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Review

Physicochemical Characteristics of Cardiological Drugs and Practical Recommendations for Intravenous Administration: A Systematic Review

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Abstract: Most cardiological drugs need intravenous administration to have a fast effect in an emergency. Intravenous administration is linked to complications, such as tissue infiltration and thrombophlebitis. Aiming to supply an effective tool for the development of appropriate policies, this systematic review provides practical recommendations about the diluent, pH, osmolarity, dosage, vesicant properties, and phlebitis rate of the most commonly used cardiological drugs evaluated in randomized controlled trials (RCTs) till 31 August 2024. The authors searched for available IV cardiological drugs in RCTs in PUBMED EMBASE®, EBSCO-CINAHL®, and Cochrane Controlled Clinical trials. Drugs' chemical features were obtained online, in drug data sheets, and in scientific papers, establishing that the drugs with a pH of <5 or >9, an osmolarity > 600 mOsm/L, and a high incidence of phlebitis reported in the literature, as well as vesicant drugs, require utmost caution during administration. A total of 857 papers were evaluated and 316 studies were included. A total of 84 cardiological drugs were identified, of which only 31 (37%) can be safely infused via a peripheral route. Thrombolytics and anticoagulants are considered the safest classes of drugs, with only one drug flagged as a "red flag" medication. However, a higher percentage of drugs in other categories meet the "red flag" criteria, including antiarrhythmics (52%), antiplatelet agents (67%), diuretics (67%), antihypertensives (70%), other drugs (77%), and vasoconstrictors and inotropics (89%). Understanding the physicochemical properties of cardiological drugs is essential for significantly improving patient safety and preventing administration errors and local side effects.

Keywords: cardiological drug; antiarrhythmic; antiplatelet agent; diuretic; antihypertensive; cardiotonic agent; thrombolytic; anticoagulant; intravenous administration; thrombosis; pH; osmolarity; vesicant; central catheter; peripheral catheter

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1. Introduction

Intravenous therapy (IV) represents one of the cornerstones for the administration of drugs; approximately 80% of hospitalized patients receive a peripheral vascular access device (PVAD): a catheter inserted in a superficial vein with the tip lying in the peripheral circulation [1]. While IV therapy has advantages such as easy bioavailability of the drug, a constant therapeutic dosage through continuous infusion, and the ability to administer drugs that are non-absorbable via the enteral route, it also comes with certain risks [2]. Repeated contact of the infusate with a specific point of the venous wall can lead to inflammation (phlebitis), thrombosis, and leakage of the infusate into extravascular tissues (infiltration) [3]. To minimize these complications, it is crucial to ensure that the infusion enters a vessel with sufficient dimensions and flow to obtain effective hemodilution of the drug, particularly when administering drugs with chemical characteristics very different from blood [4]. To overcome these limitations in clinical practice, it is common to use specific devices called central venous access devices (CVADs) whose tip lies in the Cavo-Atrial Junction or the lower third of the Superior Vena Cava [5] and immediately near the Right Atrium or above the renal veins if the catheter reaches the Inferior Vena Cava [6]. In the literature, CVADs are recommended for drugs with extreme pH levels (<5 or >9), high osmolarity (>600 mOsm), and the potential to cause tissue damage if they leak outside of the blood vessel (i.e., vesicant drugs) [7]. On the one hand, is essential to recognize that certain drugs can have harmful effects if not administered through CVADs. On the other hand, inserting these devices is not always feasible, especially in emergencies or when a clinician cannot perform the procedure quickly and safely. Placing these catheters carries inherent risks, such as thrombosis, bloodstream infections, and procedural complications [8,9]. These risks persist in real-world practice despite healthcare organizations' efforts to mitigate them.

A recent paper [10] by the Task Force on Vesicants from the Infusion Nurses Society (INS) emphasizes the importance of addressing the issue of extravasation, which refers to the infiltration of vesicant drugs. The Task Force recommends a multimodal approach, including training for personnel and the development of specific policies and procedures. Among these recommendations, it is advised that lists of hazardous drugs be made available in all hospital units for reference. These lists include vesicant chemotherapy drugs, high-osmolarity parenteral nutrition, certain antibiotics and antivirals, vasoactive amines, and other commonly prescribed medications [10,11]. Providing this information helps healthcare professionals make informed decisions and ensures safe drug administration [12,13].

The current literature landscape lacks systematic reviews of drug characteristics on this topic. This systematic review examines cardiological drugs, intending to provide a valuable tool for healthcare organizations to develop policies to administer these drugs safely, similar to a previous article regarding some of the most commonly used antimicrobial drugs worldwide [14].

The included medications are very different from each other, both in terms of effect and indication. Still, they target the cardiovascular system and have an identical route of administration: intravenous.

Pharmaceuticals utilized for maintaining hemodynamic status have a significant presence in this category, like vasoactive agents that support systemic circulation and inotropic drugs that enhance the contractile capacity of the cardiac muscle. The vasoactive agents are employed to improve the blood flow to the body's various organs, while inotropic drugs increase the force and velocity of the cardiac muscle contraction. The usage of these drugs is critical for addressing medical conditions where there is a need to enhance the heart's performance and maintain the overall hemodynamic balance of the body.

Furthermore, drugs that are usually used in stable or chronic patients and, during intensive care, are used in high doses and intravenously were examined.

It is not easy to find data about the preferred line administration (central or peripheral), pH, osmolarity, diluent, and infusion rate of many of these drugs. When available, they are often contrasting due to the lack of standardized protocols in this setting. This can lead to the wrong choice of vascular access device (VAD) being used, increasing the risk of complications due to "chemically induced" phenomena.

The present systematic review collects practical recommendations about diluents, pH, osmolarity, dosage, infusion rate, vesicant drugs, phlebitis rate, and advice for caution (Red Flag) of the most commonly used "cardiological drugs" evaluated in randomized controlled trials (RCTs) till 31st August 2024.

2. Materials and Methods

This systematic review followed the preferred reporting items for systematic reviews and meta-analyses (PRISMA) [15], and was registered on PROSPERO (CRD42023434665).

RCTs of available IV cardiological drugs were searched in PUBMED® EMBASE®, EBSCO-CINAHL®, and the Cochrane Controlled Clinical trials.

Search strings were developed with the assistance of a medical librarian and a MesH term browser [https://meshb.nlm.nih.gov/ (accessed on 31 August 2024)] and contained terms and synonyms for Antihypertensive Drugs (Antihypertensives; Antihypertensive Drug; Antihypertensive Agent; Antihypertensive; Anti-Hypertensives; Anti-Hypertensive Drugs; Anti-Hypertensive; Anti-Hypertensive Agent; Anti-Hypertensive Agents; Anti-Hypertensive Drug) OR Vasoconstrictor Agents (Vasoactive Agonist; Vasoactive Agonists; Vasoconstrictor; Vasoconstrictor Agent; Vasoconstrictor Drug; Vasoconstrictor Drugs; Vasoconstrictors; Vasopressor Agent; Vasopressor Agents) OR Cardiotonic Agents (Cardiac Stimulant; Cardiac Stimulants; Cardioprotective Agent; Cardioprotective Agents; Cardiotonic; Cardiotonic Agent; Cardiotonic Drug; Cardiotonic Drugs; Cardiotonics; Inotropic Agents, Positive Cardiac; Myocardial Stimulant; Myocardial Stimulants) OR Antiarrhythmic Drug (Anti-Arrhythmia Agent; Anti-Arrhythmia Drug; Anti-Arrhythmia Drugs; Anti-Arrhythmic; Anti-Arrhythmics; Antiarrhythmia Agent; Antiarrhythmia Agents; Antiarrhythmia Drug; Antiarrhythmia Drugs; Antiarrhythmic Drug; Antiarrhythmic Drugs; Antifibrillatory Agent; Antifibrillatory Agents; Cardiac Depressant; Cardiac Depressants; Myocardial Depressant; Myocardial Depressants) OR Diuretic OR Antiaggregant OR Anticoagulant (Anticoagulant Agent; Anticoagulant Agents; Anticoagulant Drug; Anticoagulant Drugs; Anticoagulation Agents; Indirect Thrombin Inhibitors) AND new AND intravenous. No MesH terms were found for "Diuretic", "Antiaggregant", "new", or "intravenous".

Only RCTs till 31 August 2024 were considered for analysis. The exclusion criteria were as follows:

- In vitro and/or animal studies.
- Papers not written in English.
- Papers not about cardiological agents.
- Papers about non-IV cardiological agents.
- Papers discussing cardiological drugs that have been withdrawn due to adverse events or removed from the market.
- Papers on cardiological agents are currently under investigation in phases II and III or awaiting approval.

All the papers that did not match the exclusion criteria were analyzed.

According to the literature, authors have given warnings of a "red flag" for solutions with a pH < 5 or >9, osmolarity > 600 mOsm/L, and a reported incidence of thrombophlebitis if infused in peripheral veins $\geq$ 5% or with vesicant properties [16].

Two authors, M.Q. and E.M., independently screened all papers for eligibility by reviewing their titles and abstracts using Covidence software. They then assessed the relevant studies' full texts for final inclusion. A third investigator, A.G., helped resolve any disagreements regarding inclusion. Finally, a manual search of the reference lists from the included articles was conducted, and recommendations from experts were also reviewed for potential inclusion.

Considering that not all RCTs reviewed reported the incidence of thrombophlebitis, after identifying the cardiological drugs, the chemical features of each drug were searched in specific databases (https://www.drugs.com/ [accessed on 31 October 2024] and https://www.fda.gov/Drugs/ [accessed on 31 October 2024]), drug data sheets, and recently published scientific papers on the topic. Three authors (D.G., A.G., and D.C.) reviewed the drug list, compared the various available sources, and resolved controversial data.

3. Results

A total of 857 papers were initially found, but 261 articles were removed before screening because they were unrelated to cardiological therapy. During the screening phase, 12 papers were excluded because they involved studies conducted on animals. Additionally, 157 articles focused on non-intravenous (non-IV) cardiological agents. Six articles regarding cardiological agents under investigation in phases II and III or awaiting approval were excluded. A total of 13 papers not written in English and 92 papers where patients withdrew due to adverse events or because the drugs were "out of market" were not considered. In total, 316 papers were ultimately considered in this systematic review (Figure 1).

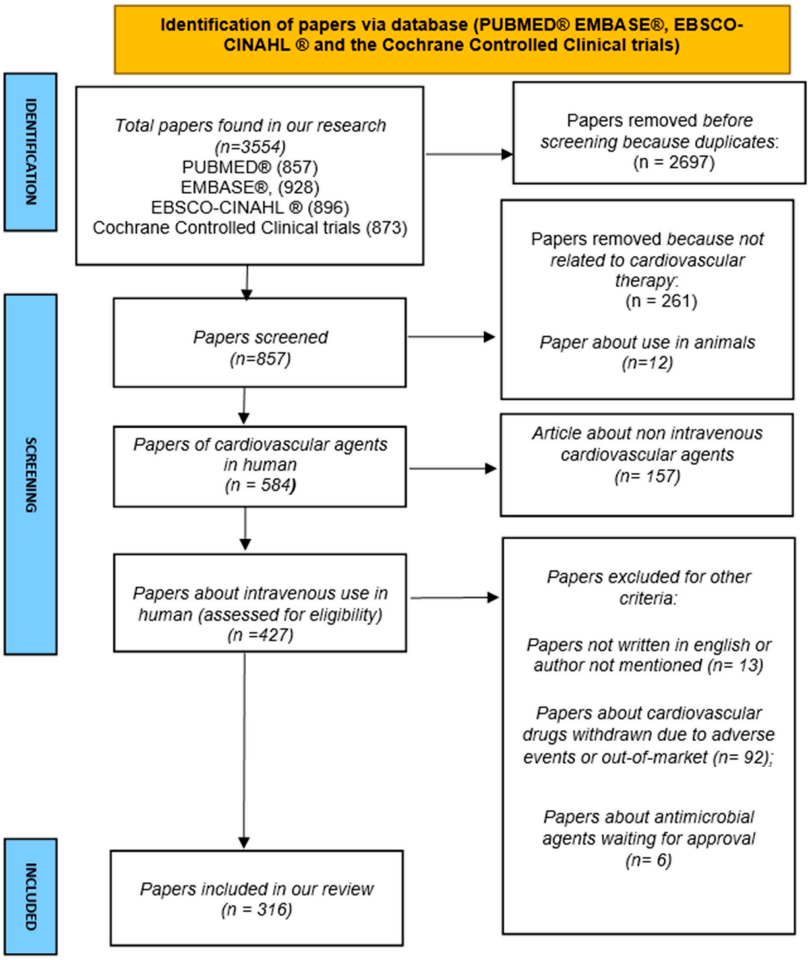

Figure 1. PRISMA flow diagram of our systematic review.

A total of 84 cardiological drugs (21 antiarrhythmics, 18 vasoconstrictor and inotropic agents, 6 thrombolytics, 6 antiaggregants, 10 antihypertensives, 4 anticoagulants, 6 diuretics, and 13 other drugs) were identified. For details regarding pH, osmolarity, dosage, infusion rates, and "red flags" for each drug examined, please refer to Table 1.

Table 1. List of cardiological drugs identified through our systematic review, with their physico-chemical characteristics and practical recommendations for intravenous administration. (phlebitis: yes = incidence ≥ 5%; no = incidence < 5%; NA: not available; 0.9% NaCl: sodium chloride 0.9%; D5W: dextrose 5% in water). Red flag and vesicant properties: red: meets criteria for CVAD insertion; green: does not meet CVAD insertion criteria.

Cardiologic Drugs and Line of Infusion							
Name	**Red Flag and/or Vesicant Properties**	**pH**	**mOsm/Kg**	**Phlebitis (Incidence ≥ 5%)**	**Diluent**	**Loading Dose**	**Maintenance Dose**
Antiarrhythmics							
Adenosine [17–22]		6–7.5	261–319	no	D5W/NS	6 mg	NA
Amiodarone [23–40]	**vesicant**	3.7–4.3	304	yes	D5W	5 mg/Kg	10–20 mg/Kg
Deslanoside [41]		5–7	NA	no	NS	NA	NA
Digoxin	**vesicant**	6.8–7.2	455	yes	D5W	8–12 mcg/Kg	¼ loading dose
[33,42–44]	**vesicant**	6.8–7.2	421	yes	NS	8–12 mcg/Kg	¼ loading dose
Diltiazem [43–47]		3.7–4.1	NA	no	D5W/NS	0.25 mg/Kg	10 mg/h
Disopyramide [48]		4–5	NA	no	NS	NA	NA
Esmolol [49–57]	**vesicant**	4.5–5.5	300	no	NS	0.5 mg/Kg	0.05–0.2 mg/Kg/min
Flecainide [58]		5.8	300	no	D5W/NS	2 mg/Kg	1.5 mg/Kg/ for 1 h then 0.1–0.25 mg/Kg/h
Ibutilide [59–62]		4.6	NA	no	D5W/NS	NA	0.1 mg/Kg (max 1 mg)
Labetalol		3–4.5	249	no	D5W	20 mg	1–2 mg/min
[53,63–66]		3–4.5	229	no	NS	20 mg	1–2 mg/min
Landiolol [57,67–70]		6.3	1896	no	D5W/NS	100 mcg/Kg/min	10–40 mcg/Kg/min
Lidocaine [30,71–75]		6.5	280–305	no	D5W	1–1.5 mg/Kg	NA
Metoprolole [76–87]		6–7	NA	no	NS	5–15 mg	NA
Phenytoin [88]		12	312	yes	NS	3.5–5 mg/Kg	< 50 mg/min
Procainamide [88]		4–6	NA	no	D5W/NS	20 mg/min	2–6 mg/min
Propafenone [37,60]		6.5	NA	no	NS	1 mg/Kg	0.5–1 mg/min for 3 h
Propranolol [51,55,56,89,90]		3.9–6.4	NA	NA	D5W/NS	1–3 mg at 1 mg/min	Not recommended
Quinidine gluconate [91]		5.5–7	NA	no	NS	NA	Max 10 mg/Kg at 0.25 mg/Kg/min
Sotatol [29,33,61,92]		6–7	NA	no	D5W/NS	0.5–1.5 mg/Kg in 30 min	1 mg/Kg in 4–6 h
Verapamil [86,93–97]		5–6	NA	no	NS	2.5–10 mg	NA
Vernakalant [98]		5.5	270–320	no	D5W/NS	NA	3 mg/Kg over 10 min
Vasoconstrictor and Inotropic							
Aminophylline [99]	**vesicant**	8.6–9	124	yes	D5W/NS	25 mg/min	0.25–0.9 mg/Kg/h
Alprostadil [100]		4–8	NA	no	D5W/NS	NO	10 mcg/day in 1–2 h upgradable to 20 mcg
Amrinone [101]		3.2	300	yes	D5W	0.75 mcg/Kg	5–10 mcg/Kg/min
Desmopressin [102,103]		3.5–6	NA	No	NS	NA	1–2 mcg x 2/day
Dexmedetomidine [74,104]		4.5–7	NA	no	D5W/NS	1 mcg/kg over 10 min	0.2–0.7 mcg/Kg/h
Dobutamine	**vesicant**	2.5–4	269	yes	D5W	NA	2–20 mcg/Kg/min
[100,105–120]	**vesicant**	2.5–4	251	yes	NS	NA	2–20 mcg/Kg/min

Table 1. *Cont.*

Cardiologic Drugs and Line of Infusion							
Name	**Red Flag and/or Vesicant Properties**	**pH**	**mOsm/Kg**	**Phlebitis (Incidence ≥ 5%)**	**Diluent**	**Loading Dose**	**Maintenance Dose**
Dopamine [100,121–125]	**vesicant**	2.5–5	560	yes	D5W/NS	Variable	Variable
Enoximone [126,127]		12	NA	no	NS	0.5 mg/Kg	5–20 mcg/Kg/min
Epinephrine [122,128–132]	**vesicant**	2.5–3.5	NA	yes	D5W/NS	NA	0.05–2 mcg/Kg/min
Epoprosterenol [133–138]		10.3–10.8	NA	no	NS	2 ng/Kg/min	titrate 1–2 ng/Kg/min until target
Iloprost [139]		7.7–8.7	430–490	no		0.5 ng/Kg/min	increase 0.5 ng/Kg/min (dose max: 2 ng/Kg/min)
Isoproterenol [140,141]		2.5–4.5	NA	no	D5W/NS	0.02–0.06 mg	2–20 mcg/min
Levosimendan [108–111,113,142–160]		5–7	450–550	no	NS	6–12 mcg/Kg	0.05–0.2 mcg/Kg/min
Milrinone [107,119,120,161–165]		3.2–4	261–319	no	D5W/NS	50 mcg/Kg	0.375–0.75 mcg/Kg/min
Norepinephrine [122,132,166,167]	**vesicant**	3–4.5	280–300	yes	D5W	NA	0.01–3.3 mcg/Kg/min
Phenilephrine [130,131,168]	**vesicant**	4.7–5.3	270–300	no	D5W/NS	50–100 mcg	0.5–6 mcg/Kg/min
Terlipressine [102,169]	**vesicant**	3.7–4.2	290–360	no	NS	NA	1–2 mg × 3–4/day
Vasopressin [132,170]	**vesicant**	3.5	NA	no	NS	NA	0.01–0.03 UI/min
Thrombolytics							
Alteplase [171–178]		6.7–7.8	215	no	D5W/NS	Variable	Variable
Anistreplase [179]		4–5	NA	no	NS	30 mg in 5 min	NA
Reteplase [180,181]		6	NA	no	NS	NA	10 UI over 2 min
Streptokinase [177,182,183]		7.3	NA	no	NS	250,000 UI	100,000 UI/h
Tenecteplase [184,185]		7.3	290	no	NS	based on weight	based on weight
Urokinase [186]		6–7.5	NA	no	NS	3300–4400 UI/kg	3300–4400 UI/kg/h
Antiaggregants							
Abciximab [180,181,184,187–193]		7.2	NA	no	D5W/NS	0.25 mg/Kg	0.125 mcg/min
Argatroban [194]		3.2–7.5	NA	no	NS	350 mcg/Kg	25 mcg/Kg/min (targeted on ACT)
Bivalirudin [182,195–202]		4.6–6	250–450	no	D5W/NS	0.75 mg/Kg	1.75 mg/Kg/h
Cangrelor [196,203]		8–9.5	287–290	no	D5W/NS	30 mcg/Kg	4 mcg/Kg/min
Eptifibatide [176,188,204,205]		5.35	NA	yes	NS	180 mcg/Kg	2 mcg/Kg/min
Tirofiban [192,206,207]		5.5–6.5	NA	no	NS	25 mcg/Kg	4 mcg/Kg/min
Antihypertensives							
Clevidipine [208]		6–8	341	no	not to diluite	1–2 mg/h	4–6 mg/h
Clonidine [209–217]		4.5–5.5	300	no	NS	NA	0.2 mcg/Kg/min
Enalaprilat [218–221]		6.5–7.5	NA	no	D5W/NS	1.25 mg	1–5 mg/6 h in bolus
Fenoldopam [222–224]		7.2	NA	no	D5W/NS	NA	0.01–1.6 mcg/Kg/min
Hydralazine [225–228]		3.4–4.4	NA	no	D5W	NA	20–40 mg repeatable (Max dose 300 mg)
Nicardipine [52,229–233]		3.5	300	no	D5W/NS	NA	5–15 mg/h
Nitroglicerin [234]		4	428–465	no	D5W/NS	NA	5–20 mcg/min

Table 1. *Cont.*

Cardiologic Drugs and Line of Infusion							
Name	**Red Flag and/or Vesicant Properties**	**pH**	**mOsm/Kg**	**Phlebitis (Incidence ≥ 5%)**	**Diluent**	**Loading Dose**	**Maintenance Dose**
Nitroprusside [22,54,85,224,235–238]		3.2–6.5	305	no	D5W	NA	0.3–10 mcg/Kg/min
Phentolamine [239]		4.5–6.5	NA	no	NS	1–5 mg in bolus	NA
Urapidil		5.6–6.6	815	no	D5W	0.3 mg/Kg	4–30 mg/h
[238,240,241]		5.6–6.6	785	no	NS	0.3 mg/Kg	4–30 mg/h
Anticoagulants							
Danaparoid [242,243]		7	NA	no	NS	1200–1500 UI	400 UI/h for 4 h
Deltaparine [244]		5–7.5	NA	no	not to diluite	Variable	Variable
Enoxaparine [171,176,177,182,183,186,201,245–258]		5.5–7.5	NA	no	not to diluite	Variable	Variable
Unfractionated Heparin (UFH) [184,185,195,199,200,206,258–281]		5–6	298	no	D5W	80 UI/Kg	18 UI/Kg/min
		6–8	322	no	NS	80 UI/Kg	18 UI/Kg/min
Diuretics							
Acetazolamide [282]	**vesicant**	9.6	NA	Yes	NS	NA	250–375 (5 mg/Kg/die)
Bumetanide [124,283]		6.8–7.8	NA	no	D5W/NS	1 mg	0.5–2 mg/h
Ethacrynic acid [284]		7	NA	no	NS	0.5 mg/Kg	0.5–1 mg/Kg in C.I.
Furosemide [285–301]		8–9.3	286–300	no	NS	NA	20–1000 mg/die
Mannitol [125,302,303]	**vesicant**	6.3	1335	yes	not diluite	NA	1.5–2 g/Kg over 30–60 min
Potassium canreonate [304,305]		10	NA	no	D5W/NS	NA	Up to 800 mg/die
Other Drugs							
Calcium chloride [306]	**vesicant**	4.3	400	yes	D5W	0.5–2 g	NA
	vesicant	4.5	361	yes	NS	0.5–2 g	NA
Calcium	**vesicant**	6–8.2	316	yes	D5W	1.5–3 g	NA
Gluconate [307]	**vesicant**	6–8.2	298	yes	NS	1.5–3 g	NA
Conivaptan [308]		3.4–3.8	NA	yes	D5W	20 mg over 30 min	20 mg over 24 h
Dextrose ≥ 10% [309]	**vesicant**	3.5–6.5	505	yes	D10W	Variable	Variable
Ferric carboxymaltose [310]		5–7	NA	no	NS	NA	500–1000 mg
Ferric derisomaltose [311]		5–7	NA	no	NS	NA	20 mg/Kg (max 1000 mg)
Glucagon [309]		1.8–2.2	NA	yes	NS	NA	0.5–1 mg
Magnesium Sulfate [312–323]	**vesicant**	5.5–7	400–500	no	NS	1–2 g	0.5–1 g/h
Oxytocin [324]		3.5	NA	no	NS	0.5–1 mU/min	increment of 1–2 mU/min
Salbutamol [141]		3.5	NA	no	NS	4 mcg/Kg	3–20 mcg/min
Sodium bicarbonate ≥ 8.4% [325]	**vesicant**	8.34	2000	yes	NA	Variable	Variable
Tranexamic Acid [326–328]		6.5–8	316	no	NS	10 mg/Kg	NA
		6.5–8	346	no	D5W	10 mg/Kg	NA

Table 1. *Cont.*

Cardiologic Drugs and Line of Infusion							
Name	**Red Flag and/or Vesicant Properties**	**pH**	**mOsm/Kg**	**Phlebitis (Incidence ≥ 5%)**	**Diluent**	**Loading Dose**	**Maintenance Dose**
Potassium chloride (10.1–29.9 mEq/100 mL) [329]	**vesicant**	4.2–6	202–598	yes	D5W/NS	Variable	Variable
Potassium chloride (30 mEq/100 mL) [329]	**vesicant**	4.2–6	763	yes	D5W/NS	Variable	Variable

- *Antiarrhythmics*

Eleven identified medicines are at risk based on specific criteria, which include high rates of phlebitis (≥5%), extreme pH levels, high osmolarity values, or vesicant properties. Among these, eight exhibit extreme pH levels; one shows a high incidence of phlebitis in the literature, and two possess extreme pH and high phlebitis reports. Notably, Amiodarone, Esmolol, and Digoxin are classified as vesicant drugs. Only Landiolol has osmolarity values exceeding 600 mOsm/L, while ten drugs can be safely infused through PVADs.

Most antiarrhythmics (47.6%) require either 5% dextrose in water (D5W) or 0.9% sodium chloride (NS) as a diluent. Four drugs must be administered exclusively with D5W, while seven require saline infusion with NS.

- *Vasoconstrictor and Inotropic (V&I) Drugs*

Sixteen V&Is meet the specified precautionary criteria: thirteen are suitable for low pH, three for high pH, and six for extreme pH with a high risk of phlebitis. The recommended agents for extreme pH and vesicant characteristics include Aminophylline, Terlipressin, Vasopressin, Phenylephrine, Norepinephrine, Epinephrine, Dopamine, and Dobutamine.

Eight drugs can be diluted with either D5W or NS, while three require D5W for infusion. The remaining seven drugs must be administered solely with NS.

- *Thrombolytics*

The majority of thrombolytics can be infused safely with a PVAD. Only Anistreplase requires a CVAD due to its low pH. Alteplase can be diluted with either NS or D5W, while the remainder should be used with NS.

- *Antiaggregants*

Four drugs in this class meet the "Red Flag" criteria. Two are due to an acid pH lower than 5, and Cangrelor has an alkaline pH over 9. Only Eptifibatide has high reports of phlebitis (≥5%). All these drugs must be diluted with NS, while three (Abiciximab, Bivalidurin, and Cangrelor) can also use D5W.

- *Antihypertensives*

In total, 70% of antihypertensives evaluated are included in the "Red Flag" criteria. Six drugs have a low pH, while Urapidil has a high osmolarity. Clonidine and Phentolamine require NS for dilution, while Hydralazine, Nitroprusside, and Urapidil require D5W; the remaining antihypertensives can use both solutions.

- *Anticoagulants*

All these drugs can be infused safely through a PVAD. Danaparoid must be diluted with NS, while unfractionated heparin (UFH) can be used in both solutions.

- *Diuretics*

Furosemide and Potassium canreonate are hazardous drugs due to their alkaline pH. Mannitol has a high osmolarity that needs a high flow to be diluted. Acetazolamide is a well-known vesicant drug. Potassium canreonate and Bumetanide can be diluted with NS or D5W, while the others (except Mannitol) require NS.

- *Other drugs*

Only three drugs can be safely infused via PVAD: the new formulations of iron (Ferric isomaltose and Ferric carboxymaltose) and Tranexamic Acid. Due to their vesicant properties, the "red flag drugs" are electrolyte supplements (Calcium chloride, Calcium Gluconate, Magnesium Sulfate, Potassium chloride) or contain sodium bicarbonate and dextrose over ten percent. The remaining "red flag drugs" have low pH. Three accept both NS and D5W for dilution; one requires D5W and six NS.

4. Discussion

This systematic review compiles a list of the most commonly used cardiological drugs, whether they are currently available or will soon be released. Data on various factors, including diluent, pH, osmolarity, dosage, infusion rate, vesicant properties, the incidence of phlebitis, and the presence or absence of specific "red flag" criteria, were obtained for each medication studied. The goal is to assist institutions in developing a policy for the safe intravenous administration of cardiological drugs.

The results show that only 31 of 84 drugs (37%) can be safely infused in a PVAD.

Thrombolytics and anticoagulants are considered the safest classes of drugs, with only one molecule identified as a "red flag drug". In contrast, more molecules in other categories meet the "red flag" criteria. Specifically, this percentage includes antiarrhythmics (52%), antiplatelet agents (67%), diuretics (67%), antihypertensives (70%), other drugs (77%), and V&Is (89%).

Extreme pH is the first reason. Thirty-five (43%) drugs have a pH lower than 5, and eight (10%) have a pH over 9.

It is important to note that clinicians typically cannot modify pH values. The literature indicates that when vessel walls are exposed to pH levels different from blood, changes in the endothelium can occur, resulting in inflammatory responses and damage to the integrity of the *Tunica Intima*, affecting the glycocalyx, a layer of complex carbohydrates covering endothelial cells' luminal surface. This gel-like meshwork extends into the bloodstream from the endothelial cell membrane and acts as an insulator, protecting the endothelial cells from damage [330].

However, mechanical rubbing and the shear stress from flushing can compromise this tissue's delicate and dynamic nature. This can trigger an inflammatory response, leading to phlebitis and thrombosis. The situation worsens when harsh infusates—some of which may be unsuitable for peripheral veins—flow against the exposed endothelial cells, which are no longer protected by the glycocalyx [10,11,14]. This ultimately results in complications and an increased risk of catheter failure.

Borgonovo et al. [14] determined the infusion time for antimicrobial agents in a similar paper. However, this information was not added to this systematic review because most drugs require continuous infusion, and the dosage depends on vital signs or blood exams (coagulation parameters for anticoagulants). Data about the effect of the constant infusion of vesicant drugs are lacking in the literature. Recently, a randomized controlled trial about continued infusion of Vancomycin through a PVAD was prematurely stopped due to the increased risk of thrombosis [331].

Instead, the literature reports data about the continued infusion of vasoconstrictor and cardiotonic agents through short peripheral catheters (SPCs, a type of PVAD < 6 cm long) [5]. The Infusion Therapy Standards of Practice 2024 avoid this choice and limit peripheral vasopressor administration through SPCs to a short duration (e.g., less than 24 h) before transitioning to a CVAD. Vasopressors are recognized as potent vesicants, and most of these medications are flagged as high risk due to documented cases of patient injuries [332]. This risk arises from their vasoconstrictive action, often used in significant hypoperfusion situations. Therefore, it is crucial to select and maintain VADs with great care.

This systematic review found hyperosmolarity in three drugs (Landiolol, Urapidil, and Mannitol). Mannitol and Glucose in a 10% solution are well-known vesicant drugs due to their high osmolarity (between 549 and 555 mOsm/L). In an in vivo experiment conducted on rats, tissue exposed to a 10% solution of Mannitol or Glucose showed signs of damage, such as cellular shedding and infiltration by inflammatory cells. Moreover, induration, ulceration, and necrosis occur with 25% Mannitol or Glucose solutions (osmolarity of 1388 mOsm/L) [333].

Safe administration is a fundamental aspect of pharmacological treatment. VAD failure due to complications, such as inflammatory events or infusate leakage from the venous wall, can result in severe consequences: tissue damage, delays in therapy administration, increased costs, prolonged hospitalization, and potential compensation claims [334]. In 2022, the UK National Health Service Resolution published an analysis of litigation claims related to extravasation, revealing that the financial burden on the healthcare system for compensation and treatment amounted to GBP 16 million over a ten-year observation period [335].

Using SPCs for intravenous therapy is the most common strategy worldwide. However, despite its undeniable advantages—including cost efficiency, ease of use, and simplicity of management—this approach is accompanied by a significant risk of complications [336]. A meta-analysis conducted in 2019, which included 35 studies involving 20,697 catheters used in 15,791 patients, found that the incidence of phlebitis was 30.7 per 100 catheters (95% confidence interval: 27.2 to 34.2). This study identified several important risk factors for the development of phlebitis: longer dwelling time, antibiotic infusion, female gender, forearm insertion, presence of infectious diseases, and the use of Teflon cannulae [337].

A central catheter can help maintain scheduled drug administration by preventing missed doses and eliminating the need to interrupt continuous infusions, which often occurs with complicated peripheral cannulas. This approach ensures more consistent and reliable drug delivery, enhancing overall patient care and minimizing the risk of complications associated with peripheral access.

Superficial judgments should not mislead people about the data suggesting the mandatory use of CVADs, as choosing between these and PVADs can often be complex in everyday practice. In addition to the critical issues mentioned in the introduction, other factors suggest that the decision to insert a CVAD may not always be justified. For instance, consider antiarrhythmic drugs like Adenosine and Amiodarone, often given in single boluses or for very short durations. Likewise, diuretics such as Furosemide, although they meet the criteria to be considered a "red flag drug", are frequently administered in small bolus doses.

It is fascinating to note the increasing number of documents in the literature about the use of midline catheters (a different type of PVAD) for the administration of vasopressor drugs and vesicant drugs in those catheters [332,338–340]. Nonetheless, the authors concur with Hadaway and Gorski [341], who recommend that this type of catheter be avoided or used with extreme caution until more definitive data are available from the literature.

A well-designed RCT is the only solution for this risk issue related to antiarrhythmics or diuretic infusion utilizing a midline catheter instead of a central venous catheter.

Therefore, a multifactorial approach is essential to addressing this issue. Several factors must be considered, including patient conditions, the number and quality of suitable veins, the selection of vascular devices, treatment duration, proper device usage, and implementation of an effective monitoring system. It is also crucial to consider the chemical characteristics of the drugs being administered, as pH and osmolarity are well-recognized risk factors [342,343].

Many of these drugs are commonly used for critically ill patients, where insertion of CVADs is recommended [2]. However, they are also frequently used in non-intensive care settings across various departments, often with dosages at which placing a CVAD is unnecessary.

The authors emphasize that the judgment of clinicians who prescribe and administer these medications is crucial for ensuring safe and effective treatment. Staff must be aware of the risks associated with chemical phlebitis and extravasation and implement measures to treat and prevent these events. Brørs et al. recently confirmed that strict adherence to clinical practice guidelines for Amiodarone infusion effectively reduces the occurrence of phlebitis [344].

In this context, ultrasound has emerged as a promising monitoring tool. It has demonstrated the ability to predict failures of short peripheral catheters [345,346] and to evaluate hemodilution at the catheter tip [4] (an essential factor in assessing the risk of chemical phlebitis). Additionally, ultrasound has proven more effective than clinical evaluation in identifying phlebitis events [347] and describing infiltrates [348]. Finding information on essential factors such as pH, osmolarity, required diluents, and infusion rates for each cardiological drug is challenging. Even when this information is available, it is often inconsistent across different sources. In the authors' opinion, this inconsistency limits the effectiveness of this review and emphasizes the need to standardize this information to achieve uniformity in future guidelines.

This systematic review includes only English-language articles; this limitation can introduce selection bias, but it allows for the evaluation of universally understood papers.

Another limitation is the absence of a detailed pathophysiological description of phlebitis cases. This lack of information makes distinguishing between phlebitis caused by chemical factors, infections, or mechanical issues in the evaluated studies challenging. Similar to the previous limitation, this also highlights the variability of data available in the literature and underscores the need for further research.

Finally, it is important to note that commercially available cardiological medicines are often produced by different pharmaceutical manufacturers, who may add various adjuvants or make structural modifications. These changes can alter the drug's biochemical properties, potentially resulting in varying degrees of vesicant properties and the likelihood of causing phlebitis. As a result, the physicochemical characteristics of the original molecules may differ significantly from those of the commercially available versions. This variation represents an additional limitation of our study.

5. Conclusions

IV therapy is a crucial component of everyday clinical practice. While it is commonly utilized, it is also associated with various complications. The physicochemical properties of the medication being administered play a vital role in complications related to VADs, mainly when a vesicant or irritant solution is delivered using an inappropriate vascular device. Understanding the physicochemical characteristics of drugs is essential for selecting a suitable VAD, which can help minimize the risk of vascular damage. Considering these

limitations, the list created, alongside existing lists of other IV drugs, could serve as a valuable tool for clinicians and healthcare institutions. This resource aims to enhance the selection of the most appropriate VAD, reducing the likelihood of administration errors and local side effects like phlebitis and thrombosis.

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