduit function;
- Left atrial total emptying fraction, defining the LA reservoir function.

Similarly, the LA areas (maximal, minimal, and at the beginning of the P wave) were measured (Figure 1B). The LA ejection fraction was calculated from maximal and minimal areas, being reduced if  $\leq 45\%$  [15].

Left atrial 3D maximum volume was calculated using the QLAB-3D Quantification (3DQ) Advanced application (Figure 1E).

The transmitral flow velocity was measured by pulsed Doppler echocardiography. Peak velocity of the early filling wave (E wave) and of the late filling wave (A wave) were determined (Figure 1C), considering a peak A wave velocity  $\geq 10$  cm/s an indicator of the presence of some atrial contraction [16].

The lateral and septal mitral annulus peak velocities related to early relaxation (e' wave) and to atrial contraction (a' wave) were evaluated by tissue Doppler imaging (TDI, Figure 1D). A TDI a'  $\leq 7$  cm/s was considered an index of anomalous LA active contractile function [17].

Furthermore, atrial conduction time was measured: the PA-TDI interval was calculated, defined as the time interval between the beginning of the P wave and the TDI a' wave (Figure 1D). The standard deviation of PA-TDI measurements performed on all segments was also calculated for every single patient.

Eventually, LA global longitudinal strain by two-dimensional speckle tracking was calculated for every patient by QLAB CMQ Cardiac Motion Quantification (Figure 1F).

### 2.3. Clinical Follow-Up and Event Definition

After discharge patients were followed by outpatient visits, including clinical examinations and ECG at 3, 6, and 12 months and then yearly. At least once a year, 24 h ECG Holter monitoring was performed. In case of symptoms recurrence between follow-up visits, patients were reassessed by clinical examination, ECG, and Holter monitoring. Electrophysiological study and transcatheter AF ablation were performed when indicated. All patients in the study were followed for at least six months.

A blanking period of three months was considered; following this interval any AF episode, persistent or paroxysmal, was accounted as an event.

### 2.4. Statistical Analysis

Categorical variables are reported as counts and percentages, while continuous variables as means and standard deviations (SDs). Correlations between parameters and study groups were tested in cross tabulation tables by means of the Pearson Chi-Square or Fisher's exact test and by one-way ANOVA, respectively, for categorical and continuous variables. McNemar's test was used on paired categorical variables. Kaplan Meier curves were computed to describe AF free survival over time. A two-sided  $p$ -value  $< 0.05$  was considered statistically significant; all analyses were performed on SPSS 20.0 (IBM Corp., Armonk, NY, USA).

### 3. Results

From October 2006 to November 2015, 48 patients were submitted to minimally invasive mitral valve repair and concomitant AF cryoablation. The baseline characteristics of the study population are listed in Table 1.

**Table 1.** Preoperative characteristics of the study population stratified by AF relapses at follow-up. (AF, atrial fibrillation; AP, antero-posterior; BMI, body mass index; BSA, body surface area; COPD, chronic obstructive pulmonary disease; LS, long-standing; MV, mitral valve; NYHA, New York Heart Association functional class; PAPs, systolic pulmonary artery pressure; SI, supero-inferior; SR, sinus rhythm; TV, tricuspid valve).

|   | N = 48          | AF Relapse<br>(N = 12/42 28.6%) | SR Maintenance<br>(N = 30/42 71.4%) | p-Value |
|---|-----------------|---------------------------------|-------------------------------------|---------|
| Age (years)   | 67.7 ± 9.8      | 69.0 ± 6.9                      | 66.7 ± 11.3                         | 0.516   |
| Male gender (N,%)                                   | 31 (64.6%)      | 5 (41.7%)                       | 20 (66.7%)                          | 0.127   |
| NYHA class ≥III (N,%)                               | 31 (64.6%)      | 10 (83.3%)                      | 17 (56.7%)                          | 0.054   |
| BSA (mq)  | 1.8 ± 0.19      | 1.78 ± 0.21                     | 1.82 ± 0.19                         | 0.502   |
| Obesity (BMI > 30) (N,%)                            | 14 (29.2%)      | 4 (33.3%)                       | 9 (30.0%)                           | 0.619   |
| COPD (N,%)  | 8 (16.7%)       | 2 (16.7%)                       | 5 (16.7%)                           | 0.615   |
| Hypertension (N,%)                                  | 32 (66.7%)      | 9 (75.0%)                       | 21 (70.0%)                          | 0.496   |
| Diabetes (N,%)                                      | 5 (10.4%)       | 1 (8.3%)                        | 4 (13.3%)                           | 0.488   |
| Dysthyroidism (N,%)                                 | 11 (22.9%)      | 2 (16.7%)                       | 9 (30.0%)                           | 0.231   |
| Previous cerebrovascular accidents (N,%)            | 5 (10.4%)       | 1 (8.3%)                        | 4 (13.3%)                           | 0.488   |
| CHA2DS2 score                                       | 2.29 ± 1.17     | 2.12 ± 0.93                     | 2.33 ± 1.27                         | 0.542   |
| CHA2DS2VASc score                                   | 3.41 ± 1.52     | 3.47 ± 1.28                     | 3.37 ± 1.63                         | 0.825   |
| Antiarrhythmic therapy at the time of surgery (N,%) | 17 (35.4%)      | 5 (41.7%)                       | 12 (40.0%)                          | 0.473   |
| Type of AF  |                 |                                 |                                     |         |
| Paroxysmal (N,%)                                    | 7 (14.6%)       | 0 (0.0%)                        | 7 (23.3%)                           | 0.001   |
| Persistent/LS persistent (N%)                       | 40 (83.3%)      | 12 (100%)                       | 22 (73.3%)                          |         |
| AF duration (days)                                  | 1077.6 ± 2052.4 | 1347.9 ± 2406.3                 | 550.4 ± 849.9                       | 0.127   |
| Left ventricular ejection fraction (%)              | 57.1 ± 10.5     | 57.5 ± 10.1                     | 57.6 ± 11.0                         | 0.984   |
| Etiology of MV disease                              |                 |                                 |                                     |         |
| Degenerative  | 32 (66.7%)      | 7 (58.3%)                       | 22 (73.3%)                          | 0.289   |
| Rheumatic   | 1 (2.1%)        | 1 (8.3%)                        | 0 (0.0%)                            |         |
| Functional  | 13 (27.1%)      | 4 (33.3%)                       | 6 (20.0%)                           |         |
| Left atrial AP diameter (mm)                        | 50.9 ± 10.0     | 51.1 ± 7.0                      | 51.8 ± 12.1                         | 0.899   |
| Left atrial SI diameter (mm)                        | 65.5 ± 9.1      | 68.3 ± 10.4                     | 66.6 ± 8.1                          | 0.754   |
| PAPs (mmHg)   | 43.2 ± 14.1     | 42.9 ± 12.0                     | 44.1 ± 15.8                         | 0.822   |

Twenty (41.7%) patients underwent simple valve repair while 28 (58.3%) were submitted to complex valve repair. Seven subjects (14.6%) received concomitant tricuspid valve surgery. Only one procedure was electively converted to full sternotomy (2.1%) due to unexpected severe pleural adhesions. Total clamp time was 99.5 ± 25.6 min. There was no reopening for any cause.

About one third of the study population (18, 37.5%) suffered AF relapses during hospitalization, while 39 (81.3%) patients were discharged in SR. One patient (2.1%) required PM implantation in the subacute phase. Early mortality was 2.1% (one patient died due to respiratory complications following cardiac arrest resuscitated in the ward).

By April 2016, 42 (87.5%) patients completed the follow-up after a mean of 3.8 ± 2.2 years from the procedure. The study flow chart is depicted in Figure 2.

Except the patient who died few days after surgery, the remaining four deaths were not due to cardiovascular causes.

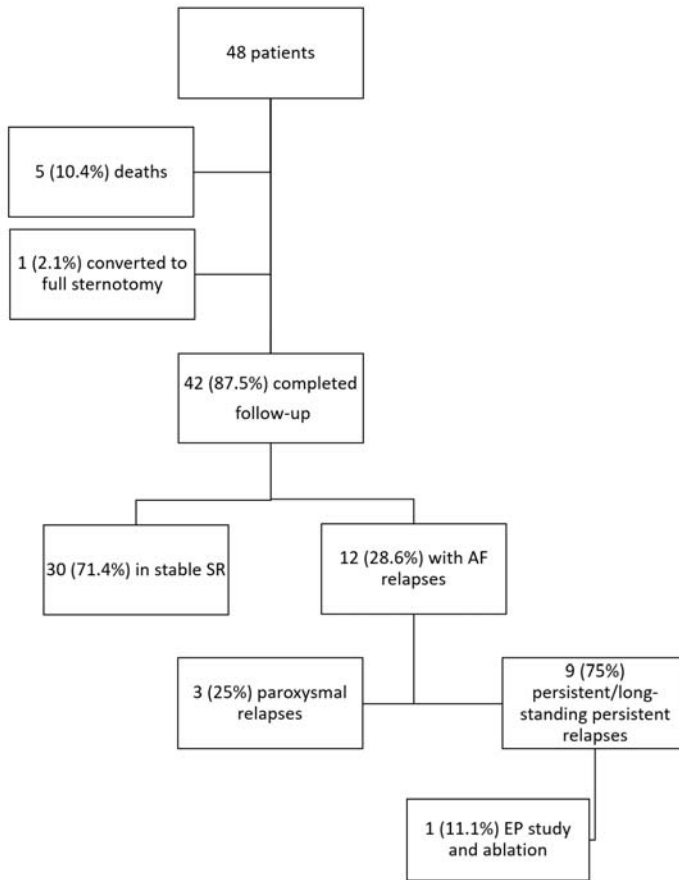
In this time frame no patient required redo surgery.

NYHA functional class showed a significant improvement (NYHA ≥ 3 patients decreased from 64.6% pre-surgery to 4.8% at follow-up, *p* < 0.001). Three (7.1%) patients required PM implantation during follow-up.

Thirty patients (71.4%) maintained SR throughout the follow-up. Out of the 12 (28.6%) patients suffering AF relapses, three (25%) had paroxysmal episodes, while nine (75%) developed persistent AF (Figure 2). Five (41.7%) patients relapsed with an atypical atrial flutter, while the remaining



seven (58.3%) as AF. Out of all patients, one patient (8.3%) suffered symptomatic recurrences and was referred for electrophysiological study and transcatheter redo ablation. Following transcatheter ablation he relapsed with an asymptomatic focal atrial tachycardia. A total of 16 (38%) patients were on antiarrhythmic therapy at follow-up; this percentage did not significantly vary between patients maintaining SR (10, 33%) or suffering AF relapses (6, 50%;  $p = 0.315$ ). Oral anticoagulation was discontinued, instead, in 16 patients (53%) maintaining stable SR at the follow-up end, whereas it was continued in all the patients with documentation of AF relapses.



**Figure 2.** Study flow chart. AF: atrial fibrillation; EP: electrophysiological; SR: sinus rhythm.

Freedom from arrhythmias is reported in Figure 3, showing a 91.7% one-year freedom from AF relapses.

During follow-up, four (9.5%) patients suffered from cerebrovascular accidents; two of these subjects had a long-standing persistent AF relapse and were in AF at the time of the event, while the other two were in SR.

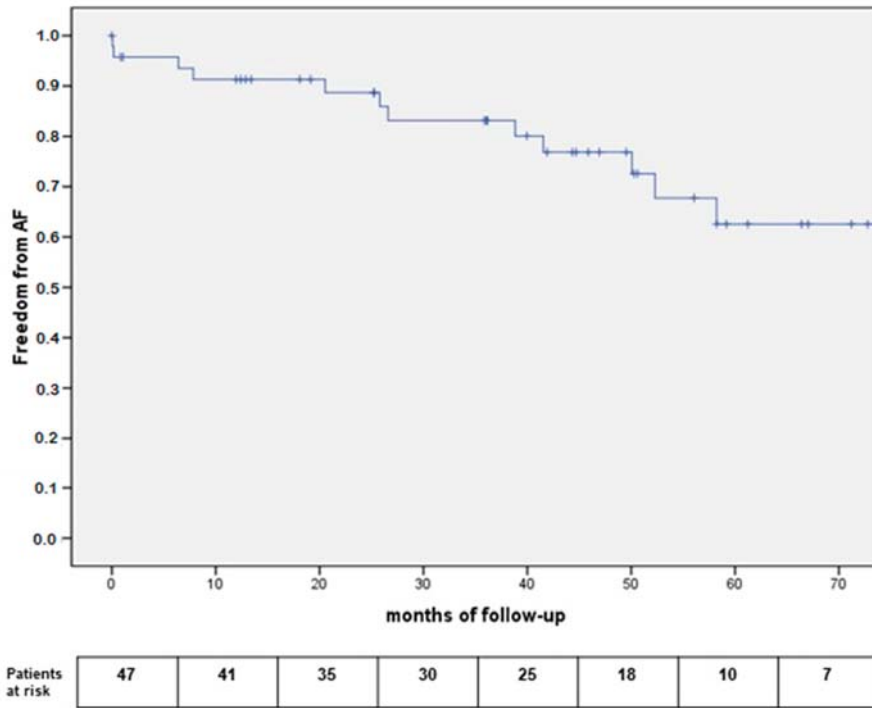


Figure 3. Kaplan Meier curves for freedom from AF relapses.

Thorough LA morphology and function was assessed at follow-up within 29 patients (69.0%) treated by mitral repair; out of the other 19 patients submitted to mitral valve repair who did not undergo the LA focused echocardiographic evaluation, one (2.1%) was converted to full sternotomy, five (10.4%) died (two of cancer, two of other non-cardiac causes, and only one due to respiratory complications following cardiac arrest), and the remaining 13 patients (27.1%) were contacted only by telephone or fax, owing to problems of access due to long distances between the medical center and the patients’ residences, being our hospital a reference center for surgery.

Among the 29 patients, four (13.8%) had paroxysmal AF, whereas 25 (86.2%) had persistent/long-standing persistent AF at baseline.

In this subset, 22 patients (75.9%) presented a good outcome of mitral repair with a residual mitral regurgitation absent or trivial in 15 subjects (68.2%) and mild in seven (31.8%).

At the moment of the echocardiographic scan, 22 subjects (75.9%) were in SR, while six (20.7%) were in atrial fibrillation/atypical atrial flutter, and one (3.4%) presented an atrial paced rhythm. At univariate analysis the residual mitral regurgitation did not relate to AF relapses ( $p = 0.103$ ).

Table 2 shows details concerning all measurements and functional parameters stratified by heart rhythm at the time of the echo scan. Patients suffering relapses reported more enlarged left atria and more significantly impaired LA function.

Similar trends emerged, as shown in Table 3, if measurements and functional parameters were stratified by heart rhythm during follow-up: 20 (69.0%) SR and nine (31.0%) AF recurrences.

**Table 2.** Echocardiographic parameters and atrial functional evaluations, expressed as mean of the total population and stratified on the basis of presenting rhythm during echocardiography. (AF, atrial fibrillation; AP, antero-posterior; BSA, body surface area; DT, deceleration time; EF, ejection fraction; LA, left atrial; LV, left ventricular; PAPs, systolic pulmonary arterial pressure; RA, right atrial; SI, supero-inferior; SR, sinus rhythm).

|  | N = 29       | SR (N = 22/29) | AF (N = 6/29) | p-Value |
|--|--------------|----------------|---------------|---------|
| Max LA AP diameter (mm)                                  | 53.4 ± 6.7   | 51.5 ± 5.9     | 59.8 ± 6.0    | 0.018   |
| Min LA AP diameter (mm)                                  | 46.7 ± 7.2   | 44.4 ± 6.0     | 55.0 ± 5.1    | 0.002   |
| Total LA emptying fraction derived from AP diameters (%) | 12.7 ± 4.4   | 14.1 ± 4.1     | 8.0 ± 1.6     | 0.006   |
| Max LA SI diameter (mm)                                  | 68.3 ± 5.4   | 67.2 ± 4.6     | 74.0 ± 3.7    | 0.003   |
| Max LA area (cmq)  | 31.8 ± 5.2   | 30.4 ± 4.3     | 37.3 ± 5.5    | 0.010   |
| Min LA area (cmq)  | 27.0 ± 5.1   | 25.3 ± 3.8     | 33.4 ± 4.8    | 0.001   |
| LA ejection fraction derived from areas (%)              | 15.5 ± 5.4   | 16.7 ± 5.3     | 10.5 ± 2.8    | 0.028   |
| Max LA volume (mL)                                       | 120.4 ± 32.6 | 111.5 ± 25.9   | 152.8 ± 39.0  | 0.016   |
| Max LA volume/BSA (mL/mq)                                | 65.6 ± 15.8  | 60.9 ± 12.5    | 80.7 ± 18.2   | 0.010   |
| Min LA volume (mL)                                       | 93.5 ± 28.7  | 84.4 ± 21.1    | 127.7 ± 30.9  | 0.002   |
| Min LA volume/BSA (mL/mq)                                | 60.0 ± 14.5  | 46.2 ± 11.2    | 67.5 ± 14.4   | 0.002   |
| 3D LA volume (mL)  | 111.6 ± 38.2 | 100.2 ± 25.5   | 158.1 ± 51.7  | 0.005   |
| 3D LA volume/BSA (mL/mq)                                 | 61.1 ± 18.9  | 54.9 ± 12.4    | 84.0 ± 24.9   | 0.003   |
| Total LA emptying fraction derived from volumes (%)      | 22.7 ± 8.0   | 24.4 ± 7.9     | 16.0 ± 5.7    | 0.061   |
| Global longitudinal LA strain (%)                        | 8.5 ± 3.8    | 9.7 ± 3.6      | 5.2 ± 1.7     | 0.013   |
| E wave (cm/s)  | 137.2 ± 23.7 | 136.4 ± 25.8   | 143.5 ± 14.4  | 0.552   |
| A wave (cm/s)  | 56.2 ± 19.8  | 57.1 ± 19.8    |               | 0.286   |
| Inferior septal a' wave (cm/s)                           | 5.8 ± 2.0    | 5.9 ± 2.0      |               | 0.508   |
| Lateral a' wave (cm/s)                                   | 4.5 ± 1.6    | 4.6 ± 1.6      |               | 0.356   |
| Averaged a' wave (cm/s)                                  | 5.2 ± 1.5    | 5.2 ± 1.5      |               | 0.352   |
| P-lateral a' wave interval (ms)                          | 110.6 ± 31.9 | 110.3 ± 32.7   |               | 0.866   |
| LV EF (%)  | 57.3 ± 8.0   | 57.9 ± 6.8     | 53.8 ± 11.7   | 0.352   |
| PAPs (mmHg)  | 37.7 ± 9.4   | 37.0 ± 9.6     | 38.2 ± 9.4    | 0.479   |

Table 3 points out the markedly enlarged dimensions of the LA, compared to healthy subjects [18], also in patients who maintained SR during the follow-up: the maximum anteroposterior diameter was 51.4 ± 6.2 mm (versus normal values of <41 mm); the maximum indexed volume 60.6 ± 13.1 mL/mq (versus normal values of 22 ± 6 mL/mq); the minimum indexed volume 45.4 ± 10.9 mL/mq (versus normal values of 11 ± 4 mL/mq); the preA indexed volume 51.3 ± 11.6 mL/mq (versus normal values of 15 ± 5 mL/mq); the maximum indexed 3D volume 56.2 ± 13.2 mL/mq (versus normal values of 15–41 mL/mq). However, these same parameter results significantly increased in patients suffering AF relapses at follow-up.

Similarly, SR patients showed a reduction in atrial function when compared to normal values of healthy controls (transmitral A wave velocity 54.7 ± 20.0 cm/s versus 80 ± 20 cm/s [19]; TDI lateral a' wave 4.6 ± 1.7 cm/s, septal a' wave 6.0 ± 2.0 cm/s, averaged a' wave 5.3 ± 1.5 cm/s versus values >7.3 cm/s [17]; LA ejection fraction by areas 17.2 ± 5.0% versus 45% [15]; total emptying fraction by volumes 25.1 ± 7.3% versus normal values ranging from 45% to 65 ± 9% [18,20,21]; active and passive emptying fractions by volumes 11.4 ± 5.4% and 15.5 ± 6.3% versus 46.6 ± 11.7% and 44.3 ± 12.1% [22], respectively; global strain 9.8 ± 3.8% versus 22.9 ± 11.7% [23]). All these parameters, however, were less severely depressed compared to patients with arrhythmia relapses.

At follow-up, patients who suffered from ischemic cerebral events had maximal LA volume/BSA 61 ± 17.8 mL/mq, minimum LA volume/BSA 45.4 ± 5.2 mL/mq, total LA emptying fraction derived from volumes 23.6 ± 13.7%, lateral a' wave 4.3 ± 0.2 cm/s, and SD of PA-TDI measurements 0.45 ± 0.08. The two patients with strokes in SR showed, instead, extremely enlarged LA volume (>70 mL/mq). One patient suffering a cerebrovascular event despite SR had discontinued oral anticoagulation therapy. The other three patients were on anticoagulation therapy at the time of stroke.

**Table 3.** Echocardiographic parameters and atrial functional evaluations, stratified according to SR maintenance and type of AF recurrence during follow-up. (AF, atrial fibrillation; AP, antero-posterior; BSA, body surface area; DT, deceleration time; EF, ejection fraction; LA, left atrial; LS, long-standing; LV, left ventricular; PAPs, systolic pulmonary arterial pressure; RA, right atrial; SD, standard deviation; SI, supero-inferior; SR, sinus rhythm).

|   | Stable SR<br>(N = 20/29) | AF Relapse<br>(N = 9/29) | Paroxysmal<br>AF Relapse<br>(N = 3/29) | Persistent/LS<br>Persistent AF<br>Relapse (N = 6/29) | p-Value |
|---|--------------------------|--------------------------|--|--|---------|
| Max LA AP diameter (mm)                                       | 51.4 ± 6.2               | 57.8 ± 5.9               | 53.7 ± 3.2                             | 59.8 ± 6.0   | 0.019   |
| Min LA AP diameter (mm)                                       | 44.3 ± 6.3               | 52.2 ± 6.0               | 46.7 ± 3.2                             | 55.0 ± 5.1   | 0.002   |
| P wave LA AP diameter (mm)                                    | 47.5 ± 6.1               |                          | 49.7 ± 4.2                             |  | 0.565   |
| Active LA emptying fraction<br>derived from AP diameters (%)  | 7.0 ± 3.2                |                          | 5.9 ± 3.0                              |  | 0.601   |
| Passive LA emptying fraction<br>derived from AP diameters (%) | 7.7 ± 3.4                |                          | 7.5 ± 2.3                              |  | 0.945   |
| Total LA emptying fraction<br>derived from AP diameters (%)   | 14.1 ± 4.2               | 9.7 ± 3.0                | 13.1 ± 1.9                             | 8.0 ± 1.6  | 0.006   |
| Max LA SI diameter (mm)                                       | 67.0 ± 4.9               | 71.4 ± 5.2               | 66.3 ± 4.0                             | 74.0 ± 3.7   | 0.009   |
| Max LA area (cmq)   | 30.1 ± 4.3               | 35.6 ± 5.3               | 32.2 ± 3.1                             | 37.3 ± 5.5   | 0.007   |
| Min LA area (cmq)   | 24.9 ± 3.8               | 31.4 ± 4.9               | 27.5 ± 2.2                             | 33.4 ± 4.8   | <0.001  |
| P wave LA area (cmq)  | 27.0 ± 4.0               |                          | 28.9 ± 2.2                             |  | 0.430   |
| LA ejection fraction derived<br>from areas (%)                | 17.2 ± 5.0               | 11.8 ± 4.6               | 14.3 ± 7.2                             | 10.5 ± 2.8   | 0.022   |
| Max LA volume (mL)  | 109.9 ± 26.4             | 143.8 ± 34.4             | 125.7 ± 13.6                           | 152.8 ± 39.0   | 0.012   |
| Max LA volume/BSA (mL/mq)                                     | 60.6 ± 13.1              | 76.8 ± 16.2              | 69.0 ± 9.1                             | 80.7 ± 18.2  | 0.016   |
| Min LA volume (mL)  | 82.4 ± 21.0              | 118.2 ± 28.7             | 99.3 ± 10.2                            | 127.7 ± 30.9   | 0.001   |
| Min LA volume/BSA (mL/mq)                                     | 45.4 ± 10.9              | 63.3 ± 14.2              | 55.0 ± 11.6                            | 67.5 ± 14.4  | 0.002   |
| P wave LA volume (mL)   | 92.9 ± 22.7              |                          | 104.3 ± 8.1                            |  | 0.402   |
| P wave LA volume/BSA (mL/mq)                                  | 51.3 ± 11.6              |                          | 57.6 ± 10.4                            |  | 0.380   |
| 3D LA volume (mL)   | 101.6 ± 26.6             | 134.0 ± 51.6             | 93.9 ± 11.2                            | 158.1 ± 51.7   | 0.005   |
| 3D LA volume/BSA (mL/mq)                                      | 56.2 ± 13.2              | 71.9 ± 25.6              | 51.7 ± 8.4                             | 84.0 ± 24.9  | 0.005   |
| Active LA emptying fraction<br>derived from volumes (%)       | 11.4 ± 5.4               |                          | 4.9 ± 3.0                              |  | 0.057   |
| Passive LA emptying fraction<br>derived from volumes (%)      | 15.5 ± 6.3               |                          | 16.5 ± 9.0                             |  | 0.809   |
| Total LA emptying fraction<br>derived from volumes (%)        | 25.1 ± 7.3               | 17.5 ± 7.4               | 20.4 ± 10.9                            | 16.0 ± 5.7   | 0.039   |
| Global longitudinal LA strain (%)                             | 9.8 ± 3.8                | 5.8 ± 1.9                | 7.0 ± 2.0                              | 5.2 ± 1.7  | 0.021   |
| E wave (cm/s)   | 131.4 ± 24.2             | 150.0 ± 17.6             | 163.0 ± 18.2                           | 143.5 ± 14.4   | 0.070   |
| A wave (cm/s)   | 54.7 ± 20.0              |                          | 66.1 ± 19.5                            |  | 0.364   |
| Inferior septal a' wave (cm/s)                                | 6.0 ± 2.0                |                          | 4.9 ± 2.2                              |  | 0.409   |
| Lateral a' wave (cm/s)  | 4.6 ± 1.7                |                          | 3.6 ± 0.8                              |  | 0.306   |
| Averaged a' wave (cm/s)                                       | 5.3 ± 1.5                |                          | 4.3 ± 1.5                              |  | 0.274   |
| P-lateral a' wave interval (ms)                               | 110.8 ± 28.9             |                          | 109.0 ± 57.3                           |  | 0.930   |
| SD P-a' wave intervals  | 0.56 ± 0.31              |                          | 0.63 ± 0.47                            |  | 0.736   |
| LV EF (%)   | 58.0 ± 7.2               | 55.8 ± 9.8               | 59.7 ± 3.5                             | 53.8 ± 11.7  | 0.484   |
| PAPs (mmHg)   | 36.2 ± 9.3               | 40.7 ± 9.5               | 45.7 ± 9.0                             | 38.2 ± 9.4   | 0.284   |

#### 4. Discussion

It is reasonable to infer that a lack of recovery of an efficient mechanical atrial activity, even potentially in the presence of SR, facilitates intra-atrial thrombus formation and subsequent systemic thromboembolic phenomena.

Previous studies on surgical AF ablation concomitant to valve surgery reported a highly variable incidence, from 21% to 87%, of both SR restoration and atrial contraction recovery [24,25].

Following the classic LA Maze ablation, it has already been proven that, despite successful SR restoration, there is a progressive loss of LA function, especially within patients affected by rheumatic mitral disease [26].

Following the latest less extensive LA ablation protocols, sparing large areas of the LA, instead, data are controversial. On one side, Loardi et al. analyzed 122 patients: based on transmitral peak A velocity as an atrial contraction index, they proved that 76% of the subjects presented SR and a normal atrial function at three months, and this percentage even increased to 98% after two years [27]. Similarly, Reyes et al. [28], out of 33 patients, highlighted the presence of a transmitral flow in 70% of SR patients at six months follow-up. Analogous results were reported by Manasse et al. [29].

On the other side, in patients with stable SR at six months follow-up, Johansson et al. [30] demonstrated a significant reduction in transmitral A wave velocity in 15 subjects submitted to combined surgery procedure as compared with 14 subjects submitted to mitral valve surgery alone. Boyd et al. suggested that the ablation procedure might have been responsible for the atrial dysfunction observed [31]. In addition, Schiros et al., comparing 35 degenerative mitral regurgitation patients undergoing combined surgery to 51 normal controls by means of cardiac magnetic resonance imaging, asserted that LA volumes and function do not return to normal values at one year distance (in particular, total atrial emptying fraction derived from volumes resulted in 45% pre-operative and 42% at one year post-surgery, versus 54% in controls) [32] supporting the relevant role of the underlying intrinsic disease of the atrial myocardium. Similar results were also reported by Kim et al. [33] within 12 patients: at one month follow-up the LA emptying fraction at computed tomography was  $16.8 \pm 6.3\%$  (significantly lower than in controls,  $47.9 \pm 11.2\%$ ,  $p < 0.001$ ) despite SR, and atrial contractile function did not improve over the following six months.

Lastly, Compier et al. placed emphasis on the fact that, notwithstanding the limited lesion set during concomitant cardiac surgery, LA compliance, transport function and contraction, decreased after ablation, were not restored in approximately half of the patients with post-procedural SR [34].

The present study highlights the markedly enlarged dimensions and reduced LA function also in patients who maintained SR during the entire follow-up period, compared to data reported in the literature for healthy subjects (see Results section). However, these parameters are more severely depressed, compared to healthy subjects, when patients suffer arrhythmia relapses (Table 3). These results support that concomitant AF cryoablation, by SR maintenance, guarantees an advantage, even if in the setting of deteriorated LAs, in terms of reverse remodeling.

Similar results were found in the HESTER (Has Electrical Sinus Translated into Effective Remodelling?) study [35]: in this experience, adjunct surgical maze was associated with the recovery of LA function but with a mean active LA ejection fraction (ALAEF) lower in maze patients than in control subjects. Providing evidence that function is restored after adjunct maze, potential clinical benefits in reducing thromboembolic and heart failure risk will arise. Determining whether patients can safely stop taking anticoagulants after SR is restored by a maze procedure requires, instead, longer term follow-up and stroke surveillance, beyond those of the HESTER study. In any case, the varying rates of LA functional recovery after maze strongly suggest that, at least, it would be judicious to measure LA function before considering anticoagulation withdrawal.

As stated in a previous study of our group [12] we suggest that, at least within patients with severely enlarged left atrium, previous cardiac surgery and catheter or surgical AF ablation, especially if repeated, the assessment of atrial contractility by transthoracic echocardiography should be performed before discontinuing oral anticoagulants (OAC), also in patients who maintain SR, despite confirmation

by serial ECG or Holter monitorings. In our opinion, SR and LA contractility recovery represent two sides of the same coin, and both should be weighted carefully with the objective of selecting patients who could benefit from OAC continuation/discontinuation following an AF ablation.

There is a real need for improvement in patient stratification and personalization of care after AF ablation. Our understanding of which patients should continue anticoagulants for stroke prevention needs to be further refined to reduce the number of patients receiving anticoagulation after a successful AF ablation, and consequently lower the number of hemorrhagic complications, while endorsing the continuation of OAC in patients with a higher risk profile, and prevent thromboembolic events. In this context, we believe echocardiographic assessment of the restoration of an efficient LA contractility should be included among decisional criteria.

Further prospective studies are needed to define the LA dimensions and function cut-off values determining an increase in the risk for thromboembolic complications in patients with restored stable SR. Moreover, quantitative assessment of LA function may have clinical utility in guiding early surgical intervention and concomitant ablation in patients with mitral regurgitation and AF [36,37].

### *Study Limitations*

This report is an observational and retrospective study. The limited sample size may have influenced the statistical power of the analysis. A comparison with baseline echocardiographic data is not completely feasible because a detailed echocardiography focused on LA morphology and function was not routinely performed before surgery. In addition, echocardiographic follow-up data were not available for the entire cohort of patients. Despite this limitation, we believe our data are representative and of interest. In fact, despite patients lost to follow-up, echocardiographic parameters concerning atrial function in patients followed and with stable SR, after the combined surgical procedure, proved statistically better than in subjects with AF relapse. Being aware that arrhythmia monitoring based on serial 24 h ECG Holter tracings or, even better, implantable recorders would be more accurate, in a mostly persistent AF setting, consideration of any AF relapse, also those present only once during the follow up, should limit event underestimation.

The present study is a starting point; in any case, we are convinced that the concept introduced by the present manuscript may have wider developments in clinical practice.

## **5. Conclusions**

Surgical AF cryoablation concomitant to minimally invasive mitral valve repair was determined to be highly effective in maintaining SR and reducing AF burden at long-term follow-up.

The present study highlights the markedly enlarged dimensions of the LA also in patients who maintained SR during the entire follow-up period.

However, at the echocardiographic evaluation, data concerning atrial function in patients with stable SR after the combined surgical procedure are significantly better than in subjects with AF relapse at follow-up. This finding supports the implementation of AF cryoablation concomitant to MIMVS.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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Article

# Outcome after Interdisciplinary Treatment for Aneurysmal Subarachnoid Hemorrhage—A Single Center Experience

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**Abstract:** *Background and Objectives:* To identify predictors of outcome after aneurysmal subarachnoid hemorrhage (aSAH) in our interdisciplinary setting. *Materials and Methods:* 176 patients who had been treated for aSAH by a team of neurosurgeons and neuroradiologists between 2009 and 2017 were analyzed retrospectively. Age, gender, clinical presentation according to the Hunt and Hess (H&H) grading on admission, overall clot burden, aneurysm localization, modality of aneurysm obliteration, early deterioration (ED), occurrence of vasospasm in transcranial Doppler ultrasonography, delayed cerebral ischemia (DCI), spasmolysis, decompressive craniectomy (DC), cerebrospinal fluid (CSF) shunt placement, deep vein thrombosis (DVT), pulmonary embolism (PE), severe cardiac events (SCE), mortality on Days 14, and 30 after admission, and outcome at one year after the hemorrhage according to the Glasgow Outcome Scale (GOS) were recorded. Chi square, Fisher's exact, Welch's t, and Wilcoxon rank sum served as statistical tests. Generalized linear models were fitted, and ordered logistic regression was performed. *Results:* SCE ( $p = 0.049$ ) were a significant predictor of mortality at 14 days after aSAH, but not later during the first year after the hemorrhage. Clipping as opposed to coiling ( $p = 0.049$ ) of ruptured aneurysms was a significant predictor of survival on Day 30 after aSAH, but not later during the first year after the hemorrhage, while coiling as opposed to clipping of ruptured aneurysms was significantly related to a lower frequency of DVT during hospitalization ( $p = 0.024$ ). Aneurysms of the anterior circulation were significantly more often clipped, while aneurysms of the posterior circulation were significantly more often coiled ( $p < 0.001$ ). Age over 70 years ( $p = 0.049$ ), H&H grade on admission ( $p = 0.022$ ), overall clot burden ( $p = 0.035$ ), ED ( $p = 0.009$ ), DCI ( $p = 0.013$ ), DC ( $p = 0.0005$ ), and CSF shunt placement ( $p = 0.038$ ) proved to be predictive of long-term outcome after aSAH. *Conclusion:* Long-term results after clipping and coiling of ruptured aneurysms appear equal in an interdisciplinary setting that takes aneurysm localization, available staff, and equipment into account.

**Keywords:** aneurysmal subarachnoid hemorrhage; outcome; interdisciplinary setting

## 1. Introduction

The high-level evidence provided by the International Subarachnoid Aneurysm Trial (ISAT) [1] led to favor coiling, a technique first described by Guglielmi [2], over clipping for the obliteration of ruptured cerebral aneurysms. Nonetheless, interdisciplinary settings were tailored to the local particularities at many neurovascular centers over time, due to the indisputable weaknesses of ISAT, namely the disproportionately high number of coiled aneurysms of the anterior communicating artery, and the comparison of the results of aneurysm obliteration performed by highly specialized

neuroradiologists with those performed by averagely trained neurosurgeons in ISAT. The Barrow Ruptured Aneurysm Trial (BRAT) [3] initially seemed to confirm the results of ISAT, while data from the BRAT study at six years after the hemorrhage [4] suggested that the modality of aneurysm obliteration of ruptured aneurysms of the anterior circulation would not affect long-term results as long as treatment remained in experienced hands. Furthermore, data from the BRAT study at 10 years after the hemorrhage demonstrated that rates of complete aneurysm obliteration and rates of retreatment actually favored clipping over coiling [5].

There is, however, only a limited number of publications on results after single-center interdisciplinary treatment for aSAH. Güresir et al. [6] identified intraparenchymal hemorrhage as prognostically unfavorable in 585 patients treated interdisciplinarily for aSAH. Proust et al. [7] found a decrease of verbal memory capabilities in 50 patients after clipping versus coiling of ruptured aneurysms of the anterior communicating artery, while other neuropsychological deficiencies and quality of life did not differ significantly between treatment groups. The same group [8] reported on the results of interdisciplinary treatment at six months after aSAH, according to the modified Rankin Scale (mRS) [9] in 64 patients who were 70 years of age or older at the time of bleeding; an unfavorable correlation of initially poor clinical presentation and delayed cerebral ischemia with outcome was found. Schöller et al. [10] described an initially good clinical presentation and an age of less than 70 years on admission as prognostically favorable factors. In a small series of patients with ruptured aneurysms of the posterior inferior cerebellar artery, Sejkorova et al. [11] identified an initially high Hunt and Hess (H&H) [12] grade as unfavorable for the outcome after interdisciplinary treatment. Schwartz et al. [13] found young age at the time of admission and absence of cerebral ischemia to yield a favorable prognosis in 106 cases of interdisciplinary treated ruptured cerebral aneurysms. AlMatter et al. [14] identified age, initial clinical presentation, re-rupture of the aneurysm, intraparenchymal hemorrhage, and ruptured aneurysms of the middle cerebral artery as relevant prognostic factors; they described a trend towards unfavorable outcomes after vasospasm, intraventricular hemorrhage, and rupture of large aneurysms.

In our study, we aimed to retrospectively identify predictive factors after treatment for aSAH in a single center series of 176 cases.

## 2. Materials and Methods

### 2.1. Patients

In this single center retrospective study, 176 patients admitted to our university hospital between 2009 and 2017 were included. The patients fulfilled each of the following inclusion criteria: subarachnoid hemorrhage diagnosed after cranial computed tomography (CCT) or lumbar puncture, detection of at least one cerebral aneurysm in digital subtraction angiography (DSA) or computed tomography angiography (CTA), obliteration of the ruptured aneurysm by coiling or clipping within 24 h after admission. Patients with a history of severe cognitive impairment prior to the hemorrhage, such as progressive dementia, and patients with H&H grade 5 hemorrhages who did not benefit from external ventricular drainage (EVD) insertion were not included.

Age, gender, aneurysm localization, blood distribution according to the modified Fisher scale [15], and clinical findings according to the H&H scale on admission were recorded.

Necessity of EVD insertion, modality of aneurysm obliteration, detection of cerebral vasospasm, frequencies of spasmodic contraction, delayed cerebral ischemia (DCI), decompressive craniectomy (DC), cerebrospinal fluid (CSF) shunt dependency, deep vein thrombosis (DVT), pulmonary embolism (PE), and severe cardiac events (SCE), i.e., incidents requiring electrical cardioversion or cardiopulmonary resuscitation, were recorded.

Survival at Days 14 and 30 after SAH was recorded. Follow-up at one year after the hemorrhage was recorded according to the Glasgow Outcome Scale (GOS) [16]. Favorable outcomes were defined as GOS 4 or 5.

2.2. Interdisciplinary Setting

Urgent EVD insertion was performed in cases with symptomatic hydrocephalus. Obliteration of the ruptured aneurysm was achieved within 24 h after admission. In all but one patient with a ruptured aneurysm of the middle cerebral artery (MCA), the aneurysm was clipped, while, in one patient with a ruptured aneurysm of the MCA, the aneurysm was coiled. In the remaining cases, an interdisciplinary decision as to the modality of aneurysm obliteration was made, and the ruptured aneurysm was treated accordingly. In cases with multiple aneurysms, sequence and modality of aneurysm obliteration were determined interdisciplinarily. All patients received neurosurgical intensive care.

2.3. Statistical Analysis

Statistical analysis was conducted using OpenOffice 4.1.3 and R 3.5.1 with R Studio 1.1.383 on a Mac OS X 10.14.4. Figures were created with R and R Studio. Chi square, Fisher’s exact, Welch’s t, and Wilcoxon rank sum served as statistical tests. To assess the impact of predictors on outcome variables, generalized linear models were fitted, and a proportional odds logistic regression was performed. Statistical significance was assumed with *p* values less than 0.05.

2.4. Ethical Approval

Upon our request in March 2018, the local ethics committee at the University Hospital Marburg considered an ethical approval unnecessary for this pseudonymized retrospective analysis.

3. Results

Mean age on admission was 56 years (range: 22–90 years). On admission, 63 patients (35.8%) were 60 years of age or older, and 9 patients (5.1%) were 80 years of age or older. One hundred six patients (60.2%) were female.

Overall, 167 of 176 patients (94.9%) presented with symptomatic hydrocephalus on admission and urgently received an EVD.

Clinical findings according to the H&H scale [12] on admission are given in Table 1. Information on blood distribution according to the modified Fisher scale in the initial CCT is provided in Table 2.

**Table 1.** Clinical presentation according to the Hunt and Hess (H&H) scale [12] on admission in 176 patients with aneurysmal subarachnoid hemorrhage.

| Initial H&H Grade | Number of Ruptured Aneurysms Clipped (n = 108) | Number of Ruptured Aneurysms Coiled (n = 68) | Statistical Test, <i>p</i> -Value     |
|-------------------|--|--|---------------------------------------|
| 1                 | 9  | 9  | Wilcoxon rank sum,<br><i>p</i> = 0.14 |
| 2                 | 27   | 16   |                                       |
| 3                 | 26   | 16   |                                       |
| 4                 | 29   | 17   |                                       |
| 5                 | 17   | 10   |                                       |

**Table 2.** Blood distribution in the initial cranial computerized tomography (CCT) scan according to the modified Fisher scale [15] in 176 patients with aneurysmal subarachnoid hemorrhage.

| Modified Fisher Grade | Number of Ruptured Aneurysms Clipped (n = 108) | Number of Ruptured Aneurysms Coiled (n = 68) |
|-----------------------|--|--|
| 0                     | 2  | 4  |
| 1                     | 9  | 6  |
| 2                     | 4  | 7  |
| 3                     | 38   | 18   |
| 4                     | 55   | 33   |

Clipped and coiled aneurysms by location are tabulated in Table 3. In 42 patients (23.9%), multiple cerebral aneurysms were detected. Ruptured aneurysms of the anterior circulation were significantly more often clipped, while ruptured aneurysms of the posterior circulation were significantly more often coiled (chi square test,  $p < 0.001$ ).

**Table 3.** Clipped and coiled aneurysms by location in 176 patients with aneurysmal subarachnoid hemorrhage.

| Aneurysm Location  | Number of Ruptured Aneurysms Clipped (n = 108) | Number of Ruptured Aneurysms Coiled (n = 68) | Statistical Test, p-Value |
|--|--|--|---------------------------|
| MCA <sup>1</sup>   | 52   | 1  |                           |
| ACA <sup>1</sup>   | 11   | 4  |                           |
| Acomm <sup>1</sup>   | 27   | 26   |                           |
| ICA paraophthalmic <sup>1</sup>  | 3  | 4  |                           |
| ICA supraophthalmic <sup>1</sup>   | 13   | 12   |                           |
| Pcomm <sup>1</sup>   | 2  | 0  |                           |
| SCA <sup>2</sup>   | 0  | 1  |                           |
| PICA <sup>2</sup>  | 0  | 3  |                           |
| Basilar artery <sup>2</sup>  | 0  | 13   |                           |
| Vertebral artery <sup>2</sup>  | 0  | 4  |                           |
| Ruptured aneurysms of the anterior circulation (subtotal of locations marked with superscript 1)*  | 108  | 47   |                           |
| Ruptured aneurysms of the posterior circulation (subtotal of locations marked with superscript 2)* | 0  | 21   |                           |
|  |  |  | chi square, $p < 0.001$   |

Abbreviations: MCA, middle cerebral artery; ACA, anterior cerebral artery; Acomm, anterior communicating artery; ICA, internal carotid artery; Pcomm, posterior communicating artery; SCA, superior cerebellar artery; PICA, posterior inferior cerebellar artery. Superscript 1, anterior circulation; superscript 2, posterior circulation. \* Statistically significant finding.

Events of clinical significance during hospitalization are listed in Table 4. We found a significantly higher probability of DVT in patients who underwent clipping as opposed to coiling of ruptured cerebral aneurysms (Fisher’s exact test,  $p = 0.024$ ).

**Table 4.** Events of clinical significance during hospitalization in 176 patients with aneurysmal subarachnoid hemorrhage.

| Clinical Event         | Number of Ruptured Aneurysms Clipped (n = 108) | Number of Ruptured Aneurysms Coiled (n = 68) | Statistical Test, p-Value   |
|------------------------|--|--|-----------------------------|
| EVD insertion = yes    | 102  | 65   | Fisher’s exact, $p = 1$     |
| SCE = yes              | 5  | 7  | Fisher’s exact, $p = 0.218$ |
| Vasospasm in TCD = yes | 39   | 16   | chi square, $p = 0.113$     |
| DCI = yes              | 49   | 34   | chi square, $p = 0.657$     |
| Spasmolysis = yes      | 5  | 4  | Fisher’s exact, $p = 0.736$ |
| DC performed = yes     | 29   | 13   | chi square, $p = 0.322$     |
| CSF shunt placed = yes | 48   | 31   | chi square, $p = 1$         |
| DVT detected = yes *   | 8  | 0  | Fisher’s exact, $p = 0.024$ |
| PE detected = yes      | 4  | 1  | Fisher’s exact, $p = 0.65$  |

Abbreviations: EVD, external ventricular drainage; SCE, severe cardiac event; TCD, transcranial Doppler sonography; DCI, delayed cerebral ischemia; DC, decompressive craniectomy; CSF, cerebrospinal fluid; DVT, deep vein thrombosis; PE, pulmonary embolism. \* Statistically significant finding.

Information on survival during the first month after the hemorrhage is provided in Table 5. At 30 days after the hemorrhage, we found a significantly higher probability of survival in patients who underwent clipping as opposed to coiling of ruptured cerebral aneurysms (generalized linear modeling,  $p = 0.0495$ ). Outcome according to the GOS at one year after the hemorrhage is given in Table 6. Clinical data at 14 and 30 days after the hemorrhage were available in all patients, while follow-up at one year was obtained in 133 of 176 patients (75.6%).

**Table 5.** Survival during the first month in 176 patients with aneurysmal subarachnoid hemorrhage.

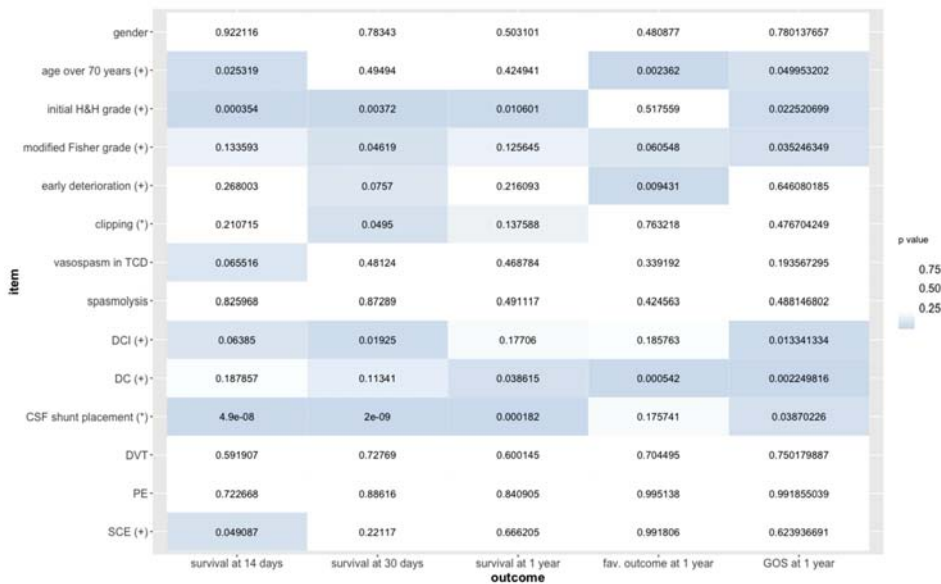
| Survival Status       | Number of Ruptured Aneurysms Clipped ( $n = 108$ ) | Number of Ruptured Aneurysms Coiled ( $n = 68$ ) | Statistical Model, $p$ -Value             |
|-----------------------|--|--|---|
| Survived at 14 days   | 102  | 60   | generalized linear modeling, $p = 0.2107$ |
| Survived at 30 days * | 101  | 58   | generalized linear modeling, $p = 0.0495$ |

\* Statistically significant finding.

**Table 6.** Outcome according to the Glasgow Outcome Scale (GOS) [16] at one year in 176 patients with aneurysmal subarachnoid hemorrhage.

| GOS         | Number of Ruptured Aneurysms Clipped ( $n = 108$ ) | Number of Ruptured Aneurysms Coiled ( $n = 68$ ) | Statistical Model, $p$ -Value                       |
|-------------|--|--|---|
| 1 at 1 year | 14   | 11   |   |
| 2 at 1 year | 6  | 0  |   |
| 3 at 1 year | 25   | 11   |   |
| 4 at 1 year | 17   | 9  |   |
| 5 at 1 year | 24   | 16   |   |
|             |  |  | proportional odds logistic regression, $p = 0.4767$ |

The impact of potentially predictive variables on outcome after aSAH is illustrated in Figure 1.



**Figure 1.** Statistical significance of potential predictors of outcome in 176 patients with aneurysmal subarachnoid hemorrhage as estimated from generalized linear models for dichotomous outcome variables (survival and fav. outcome) and proportional odds logistic regression for an ordinal outcome variable (GOS) after aneurysmal subarachnoid hemorrhage. Information on survival at Days 14 and 30 after the hemorrhage was available in all patients, while information on outcome at one year after the hemorrhage was obtained in 133 patients (75.6%). Abbreviations: H&H, Hunt and Hess; TCD, transcranial Doppler sonography; DCI, delayed cerebral ischemia; DC, decompressive craniectomy; CSF, cerebrospinal fluid; DVT, deep vein thrombosis; PE, pulmonary embolism; SCE, severe cardiac event; fav., favorable; GOS, Glasgow Outcome Scale; (\*) true (dichotomous variables) or increasing (ordered values) values predictive of survival, favorable outcome, or high GOS score; (+) true (dichotomous variables) or increasing (ordered values) values predictive of mortality, unfavorable outcome or low GOS score.

#### 4. Discussion

Various authors reported an initially poor H&H grade to predict an unfavorable outcome after aSAH [1,8,10,11,14]. This finding was confirmed in our study: according to our data, an initially poor H&H grade significantly predicted mortality at Days 14 and 30 after the hemorrhage, mortality at one year after the hemorrhage and a less favorable outcome according to the GOS at one year after the hemorrhage. We regularly refrain from obliterating ruptured cerebral aneurysms in patients who, prior to the onset of aSAH, have a history of severe cognitive impairment, such as progressive dementia, since we consider the potential benefit of aneurysm obliteration to these patients highly questionable.

Age as a predictor of outcome after aSAH has been reported before [10,13,14]. In our study, age of over 70 years on admission, being a cut-off age within the range of those of several other publications, was a strong predictor of mortality at 14 days after the hemorrhage, an unfavorable outcome and a less favorable outcome according to the GOS at one year after the hemorrhage. We share, however, the view of other authors that age alone should not be an objection as to the diagnosis and treatment of cerebrovascular diseases [17].

In other studies on aSAH, a high overall clot burden has been described as a predictive factor [18]. We found the extent of overall clot burden in the initial CCT, as recorded according to the modified

Fisher scale, to be significantly associated with mortality at 30 days after the hemorrhage, and with a less favorable outcome according to the GOS at one year after the hemorrhage.

Clipping as opposed to coiling of ruptured aneurysms was a significant predictor of survival at 30 days after aSAH, but not later during the first year after the hemorrhage. As far as we know, a similar finding has not been reported in other studies before. We suppose that the reduction of overall clot burden, which is part of the standard clipping procedure as opposed to the standard coiling procedure after aSAH, leads to a temporary relief from spasmogenic stimuli in the subarachnoid space, which may explain our finding.

Furthermore, our single center experience has shown that particularly in patients with poor H&H grades, clipping of a ruptured aneurysm is often accompanied by DC in the same session. By contrast, in patients with coiled aneurysms usually a clinical deterioration somewhat later in the course of the disease gives rise to DC. The earlier onset of the effect of DC may lead to temporary recovery in clinically poor patients who undergo clipping of ruptured aneurysms, which may contribute to the statistically significant effect of clipping on survival at 30 days after the hemorrhage as observed in our study.

Coiling as opposed to clipping of ruptured aneurysms was significantly correlated with a lower frequency of DVT, while the frequency of PE did not significantly depend on the modality of aneurysm obliteration in our patients. One may assume that acetylsalicylic acid (ASS) and heparin in doses with therapeutic effects, as regularly administered after aneurysm coiling, help to prevent DVT, while larger patient cohorts need to be analyzed to prove a potential impact of ASS and heparin on the frequency of PE after aSAH.

The fact that aneurysms of the anterior circulation were significantly more often clipped, while aneurysms of the posterior circulation were significantly more often coiled, is primarily attributable to particularities of our interdisciplinary approach.

ED has been reported to predict an unfavorable outcome after aSAH [19], which was confirmed in our study: ED was significantly related to an unfavorable outcome at 12 months after the hemorrhage.

Other authors have reported SCE as well as elevated Troponin levels, electrocardiographic or echocardiographic abnormalities, to be linked to unfavorable outcomes after aSAH [20–22]. In our patients, SCE were a significant predictor of mortality at 14 days after the hemorrhage, but not later during the first year after the hemorrhage. This finding may become relevant when clinical decisions have to be consented with the patient's next of kin: in patients with aSAH, a severely unstable cardiovascular situation during hospitalization after the hemorrhage occasionally tempts family members to fear lack of recovery and to demand intensive care not to be extended. Our study may provide a rationale to continue curative treatment in these cases.

We found that DCI was a significant predictor of mortality on Day 30 and of a less favorable overall outcome according to the GOS at one year after the hemorrhage, which is a finding other authors have reported before [14].

In our study, DC was a significant predictor of mortality, of an unfavorable outcome (i.e., GOS < 4) and of a less favorable outcome (i.e., a lower GOS) at one year after the hemorrhage. We found, however, that more than two out of three patients who required DC survived the first year after the hemorrhage. It therefore seems well warranted to indicate DC generously in patients who deteriorate due to malignant brain swelling after aSAH.

In our study, CSF shunt placement was a significant predictor of survival on days 14 and 30, and at one year after aSAH as well as of a less favorable outcome according to the GOS at one year after aSAH. This finding should be interpreted cautiously: of 97 patients who did not receive a CSF shunt, 14 (respectively, 17 and 21) patients were deceased at 14 (respectively, 30 and 365) days after the hemorrhage, while, of 79 patients who received a CSF shunt, 0 (respectively, 0 and 4) patients were deceased at 14 (respectively, 30 and 365) days after the hemorrhage. This observation is in accordance with the clinical experience that most patients with initially poor H&H grades simply do not survive long enough to receive a CSF shunt after aSAH.



### Limitations of Our Study

When interpreting our results, it should be kept in mind that this work is a single center retrospective study with an incomplete follow-up of 75.6% at one year after the hemorrhage. These facts set limitations to any generalized conclusion one would want to derive from our data. Our patients were treated at a university hospital in a country with an overall high standard of medical care.

### 5. Conclusions

SCE were predictive of mortality at 14 days after aSAH but not later during the first year after the hemorrhage.

Clipping as opposed to coiling of ruptured aneurysms was a significant predictor of survival at 30 days but not later during the first year after aSAH, while coiling as opposed to clipping of ruptured aneurysms was significantly related to a lower frequency of DVT during hospitalization.

Age over 70 years, H&H grade on admission, overall clot burden, ED, DCI, DC, and CSF shunt placement proved to be predictive of long-term outcome after aSAH.

Long-term results after clipping and coiling of ruptured aneurysms appear equal in an interdisciplinary setting that takes aneurysm localization, available staff, and equipment into account.

**Author Contributions:** Conceptualization: B.V. and C.N.; methodology: B.V. and C.N.; validation: B.V.; formal analysis: B.V. and R.R.; investigation: R.R.; resources: C.N.; data curation: B.V. and R.R.; writing—original draft preparation: B.V.; writing—review and editing: C.N., B.C., R.R., and C.A.; visualization: B.V.; and supervision: C.N.

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**Conflicts of Interest:** The authors declare no conflict of interest.

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Case Report

# Thromboembolic Events Following Atrial Fibrillation Cardioversion and Ablation: What's the Culprit?

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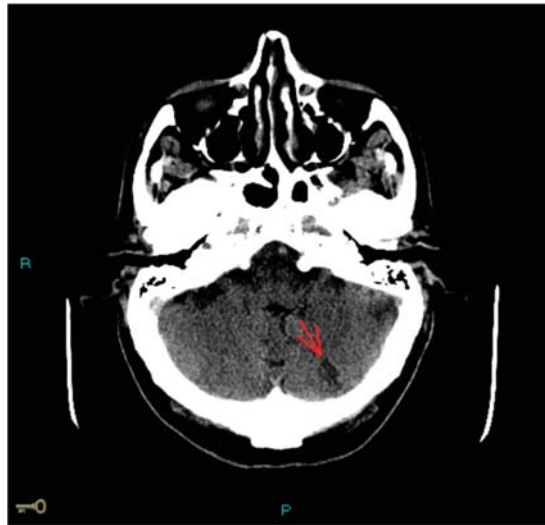
**Abstract:** Stroke is a rare but possible complication after atrial fibrillation (AF) ablation. However, its etiopathogenesis is far from being completely characterized. Here we report a case of stroke, with recurrent peripheral embolism after AF ablation procedure. In our patient, an in situ femoral vein thrombosis and iatrogenic atrial septal defect were simultaneously detected. A comprehensive review of multiple pathophysiological mechanisms of stroke in this context is provided. The case underlines the importance of a global evaluation of patients undergoing AF ablation.

**Keywords:** atrial fibrillation ablation; stroke; iatrogenic interatrial septum defect; paradoxical embolism; anticoagulant interruption

## 1. Case Report

A gentleman, 76 years old, was scheduled for catheter ablation of atrial fibrillation (AF) and atypical left atrial flutter in the context of symptomatic left ventricular dysfunction. He reported fatigue and exertional dyspnea, and presented persistent AF on EKG. He had a weight of 68 kg, and a height of 170 cm (BMI = 23 kg/m<sup>2</sup>), with high estimated thromboembolic risk (CHA<sub>2</sub>DS<sub>2</sub>VASc = 4). He was previously prescribed with anticoagulation (Dabigatran 110 mg bid), beta-blocker (bisoprolol 5 mg od), ACE-inhibitor (ramipril 5 mg od), diuretic (furosemide 50 mg) therapy. A 2D-echocardiogram documented left ventricle dilation (LVEDD (end diastolic diameter): 61 mm) with systolic dysfunction (EF (ejection fraction): 38%). A 2D-transesophageal echocardiogram (TEE) showed absence of images referable to atrial and auricular thrombosis. Single-lobe left appendage displayed reduced function with velocity peaks of 25 cm/sec. The left atrial area was 28 cm<sup>2</sup>. No relevant atherosclerotic plaques were found in the thoracic aorta. Written informed consent was obtained and the patient underwent radiofrequency electrical pulmonary veins isolation plus roof and mitral isthmus ablation lines during systemic intraprocedural heparinization (activation clotting time (ACT)-target: 300–350 s). Electrical cardioversion was also performed due to presence of persistent AF. The total procedural time was 180 min. Dabigatran was temporarily interrupted for 36 h across the procedure and the patient was discharged the next day. After one week he was admitted to the emergency department for sudden dyspnea, being hospitalized for acute heart failure. At admission the EKG showed sinus tachycardia, while chest X-ray depicted bilateral alveolar edema. During hospitalization, after achieving hemodynamic stabilization, the patient suffered aphasia and space-time disorientation with near loss of consciousness. The Angio-CT (computational tomography) showed hypodense lesions in the left cortico-subcortical temporo-occipital area and in the left cerebellar hemisphere as showed in Figure 1. Carotid and vertebral arteries were free from hemodynamic atherosclerotic plaques. Symptoms completely disappeared after two days and at the 24 h CT scan control, the lesions were stable, in the absence of hemorrhagic transformation. After a few days, the patient complained

left limb pain and an acute distal embolism was diagnosed. A new transthoracic echocardiogram revealed a further deterioration of left ventricular ejection fraction (EF: 30%) with no evidence of intraventricular thrombosis and a clearly discernable interatrial septal defect with left-to-right shunt, this was likely attributable to the trans-septal puncture performed during the ablation (Figure 2). Ultrasonography of the groin region documented in situ not compressible left femoral vein thrombosis (Figure 3). Non fractioned heparin infusion was administered with complete resolution of both the arterial embolic occlusion and venous thrombosis. After a few days, oral anticoagulation with apixaban was initiated and the patient was discharged. At the six months follow-up, he presented with mild cognitive impairment, which persisted overtime till the last visit.



**Figure 1.** Angio-CT (computational tomography) brain scan. The exam showed an acute ischemic lesion in the left cortico-subcortical temporo-occipital area and in the left cerebellar hemisphere (last one marked with red arrow).



**Figure 2.** Transthoracic echocardiogram (subxiphoid view). The exam showed a clearly discernable interatrial septal defect with left-to-right shunt identified, at rest, with color doppler.



**Figure 3.** Ultrasonographic femoral scan. The exam showed in situ thrombosis of the left femoral vein which was not compressible with the probe.

## 2. Case Discussion

The case illustrates an uncommon complication after atrial fibrillation (AF) ablation manifested with recurrent embolic events: A stroke and a leg embolism. Although stroke is a well-known described complication after AF ablation, the etiopathogenetic mechanisms underlying this complication are yet to be completely characterized. Here, we summarize and discuss all the potential factors involved in this undesirable complication.

### 2.1. Radiofrequency Lesion Set and Ablation “Per Se”

Evidence from non-randomized studies has shown that AF catheter ablation may reduce stroke risk, when successful. Among 361,913 patients with AF of the Swedish Patient Registry, catheter ablation was associated with a lower risk of stroke (HR = 0.69) and mortality (HR = 0.50). These results were even more significant in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score  $\geq 2$  (HR = 0.39) [1]. Especially in patients with CHA<sub>2</sub>DS<sub>2</sub>-VASc score of  $\geq 2$  (83% of 3953 patients) Saliba and colleagues found a reduction in stroke rate in the ablation group compared to the non-ablated group (HR = 0.61) [2]. On this ground, Hunter et al. demonstrated, in an international multicenter registry of 1273 patients, that freedom from AF was associated with stroke-free survival (HR = 0.30) [3]. However, when discussing the possibility of a catheter ablation procedure for AF treatment, physicians should clearly make their patients aware about a periprocedural stroke risk which is approximately 0.5–1% [4]. Thromboembolic risk is directly related to the amount of radiofrequency lesions applied in the left atrial cavity. In fact, radiofrequency produces colliquative necrosis, thus leading to endothelial dysfunction and activation of the Virchow triad. Hence, during ablation, tissue involvement is directly related to an increased embolic risk [5]. An approach adding linear or complex lesion sets to pulmonary vein isolation (PVI) did not demonstrate an increase in freedom from AF recurrences, thus the standard endpoint during the first procedure should be PVI alone [6]. In our case, extensive left atrial ablation was performed with PVI plus tracing of two ablation lines along the roof and the mitral isthmus. Such ablation strategy was due to the presence of atypical left atrial flutter as well as of persistent atrial fibrillation. Although stroke is considered an uncommon complication after AF ablation, a growing body of evidence is consistently reporting asymptomatic or subclinical ischemic lesions in up to 41% of patients [7,8]. An elegant Italian study by Gaita and colleagues analyzed postprocedural brain magnetic resonance imaging (MRI) of 232 consecutive patients with paroxysmal or persistent atrial fibrillation who underwent radiofrequency left atrial catheter ablation. Techniques used were PVI or PVI plus linear lesions plus

atrial defragmentation. A clinical cerebrovascular accident occurred in only 1 patient. However, brain MRI returned positive for new embolic lesions in 33 patients. Cardioversion (CV) during the procedure was associated with an increased risk of 2.75 (95 confidence interval, 1.29–5.89;  $p = 0.009$ ) [9]. Our patient underwent electrical CV during the ablation due to the presence of persistent AF at the beginning of the procedure. It has been recognized that CV is related to thromboembolic events “per se”, independently by the ablation procedure. In patients undergoing TEE-guided cardioversion, patients on direct oral anticoagulants (DOACs), such as dabigatran and apixaban, experienced low incidence of thromboembolic events during follow-ups (0.6% and 1.1%, respectively), similar to warfarin, with a favorable trend of bleeding safety profile [10,11]. The highest risk period after CV is the following week, which would be a suitable timeline for our patient considering the stroke and the peripheral embolism.

Finally, it seems that techniques other than radiofrequency, such as cryoballoon based one-shot ablation and duty-cycled phased radiofrequency ablation (PVAC) are not free from silent cerebral embolisms, suggesting other mechanisms (like air embolism) could play a pivotal role in the physiopathology of these subclinical findings [12–14].

## 2.2. Management of Anticoagulant Therapy in the Periprocedural Period

Ablation was performed in January 2017. The patient had been prescribed Dabigatran 6 months before. We decided to perform TEE due to the patient’s high thromboembolic risk ( $\text{CHA}_2\text{DS}_2\text{VASc} = 4$ ). Indeed, despite optimal oral anticoagulation with DOACs, left atrial (LA) thrombus was detected in the left appendage (LAA) in >3.6% of AF patients undergoing catheter ablation in the real world. In this setting higher  $\text{CHA}_2\text{DS}_2\text{VASc}$  ( $p = 0.02$ ), but not the type of DOAC, significantly predicted the presence of LA thrombus [15].

Dabigatran has been available in Italy since 2014. At the time of ablation there were no clear guidelines on appropriate periprocedural ablation management of such a new kind of drug. On the contrary, evidence available on uninterrupted warfarin showed reduction in bleeding and thromboembolic complications [16]. Since we used all the available tools in order to reduce bleeding complications (i.e., ultrasound guided femoral veins puncture, intracardiac echocardiography, contact force sensing catheters) [17,18], we felt confident to minimize dabigatran interruption. In fact, the last assumption was in the morning of the day before, and first retake was in the evening of the day of the procedure (36 h, total interruption time). Despite this short interruption and the use of heparinization during the procedure (target activation clotting time  $\text{ACT} = 300\text{--}350$  s), we should consider this anticoagulation break as a putative factor implicated in the patient’s recurrent embolic events. Indeed, the 2017 expert consensus statement on AF Ablation provide a Class I recommendation for performing the procedure with uninterrupted dabigatran (Class I, LOE A) or rivaroxaban (Class I, LOE B-R), and a 2A recommendation for the other Xa inhibitors for which specific clinical studies had not been performed at the time [5]. These recommendations derived from the results of the RE-CIRCUIT trial which was a head-to-head comparison between uninterrupted dabigatran and uninterrupted warfarin in patients undergoing AF ablation. The incidence of major bleeding was significantly lower with dabigatran than with warfarin (5 patients (1.6%) vs 22 patients (6.9%)). No strokes/TIA (transient ischemic attack) occurred in the dabigatran arm, while there was one TIA in the warfarin group. Idarucizumab, the specific reversal agent, was never used during the study [19]. Two years before, Cappato and colleagues published the results of the VENTURE-AF trial, comparing uninterrupted rivaroxaban vs uninterrupted warfarin. Complications (a major bleeding event, one ischemic stroke, and one vascular death) occurred only in the warfarin group [20]. More recently consistent evidences were provided also for apixaban and edoxaban. The AEIOU trial, published in 2018, randomized 300 patients undergoing AF ablation to uninterrupted versus minimally interrupted (holding 1 dose) periprocedural apixaban. A retrospective cohort of patients treated with uninterrupted warfarin at the same centers was matched to the apixaban-treated subjects for comparison. There were no stroke or SE events observed in all groups. The rates of clinically significant, major bleeding were similar for all apixaban patients compared with the matched warfarin group [21]. Finally, in 2019 Hohnloser

et al. published results from the ELIMINATE-AF trial, which confirmed the safety and efficacy of uninterrupted edoxaban vs vitamin K antagonists (VKAs) in the same setting. Among 553 patients undergoing AF ablation, brain magnetic resonance imaging was performed in 177 subjects to assess silent cerebral infarcts. There was one ischaemic and one haemorrhagic stroke, both in patients on edoxaban. Cerebral microemboli were detected in 13.8% (16) of patients who received edoxaban and 9.6% (5) of patients in the VKA group ( $p = ns$ ) [22]. Based on these clinical trials, it is now clear that a strategy of performing AF ablation on patients receiving uninterrupted anticoagulation can be performed safely and will minimize the risk of thromboembolic events. Finally, international guidelines state in the absence of controlled trial data, anticoagulation management after AF ablation should follow general recommendations (i.e., on the basis of CHA<sub>2</sub>DS<sub>2</sub>-VASc score), regardless of the presumed rhythm outcome [23].

### 2.3. Iatrogenic Interatrial Septal Defect, In Situ Thrombosis and Paradoxical Embolism

The diagnosis in our patient, of simultaneous iatrogenic interatrial septal defect (IASD) and in-situ thrombosis, is rather unique. These are two well characterized phenomena that have rarely been discovered together in this setting. Real incidence of IASD after AF ablation is under debate. Older studies, using transesophageal echocardiography (TEE), reported up to 19% rate during follow-up [24–27].

More recently, other rates have been described (5.6% following a first procedure and 2.2% following a second procedure) [28].

The risk of persistent IASD is in part related to the tools, technologies, and approaches used for catheter ablation. For example, the incidence of IASD at 1-year follow-up following cryoballoon ablation procedure for PVI is significantly higher in front of radiofrequency procedures [29–31]. After a single-puncture, using the robotic navigation system, an IASD was detected in 38 of 40 (95%) patients one day after the ablation. At 6-months follow up, the IASDs were closed only in 30 of 39 (78.9%) patients. The authors also addressed that persistent IASDs are not associated with an increased rate of paradoxical embolism or with relevant shunting [32].

On the other side, the real incidence of in situ asymptomatic femoral thrombosis after AF ablation is unknown. Asymptomatic deep venous thrombosis (DVT) formation, following sheath placement for electrophysiological studies (EPS) in general, were detected in up to 16–44% of patients. In contrast, symptomatic DVTs are much lower (0.5–0.8%) [33]. In 2004, Chen and colleagues reported a significant incidence (17.6%) of non-occlusive DVT after multiple sheath placements for EPS. Nonetheless, in the study, all venous thrombi were non-occlusive and asymptomatic. None of the femoral veins developed occlusive DVT [34]. Although there are weak supporting data, it is reasonable to conclude that limiting the number and the size of femoral vein sheaths on the same side can minimize thrombosis risk. Despite the fact that there are no large prospective or randomized trials, prophylactic heparin administration during the procedure may be considered on an individual basis for right chamber ablations, particularly for longer procedures, or in high-risk patients [35]. Large emboli migrated from leg veins can lodge in the right ventricle [36], whereas smaller emboli are likely to pass unimpeded to the pulmonary arteries. The occurrence of pulmonary embolism following EP procedures has previously been reported, especially in patients with a thrombophilic state [37]. Moreover, two cases of floating atrial thrombi following EP studies were successfully treated with thrombolysis in asymptomatic patients [38].

To the best of our knowledge, there are no reported cases of paradoxical embolism following AF ablation where in situ thrombosis and iatrogenic atrial septal defect are detected simultaneously. Indeed, DVT developed despite fully systemic heparinization during the procedure and minimal oral anticoagulation interruption.



### 3. Conclusions

In conclusion, we report a case of stroke and peripheral embolism after atrial fibrillation ablation procedure. In our patient an in situ femoral vein thrombosis and iatrogenic atrial septal defect were simultaneously detected. We highlighted and discussed each etiopathogenetic mechanism underlying this clinical condition. The case encourages a critical clinical and instrumental evaluation in the management of such undesirable complications.

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