Progress in Diagnosis and Treatment: The Last 50 Years of Stroke Prevention

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Abstract: Stroke is a major global health issue. However, up to 85% of strokes may be preventable. Following an integrated conceptual timeline, we briefly report historical notes on the birth of and advancements in research on the pathophysiology and treatments of the major risk factors associated with ischemic stroke. We finally focused on the last 50 years, representing a landmark in the progress of stroke medicine. We reviewed and reported the results of the significant trials on the main stroke risk factors. The design and the results of large-scale epidemiological studies have clarified many of the underlying mechanisms of stroke pathophysiology, which has led to impressive developments in treating diseases that were considered untreatable for centuries. Although stroke is a largely preventable disease, there are still many issues faced when implementing strategies to reduce the global burden of the disease, both in terms of primary and secondary prevention.

1. Introduction

Stroke remains a major global health problem. However, up to 85% of strokes may be preventable [1]. Primary and secondary stroke prevention has significantly evolved in the last half-century, moving to the forefront of stroke management strategies. Ten potentially modifiable risk factors cause 90% of all strokes, and the most transparent approach to reducing the stroke burden is to target these factors using novel practical approaches. The World Health Organization states that effective stroke prevention tactics include decreasing the risk associated with systemic blood hypertension, diabetes mellitus, dyslipidemia, a non-healthy diet, a sedentary lifestyle, smoking, and abdominal obesity [2]. Considering the historical aspects of the last 50 years, it is interesting that the first prospective multicenter randomized trials and first advances in stroke care appeared earlier in stroke prevention than in stroke treatment.

2. Literature Review

We briefly reported the history on the birth of and advancements in research on the pathophysiology and treatments of the major risk factors associated with ischemic stroke.

We finally focused on the last 50 years, representing a landmark in progress in stroke medicine.

We reviewed and reported the results of the significant trials on the main stroke risk factors, searching PubMed and MEDLINE.

2.1. Antiplatelets

Synthetic aspirin is derived from salicylic acid, a natural compound from myrtle, willow, and meadowsweet, which has been used in herbal medicine since ancient times for its anti-inflammatory effects. Clay tablets from the Assyrians (around 2000 BCE) showcase that willow leaves were advised for the treatment of rheumatic disease; moreover, Hippocrates (460–377 BCE) prescribed an extract of willow bark for labor and fever pain [3]. In 1876, Dr. T. MacLagan performed the first clinical study of salicylate by administering salicin to achieve the full remission of joint inflammation and fever in patients suffering from acute rheumatism. In 1897, Dr. F. Hoffman produced pure, stable acetylsalicylic acid (ASA), thus creating both aspirin and the pharmaceutical manufacturing industry. On 1 February 1899, the new substance was named and first registered as aspirin [4].

We have to wait until 1953, when Dr. Craven first suggested the role of aspirin as an antithrombotic drug, publishing his work on the prevention of coronary thrombosis [5].

Weiss and Aledort, in 1967, described the irreversible suppression determined by aspirin on platelet aggregation [6], and, four years later, Vane reported the inhibition of prostaglandin synthesis as an additional mechanism of the action of aspirin [7]. After Vane received the Nobel Prize for Medicine in 1982, aspirin became established as a drug for the treatment and prevention of cardiovascular diseases.

The first trials demonstrate successful stroke prevention by aspirin, combined with other drugs (e.g., dipyridamole, ticlopidine, and sulfinpyrazone), dating back to 1970–1980 [8,9]. The Antiplatelet Trialists' Collaboration reported in 1988 that aspirin reduced overall vascular death by 15% and the incidence of non-fatal stroke and myocardial infarction by 30% [10]; the same year, the US Food and Drug Administration (FDA) granted final approval of aspirin for ischemic stroke prevention in the United States. In 1996, a CAPRIE study reported the effectiveness of clopidogrel in stroke prevention [11]. Pooled analysis of CHANCE and POINT trials in 2019 showed the benefits of dual antiaggregant treatment with the association of clopidogrel and aspirin for the secondary prevention of minor ischemic stroke or high-risk transient ischemic attack (TIA) [12].

2.2. Anticoagulants

The first agent with anticoagulant activity was discovered in dog liver by McLean et al. in 1916., which would have been known as heparin [13]. Heparin purification and sufficient production for clinical use and the discovery of its dependency on a plasma factor (now known as antithrombin) for its anticoagulant action date back to the 1930s [14].

Oral anticoagulation has a dramatic story, starting in the 1920s with the discovery of dicoumarol when, in Canada, cattle began dying of internal bleeding without an identifiable triggering cause. F. W. Schofield, a veterinary pathologist, determined that the mysterious disease was related to the ingestion of spoiled sweet

clover hay and reported a prolonged clotting time [15]. Oral anticoagulants were first designed in the 1930s and introduced for clinical use in 1959 when dicumarol was identified as the substance contained in moldy clover [16].

A series of randomized controlled trials (RCTs) on anticoagulation with warfarin, conducted in the late 1980s and early 1990s for primary and secondary stroke prevention, reported a significant reduction in the rate of ischemic stroke in patients affected by atrial fibrillation [17]. In 1997, the IST results reported that early anticoagulation with unfractionated heparin reduced recurrent ischemic stroke but significantly increased hemorrhagic stroke, without a net decrease in recurrent stroke, death, or dependency [18]. An adjusted warfarin dose (international normalized ratio range between 2.0 and 3.0) and antiplatelet therapy have been shown to decrease stroke risk by approximately two-thirds and one-fifth, respectively, in comparison to the controls [19], but not in patients with sinus rhythm [20].

Since 2009, four large RCTs have reported the non-inferiority of four direct oral anticoagulants (DOACs) over adjusted-dose warfarin for stroke prophylaxis in non-valvular atrial fibrillation (NVAF), with a favorable risk–benefit profile [21–25]. Currently, DOACs are recommended for both primary and secondary stroke prevention management in individuals suffering from NVAF.

Regarding clinical atherosclerotic disease, the results of a post hoc sub-analysis of the COMPASS trial [26] in patients with non-lacunar, non-cardioembolic ischemic stroke, along with clinical atherosclerotic disease, reported that low-dose (2.5 mg twice daily) therapy with rivaroxaban plus aspirin (100mg daily) may significantly reduce the rate of ischemic events for both primary and secondary stroke prevention [27].

New anticoagulant agents under investigation in phase 2 trials are the activated coagulation factor XI inhibitors. From phase I studies results, they are reported as being associated with lower bleeding rates. Recent PACIFIC AF study highlighted that, in patients with NVAF, the FXIa inhibitor asundexian reduced bleeding rates compared with standard dosing of apixaban, with near-complete in vivo FXIa inhibition [28].

2.3. Carotid Revascularization

After early failures in the 1940s–1950s in China [29] and Argentina [30], the first successful carotid endarterectomy was conducted in 1953 in the USA by M. DeBakey [31]. The first RCT of carotid endarterectomy was started in 1962, and its results reported benefits from the procedure but a high rate of complications [32]. In 1987, H. J. M. Barnett designed the NASCET trial [33], a large-scale clinical trial on patients with carotid disease symptomatic for TIAs or minor stroke, to estimate the risk–benefit ratio of carotid endarterectomy. In 1991, a net benefit of the surgical intervention in patients with a stenosis of the internal carotid artery greater than 70% was reported [33]. The same year, results obtained by the European ECST trial similarly showed the benefit of endarterecomy in comparison to medical

management for patients with symptomatic severe carotid stenosis [34]. The rate of carotid endarterectomies, conducted for stroke prevention, following these results, has gradually increased over time [35].

2.4. Antihypertensive Treatment

The history of hypertension originates from ancient Chinese and Indian Ayurvedic medicine, where the quality of an individual's pulse, as palpated by the physician, was considered a gateway to the state of the cardiovascular system [36]. The modern concept of hypertension begins with the work of Dr. W. Harvey. He increased our understanding of the cardiovascular system, describing blood circulation in his text "De motu cordis" (1578–1657).

During the 18th century, the theory of blood pressure gradually gained acceptance. At the beginning of the 19th century, bloodletting evolved from a "means of restoring the balance of the humors" to a way of reducing blood pressure [37].

In the 20th century, particularly over the last 50 years, the medical community accepted that hypertension is a treatable disease and not an essential condition. Results from longitudinal studies, such as the "Framingham Heart Study" in 1974, highlighted that "benign" hypertension increased rates of death and cardiovascular disease. These risks increased proportionally with the increase in blood pressure values.

From 1967 to 2001, an increasing number of trials comparing the treatment of patients affected by moderate, then mild, diastolic and systolic hypertension with placebo (or routine care) demonstrated that lowering elevated blood pressure reduced the incidence of stroke, especially in primary prevention [35,38–42].

The PROGRESS trial in 2001 was the first large trial on the pharmacological management of hypertension in secondary stroke prevention [43]; the results showed that antihypertensive therapy with an angiotensin-converting enzyme inhibitor reduces the recurrence rate of stroke by 28% compared with placebo. Subsequently, since 2003, major international guidelines have recommended active treatment to lower blood pressure in patients with previous stroke [44–47].

Additionally, in 2014, AHA/ASA published the first set of guidelines on stroke prevention in women, reporting that there are several sex peculiarities in the pathophysiology, prevalence and therapy responses of hypertension that should be pointed to improve both the awareness and treatment of this risk factor in women [48].

2.5. Lipid-Lowering Drugs

Although commonly assumed to be a modern disease, atherosclerosis has been reported to be common in preindustrial, premodern human beings [49]. The association between atherosclerosis and lipids came much later. In 1833, cholesterol was first reported in human blood by F. H. Boudet, while in 1856, R. Virchow described atherosclerotic plaque as a fundamental lesion of atherosclerosis [50].

In 1932, Wieland reported the correct structure of cholesterol [51]. The link between lipoproteins and cardiovascular disorders backdates to the early 1950s [52]. Several drugs were investigated for their potential in reducing cholesterol plasma levels, before landing the breakthrough of statins in the 1970s: nicotinic acid, resins, fibrates.

In 1987, the first 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitor for cholesterol reduction, lovastatin, was approved for clinical use by the US FDA, followed by simvastatin and pravastatin in 1989. By 2010, two semi-synthetic and four synthetic statins (e.g., simvastatin and pravastatin, in 1991; fluvastatin, 1994, atorvastatin, 1996, rosuvastatin, 2003, and pitavastatin, 2010) were marketed [53].

In 2006, the SPARCL trial reported the efficacy of high-dose statin therapy (80 mg atorvastatin daily) for secondary stroke prophylaxis [54]. Moreover, the "Treat Stroke to Target" trial results recently reported that patients in the lower target group (LDL target < 70 mg/dL) had a reduced risk of the composite primary endpoint of major cardiovascular events compared with patients in the higher target group (LDL target range: 90–110 mg/dL) in secondary stroke prevention [55].

In 2002, ezetimibe, an inhibitor of the intestinal absorption of cholesterol and other sterols, was introduced in clinical practice. The combination of ezetimibe plus statin has a synergistic mechanism, allowing the use of lower doses of statin, thereby minimizing their associated adverse effects [56]. In this regard, the 2019 European guidelines on dyslipidemia recommend the prescription of ezetimibe in patients who do not reach lipid targets with a statin alone [57].

In 2003, N. Seidah discovered proprotein convertase subtilisin Kexin-9 (PCSK-9), and its mutation was identified as a cause of autosomal dominant hypercholesterolemia. Alirocumab and evolocumab, wholly human anti-PCSK-9 antibodies, were accepted by the FDA [58] after their positive large trials results (FOURIER [59] and ODYSSEY [60]).

2.6. Antidiabetic Treatment

The mention of an illness characterized by the "too great emptying of urine" can be found in Egyptian manuscripts, more than 3000 years ago; moreover, Indian medicine reported it as madhumeha ("honey urine") because of its feature of attracting ants [61]. The first complete description of the disease is attributed to Aretaeus, the Cappadocian in the 1st century A.D., who conceived the word diabetes and affirmed, "No essential part of the drink is absorbed by the body while great masses of the flesh are liquefied into urine" [61]. The term mellitus was added by Dr. J. Rollo much later, in 1798, to distinguish this type from insipidus diabetes, with tasteless urine. The role of the pancreas in diabetes was described in 1889 by J. von Mering and O. Minkowski by showing that its removal renders dogs diabetic. Diet and exercise were the essentials of diabetes therapy in the 19th century [62]. Nobel prizes were awarded to J. J. R. Macleod and Sir F. G. Banting, in collaboration with C. H. Best, for isolating insulin and reporting the efficacious treatment of diabetic dogs by administering them pancreatic islets extract of healthy dogs. Insulin

extract was finally purified by J. B. Collip for administration to humans; in 1922, Leonard Thompson, a 14-year-old boy, was the first patient to be successfully treated with insulin.

In 1948, H. Root first observed that hyperglycemia was linked to vascular disease. In 1993, this association was confirmed by the "Diabetes Control and Complications Trial" (DCCT) results [63].

The first oral medication for diabetes has been widespread since 1955, with the introduction of sulfonylureas [64].

Currently, diabetes is an undiscussed and impacting risk factor for stroke.

From early 2000, along with essential antidiabetic treatment, newer antidiabetic medications have become available: glucagon-like peptide-1 receptor (GLP-1R) agonists, sodium-glucose transport protein-2 inhibitors, and peroxisome proliferator-activated receptor-gamma agonists (PPAR-γ).

Among the GLP-1R agonists, preliminary data from the randomized REWIND trial showed that patients in the dulaglutide-treatment arm showed a significant reduction in ischemic stroke risk [65]. A 2020 systematic review and meta-analysis suggested that GLP-1R agonists significantly reduce incidents and non-fatal strokes [66].

In the case of insulin resistance, pioglitazone, a PPAR-γ agonist, demonstrated its efficacy for secondary stroke prevention. Secondary analysis of the IRIS trial reported that patients who suffered from an ischemic stroke or TIA, with no history of diabetes but affected by insulin resistance, if treated with pioglitazone, had a significant reduction in ischemic stroke rates when compared to placebo [67].

3. Conclusions

In the last 50 years, stroke medicine has undergone impressive advances thanks to new imaging techniques, stroke units' birth and spread, and revascularization therapies, making an "untreatable" disease curable.

Although it is widely acknowledged that stroke is a largely preventable disease [1], both in primary and secondary prophylaxis, taking into account the continuous development of pharmacological approaches and surgical, vascular procedures, there are still substantial gaps to achieving actions to reduce the global burden of the disease, notably in low–middle-income countries [68].

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