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# Mapping the characteristics, methodological quality and standards of reporting of network meta-analyses on antithrombotic therapies: An overview

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ABSTRACT

*Background:* Although a large number of network meta-analyses (NMAs) in the field of cardiology are available, little is known about their methodological quality. We aimed to map the characteristics and critically appraised the standards of conduct and evidence reporting of NMAs assessing antithrombotic therapies for the treatment or prophylaxis of heart diseases and cardiac surgical procedures.
*Methods:* We systematically searched PubMed and Scopus to identify NMAs comparing the clinical effects of antithrombotic therapies. Overall characteristics of the NMAs were extracted and their reporting quality and methodological quality were evaluated using the PRISMA-NMA checklist and AMSTAR-2, respectively.
*Results:* We found 86 NMAs published between 2007 and 2022. Comparisons among direct-acting oral anticoagulants were available in 61 (71%) NMAs. Although around 75% of NMAs stated that they followed international guidelines for conduct and reporting, only one third provided a protocol/register. Complete search strategies and publication bias assessment were lacking in around 53% and 59% of studies, respectively. Most NMAs ($n$ = 77, 90%) provided supplemental material; however, only 5 (6%) made the complete raw data available. Network diagrams were depicted in most studies ($n$ = 67, 78%), yet network geometry was described in only 11 (12.8%) of them. Mean adherence to the PRISMA-NMA checklist was 65.1 ± 16.5%. AMSTAR-2 assessment showed 88% of the NMAs had critically low methodological quality.
*Conclusion:* Although there is a wide diffusion of NMA-type studies on antithrombotics for heart diseases, their methodological and reporting quality remains suboptimal. This may reflect fragile clinical practices due to misleading conclusions from critically low-quality NMAs.

## 1. Introduction

Mortality rates associated with thromboembolic events are extremely high worldwide, especially in low- and middle-income countries, overall accounting for 1 in every 4–5 deaths [1,2]. Between 2010 and 2013, estimates per 100,000 global deaths per condition were 105.5 for ischaemic heart disease, 42.3 for ischaemic stroke, 32.3 for venous thromboembolism and 1.7 for atrial fibrillation [2].

Patients with these conditions benefit significantly from antithrombotic interventions used as treatment or prophylaxis (e.g., anticoagulants and antiplatelet agents used alone or combined with other therapies), as they can reduce thromboembolic events [3,4]. The introduction of direct-acting oral anticoagulants (DOACs), including direct inhibitors of thrombin (dabigatran) or of factor Xa (rivaroxaban, apixaban, edoxaban) has provided additional therapeutic alternatives aimed at overcoming some challenges in the management of vitamin K antagonists (VKAs). This last is associated with several drug–drug and drug–food interactions, increased risk of bleeding, longer half-life and

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the need for further laboratory monitoring when compared to oral anticoagulants [5]. Therefore, DOACs are now recommended by the US and European guidelines as first-choice agents for most thromboembolic cases, except for some specific scenarios such as atrial fibrillation with moderate-to-severe mitral stenosis or mechanical prosthetic valves [6–9]. In cardiac surgical procedures, including percutaneous coronary interventions, other antithrombotic strategies are routinely used to enhance therapeutic efficacy while maintaining safety [10]. All these interventions have been associated with significant clinical benefits as proven by several clinical trials, systematic reviews and meta-analyses.

Network meta-analysis (NMA), an extension of pairwise meta-analysis, simultaneously combines direct and indirect evidence to obtain comparative pooled effects of pairs of treatments in a network (i.e., comparison of multiple interventions across studies) [11]. This technique, thus, provides a broader overview of the effects (e.g., efficacy, safety) of all therapeutic alternatives available in one single model [12]. In the past years, the number of published NMAs has increased exponentially in several fields, especially in cardiology [13]. Until 2010, fewer than 10 NMAs on the effect of interventions to treat cardiovascular conditions were available; this number jumped to around 56 publications between 2011 and 2014 and 80 articles between 2015 and 2018 [14,15]. This cumulative evidence led to development of further techniques (e.g., overviews, evidence gap mapping, living systematic reviews) to summarize studies' findings, rate their quality and promptly present them to end-users [16–19]. The main goal of these approaches is to increase the standards of evidence generation and synthesis, as around one third of meta-analyses in healthcare are redundant, 20% have methodological flaws beyond repair and 13% lead to misleading conclusions [15,20].

Yet, only a few overviews (i.e., systematic reviews of published systematic reviews, also called umbrella reviews) synthetizing the overloading evidence of antithrombotics in different clinical conditions such as atrial fibrillation and deep venous thrombosis have been published [18,21]. Most of them focus on a single cardiovascular disease and include only pairwise meta-analyses of randomized clinical trials (RCTs), or restrict the review by articles' publication year or language. None of them assessed both the methodological quality and standards of conduct and reporting of NMAs in this field, which may hinder the true value of information and lead to equivocal decisions in practice.

Thus, we aimed to map the characteristics and methodological quality and standards of reporting of all published NMAs on the effects of antithrombotic therapies – including antiplatelet and anticoagulant agents for the treatment or prophylaxis of heart diseases or during cardiac surgical procedures – and highlight potential evidence gaps.

## 2. Material and methods

A systematic review of systematic reviews with meta-analysis (i.e., overviews or umbrella reviews) was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, Joanna Briggs Institute and the Cochrane recommendations [22–24]. This study was registered in PROSPERO (CRD2020166468).

### 2.1. Search and eligibility criteria

We searched for NMAs comparing antithrombotic therapies in PubMed and Scopus without timeframe or language limits (last updated in March 2022). A manual search in the reference lists of included studies and conventional search engines (Google and Google Scholar) was also performed. The complete search strategies are available in the Supplementary Material (Table S1).

Two reviewers independently performed the screening (title/abstract reading) and full-text evaluation. Data extraction and methodological quality assessment of the included studies were performed by a single reviewer and checked by another trained researcher. Discrepancies during these steps were discussed with a third author.

We included NMAs comparing any antithrombotic therapy (including antiplatelet and anticoagulant agents regardless of regimen or dosage) for the treatment or prophylaxis of heart diseases or during cardiac surgical procedures. We considered any type of network (with open or closed loops) of experimental, quasi-experimental or observational trials that assessed at least three or more treatments, comparing head-to-head or against placebo/no control in adult patients (> 18 years; no restriction of gender, age or other comorbidities). To be included for analyses, studies had to have reported data on interventions' efficacy (e.g., all-mortality, cardiovascular mortality, myocardial infarction, stroke) or safety outcomes (e.g., bleeding, major bleeding, minor bleeding, gastrointestinal bleeding). Non-NMAs, study protocols, studies evaluating antithrombotic agents in non-cardiac conditions and articles written in non-Roman characters were excluded during screening (title and abstract reading) and full-text article eligibility steps.

### 2.2. Data extraction and quality assessment

We used a standardized data collection form to extract data on: (a) the studies' general characteristics; (b) methods used for the systematic review such as databases, description of full search strategies, reports on manual and grey literature searches, statement of using reporting guidelines (PRISMA statement, Cochrane recommendations), previous publication of the study protocol, methodological quality and publication bias assessment; (c) description of statistical analyses, statistical model, additional analyses, inconsistency analyses, software used for calculations; (d) report of results, graduation of evidence level (GRADE approach); (e) conflict of interest and funding declarations.

The quality of NMA conduct and reporting was assessed by means of studies' adherence to Preferred Reporting Items for Systematic Reviews and Meta-Analyses - Extension Statement for Reporting of Systematic Reviews Incorporating Network Meta-Analyses of Health Care Interventions (PRISMA-NMA), using the PRISMA-NMA checklist [25]. The PRISMA-NMA checklist contains 32 items of which 5 are specific to NMA reporting. To quantitatively assess results in an exploratory analysis, we applied a 'yes' (1 point)/'no' (0 points) scale to each item, creating a maximum score of 32 points for PRISMA-NMA.

The methodological quality of the studies was assessed through the A MeaSurement Tool to Assess systematic Reviews (AMSTAR-2) scale that allows the evaluation of systematic reviews of randomized and non-randomized studies of health interventions [26], as no specific tool for judging NMAs exists. This tool contains 16 domains for which the answers 'yes', 'partial yes', 'no' and 'not applicable' are provided. The quality rating is based on the weaknesses of the critical domains; the final score allows grading and ranking of the study as having 'critically low methodological quality' to 'high methodological quality'. Scoring the papers with PRISMA-NMA and AMSTAR-2 checklists was performed by one researcher and checked by another trained author independently.

### 2.3. Statistical analyses

Descriptive statistical analysis was performed for all variables. Variable normality was assessed with Kolmogorov–Smirnov and Shapiro–Wilk tests and re-evaluated through visual inspection of histograms/Q–Q normal plots. For continuous variables with a non-normal distribution, results were reported as median and interquartile range (IQR Q1–Q3) and categorical variables were reported as absolute and relative frequencies. All analyses were conducted in IBM SPSS Statistics v. 25.0 (Armonk, NY: IBM Corp.).

## 3. Results

A total of 639 records were retrieved from the electronic databases after removing duplicates. During the screening process, 234 articles

were included for full-text analysis, of which 86 studies were considered eligible for data extraction and analysis (Fig. 1). The list of included and excluded studies is available in Supplementary Material S2 and S3, respectively.

The descriptive characteristics of the 86 systematic reviews with NMAs available in this study are presented in Table 1. The NMAs were published between 2007 and 2022. The studies were conducted by authors from 23 different countries and international collaboration among authors from different countries for publishing NMAs represented a little less than half ($n = 38$, 44.2%) of the included studies. Atrial fibrillation was the clinical condition most evaluated in the NMAs ($n = 28$, 32.6%), followed by non-valvular atrial fibrillation ($n = 20$, 23.3%) and acute coronary syndromes ($n = 15$, 17.4%). Prior registration or availability of a protocol for the NMA was informed by only 24 studies (27.9%). Yet, most authors ($n = 64$ studies; 74.4%) stated compliance with PRISMA guidelines for conducting and reporting the study. Cochrane recommendations were followed by only 12 studies (14.0%). The median number of databases used in the systematic reviews was 3 (IQR 3–4), PubMed/MEDLINE (97.7%), Embase (74.4%) and Cochrane Central Library (58.1%) being the most frequent. Three studies did not report the databases in which the searchers' strategy was conducted. Manual searches and grey literature searches were performed by 66.3% and 23.3% of studies, respectively. Around half of the publications ($n = 40$, 46.5%) presented the full search strategy for at least one database.

Most NMAs ($n = 63$, 73.3%) included only RCTs as primary studies, while 19.8% ($n = 17$) included mixed designs and only 7.0% (n = 6) restricted their inclusion criteria to observational studies. In two articles (2.3%), cost-effectiveness analyses were additionally performed. A median of 14.0 (IQR 5–21) primary studies were included in the NMAs, accounting for 48,982.0 (IQR 11,850.0–89,434.5) patients. Only 29 (33.8%) studies defined the minimum follow-up time in the study as an inclusion criterion. Methodological quality assessment of primary studies was reported by 70 (81.4%) publications; of these, 14 (16.3%) used two different tools. The Cochrane Risk of Bias tool ($n = 54$, 62.8%), New Castle Ottawa ($n = 12$, 14.0%) and Jadad scale ($n = 6$, 7.0%) were the most commonly employed approaches. In three NMAs, the authors declared that primary studies with low methodological quality were excluded from the synthesis. Publication bias was assessed by 35 (40.7%) studies, especially by means of funnel plot ($n = 30$, 34.9%), Egger's or Begg's tests ($n = 15$, 17.4%), or both ($n = 10$, 11.6%). The GRADE approach was used only in 10 (11.6%) publications to rate the quality and level of the evidence. Conflicts of interest and external financial support were positively declared by authors of 33 (38.4%) and 37 (43.0%) studies, respectively (Table 1).

Half of the studies ($n = 43$, 50.0%) performed direct pairwise meta-analysis for the outcomes of interest (mean of 5.7 ± 3.4 meta-analyses per study). A median of 6 indirect/mixed meta-analyses were found per study (IQR 3–8), ranging from 1 to 16. A total of 484 different outcomes were evaluated in the all the NMAs with the most frequently evaluated being: stroke ($n = 76$), major bleeding ($n = 74$), mortality ($n = 65$), myocardial infarction ($n = 56$) and intracranial bleeding ($n = 34$). A total of 6000 indirect comparisons were identified in the included NMAs (median of 40 indirect comparisons per study (IQR 24–84.25), ranging from 3 to 432 comparisons). Of these, 3917 (65.3%) comparisons were among monotherapies and only five studies evaluated the effect of parenteral interventions. The most frequent indirect comparison in the studies was apixaban vs rivaroxaban 10–20 mg ($n = 186$, 3.1%). Only 16 (18.6%) NMAs evaluated drug-placebo comparisons; comparisons involving DOACs were available in 61 (70.9%) studies.

Table 2 depicts the characteristics of the statistical methods used to perform the NMA. Odds ratio ($n = 54$, 62.8%) was frequently reported as an effect-size measure. Most studies (53.5%) employed random-effect Bayesian statistics; information on the statistical model and method was not provided in $n = 6$ and $n = 16$ NMAs, respectively. A network plot was provided by 67 (77.9%) studies for at least one outcome; however, the network geometry was fully described in only 11 (12.8%) articles. Sensitivity analyses were stated as having been performed in 46 (53.5%) studies. Subgroup and inconsistency analysis (e.g., node-splitting) was performed in 31 (36.0%) and 48 (55.8%) studies, respectively. Rank order or surface under the cumulative curve (SUCRA) analysis was performed in 65 NMAs (75.6%). Only one study did not report the software used for the analysis and approximately half of the studies used two or more software programs to analyse the results (45.4%). The most frequent were R ($n = 33$, 38.4%), Stata ($n = 32$, 37.2%) and WinBUGS ($n = 27$, 31.4%).

The mean PRISMA-NMA score was 20.8 ± 5.3 (Fig. 2-A), which corresponds to 65.1 ± 16.5% of authors' adherence to this checklist. The least reported criteria were 'description of the methods used to explore the geometry of the treatment network under study and potential biases related to it' ($n = 11$, 12.8%) and 'mention of a protocol' ($n = 24$, 27.9%) (see Fig. 3 and Supplementary Material S4 and S6).

Methodological quality assessment of systematic reviews by the

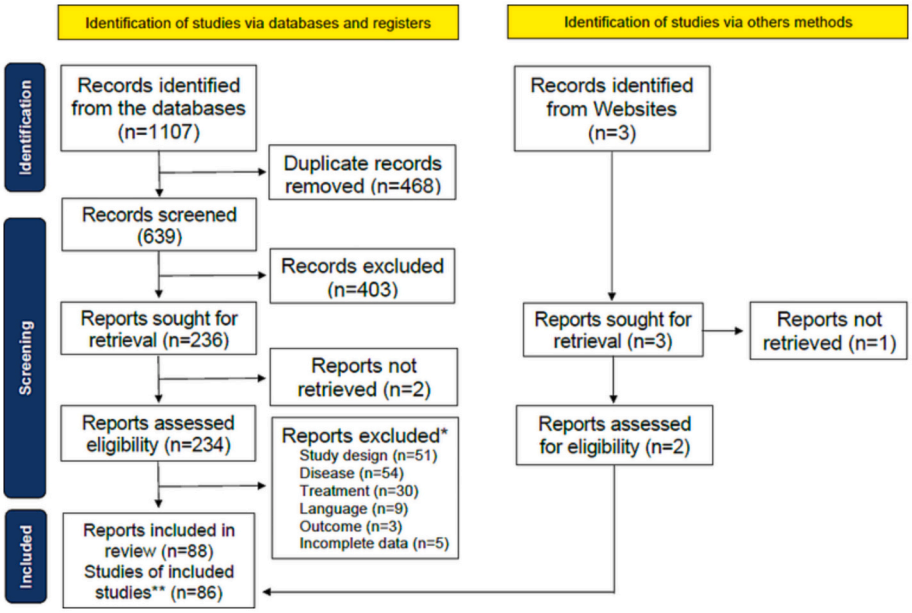


**Fig. 1.** Flowchart of the systematic review process.
* Total of 148 reports excluded: four reports were excluded for two reasons (two reports were excluded because of 'treatment' + 'disease' and two reports were excluded because of 'study design' + 'disease').
** Two studies updated their results in reports published later. The most recent report was considered for data extraction.

**Table 1**
Descriptive characteristics of network meta-analyses on antithrombotic therapy.

| Descriptive characteristic | ($n$ = 86) |
|---|---|
| Year of publication, n (%) | |
| 2021–22 | 13 (15.1) |
| 2019–20 | 31 (36.1) |
| 2016–18 | 24 (27.9) |
| 2007–15 | 18 (20.9) |
| International collaboration, n (%) | 38 (44.2) |
| Countries[1], n (%) | |
| China | 24 (27.9) |
| USA | 22 (25.6) |
| Italy | 6 (7.0) |
| Canada | 5 (5.8) |
| Taiwan | 5 (5.8) |
| UK | 5 (5.8) |
| Number of authors, n (%) | |
| 2–5 | 22 (25.6) |
| 6–10 | 49 (57.0) |
| 11–15 | 10 (11.6) |
| 16–20 | 5 (5.8) |
| Journals[1], n (%) | |
| *Am J Cardiol* | 7 (8.1) |
| *Thromb Haemost* | 4 (4.7) |
| *BMJ* | 3 (3.5) |
| *Cardiovasc Revasc Med* | 3 (3.5) |
| *Catheter Cardiovasc Interv* | 3 (3.5) |
| *Int J Cardiol* | 3 (3.5) |
| Clinical conditions[1], n (%) | |
| Atrial fibrillation | 28 (32.6%) |
| Non-valvular atrial fibrillation | 20 (23.3%) |
| Acute coronary syndromes | 15 (17.4%) |
| Comparisons of antithrombotic interventions[1], n (%) | |
| Apixaban vs rivaroxaban 10–20 mg | 186 (3.1%) |
| Rivaroxaban vs warfarin | 146 (2.4%) |
| Apixaban vs warfarin | 142 (2.4%) |
| Dabigatran 150 mg vs rivaroxaban 10–20 mg | 106 (1.8%) |
| Apixaban vs dabigatran 150 mg | 104 (1.7%) |
| Reports register (PROSPERO or other), n (%) | 24 (27.9) |
| Reports following PRISMA statement, n (%) | 64 (74.4) |
| Reports following Cochrane recommendations, n (%) | 12 (14.0) |
| Reports using GRADE, n (%) | 10 (11.6) |
| Number of databases, median (IQR)[b] | 3.0 (3–4) |
| Number of studies included, median (IQR) | 14.0 (5–21) |
| Number of patients included, median (IQR) | 48,982.0 (11,850.0–89,434.5) |
| Provides complete search strategy, n (%) | 40 (46.5) |
| Performs manual search, n (%) | 57 (66.3) |
| Performs grey literature search, n (%) | 20 (23.3) |
| Performs quality assessment of studies, n (%) | 70 (81.4) |
| Performs evaluation of publication bias of studies, n (%) | 35 (40.7) |
| Excluded low-quality studies, n (%) | 3 (3.5) |
| Provides supplemental material, n (%) | 77 (89.5) |
| Availability of raw data, n (%) | 5 (5.8) |
| Reports conflicts of interest, n (%) | |
| No conflicts | 50 (58.1) |
| Has conflicts | 33 (38.4) |
| Not mentioned | 3 (3.5) |
| Reports financial support, n (%) | |
| No financial support | 19 (22.1) |
| Financial support | 37 (43.0) |
| Not mentioned | 30 (34.9) |

IQR: interquartile range (Q1–Q3)
1. Cited only the most frequent.
2. The percentage was calculated from $n$ = 6.000 (total of indirect comparisons).

AMSTAR-2 tool showed that most studies ($n$ = 76, 88.4%) had critically low methodological quality (Fig. 2-B), while 8 (9.3%) were rated as low quality, 1 (1.2%) as moderate quality and only 1 (1.2%) as high quality. AMSTAR-2 items were properly completed by less than half of the NMAs (46.4 ± 15.9%). The NMA published by Cochrane was the only study that received the maximum score on the AMSTAR-2 items (Supplementary Material S6). The least complied-with items of this tool were 'presence of list of excluded studies and justified exclusions' ($n$ = 6, 7.0%) and 'mention of a protocol and justify any significant deviations from the protocol' ($n$ = 8, 9.3%) (see Fig. 4 and Supplementary Material S5). The critical domain items of AMSTAR-2 were less often attained by authors (median of fulfilment of 42.9%, IQR 14.3–57.1) compared with the noncritical domain items (median of 55.6%, IQR 44.4–66.7).

**Table 2**
Methodological characteristics of network meta-analyses on antithrombotic therapy.

| Methodological characteristic | (n = 86) |
|---|---|
| Presents the network plot, n (%) | 67 (77.9) |
| Statistical analysis method, n (%) | |
| Bayesian | 46 (53.5) |
| Frequentist | 20 (23.3) |
| Bayesian and frequentist | 4 (4.7) |
| Not mentioned | 16 (18.6) |
| Statistical analysis model, n (%) | |
| Fixed | 13 (15.1) |
| Random | 55 (64.0) |
| Fixed and random | 12 (14.0) |
| Not mentioned | 6 (7.0) |
| Describes in the methods the network geometry, n (%) | 11 (12.8) |
| Presents in the results the summary of the network geometry, n (%) | 46 (53.5) |
| Performs subgroup analysis, n (%) | 31 (36.0) |
| Performs sensitivity analysis, n (%) | 46 (53.5) |
| Performs inconsistency analysis, n (%) | 48 (55.8) |
| Performs rank order or SUCRA analysis, n (%) | 65 (75.6) |

## 4. Discussion

This overview mapped the characteristics and critically appraised the standards of conduct and evidence reporting of 86 peer-reviewed NMAs published between 2007 and 2022 on the effect of antithrombotic therapies in heart diseases and cardiac surgical procedures. We found that 88.4% of the evaluated studies have critically low methodological quality according to AMSTAR-2 and that adherence to the PRISMA-NMA recommendations is still underwhelming – less than two thirds of studies completely comply with these checklist items.

Globally, there is an increasing trend in the publication of NMAs – including in the field of cardiology [14], as also demonstrated in our study (e.g., 2 articles available in 2010 compared to 84 in 2022). This pattern could be due, among other things, to the technological advances resulting in facilitated access to internet, electronic databases and software with simplified algorithms for tracking new studies [27], improvement in methods for developing NMAs [28], academic pressure for publication [29], financial incentive to carry out this type of research [20,30–32] and encouragement given by health technology assessment agencies, researchers and other stakeholders to use these methods [33]. Yet, suboptimal NMAs are still very common, and their findings may lead to several biases in data interpretation which negatively impact decision-making in clinical practice [15,20]. In an exploratory search on the PubMed database through 2012, there were approximately 170 RCTs referencing DOACs. From 2012 to date, about 470 RCTs have been published. We found that approximately 71% of NMAs compared therapies involving DOACs. The most frequent comparisons were among different DOACs, DOACs vs warfarin or different doses of DOACs. Indirect comparisons of these drugs have been justified due to the high cost of head-to-head comparisons, which would require a large number of patients [34,35,36]. Doundoulakis et al. recently showed that there is an important overlap of evidence between existing systematic reviews on non-VKA oral anticoagulants, especially in atrial fibrillation [18]. Between 2012 and 2017, the authors found that the number of systematic reviews which collected their data from randomized and non-randomized studies ($n$ = 57) was far greater than the number of randomized trials ($n$ = 14), with no additional findings or new discussions. Although overlap is often inevitable when results get updated based on new evidence, the current extensive review overlap suggests that there is a waste of efforts (e.g., human resources and research

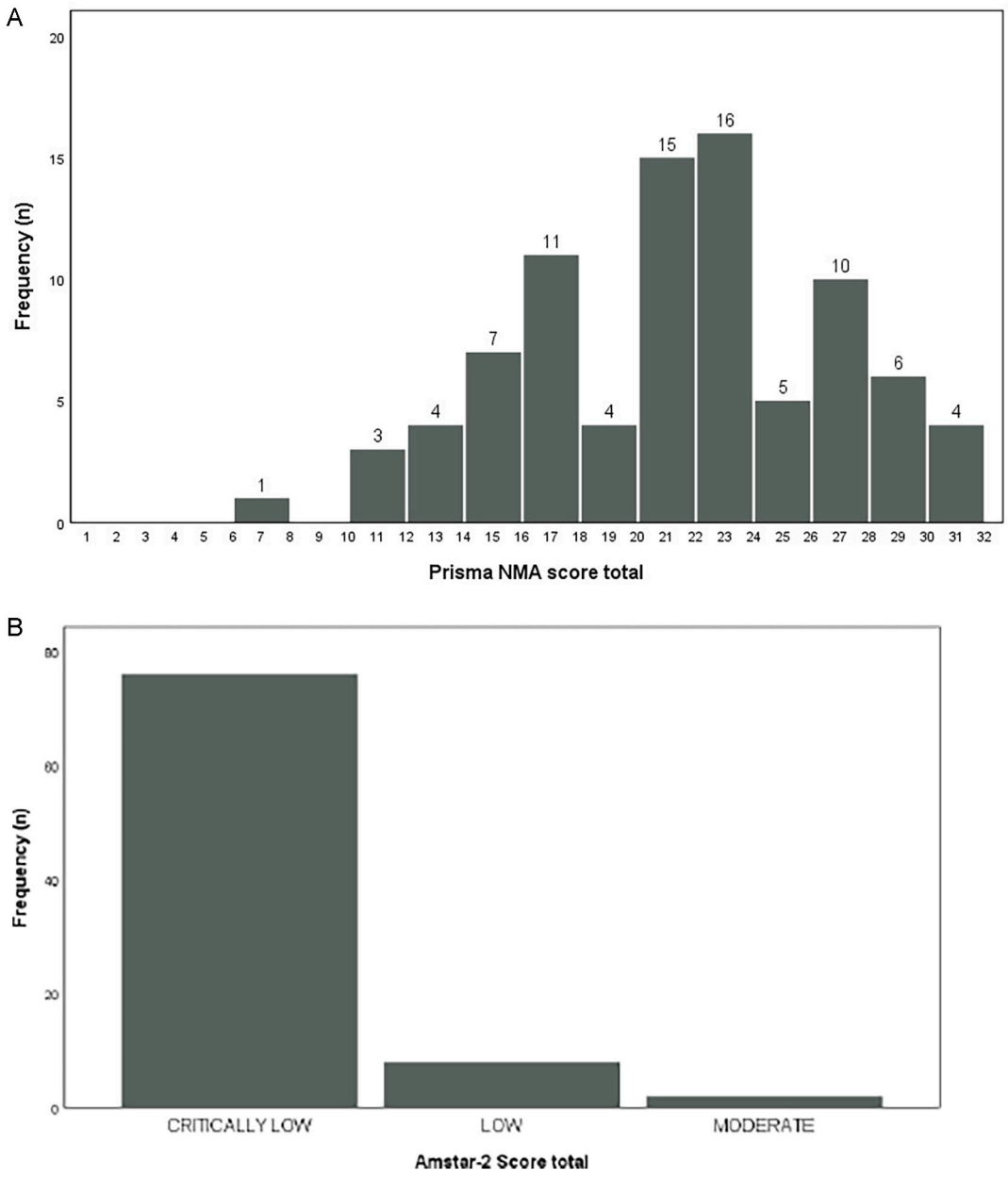


**Fig. 2.** A. Distribution of PRISMA-NMA scores. Values range from 0 to 32; B. Quality classification of NMAs according to AMSTAR-2.

funding) with few primary studies covered by multiple overlapping reviews. This may also hinder the identification and selection of the best available evidence to be used in practice by end-users [20,37].

Previous research assessing the quality of systematic reviews and pairwise meta-analysis in the field of cardiology [35,38–41] similarly showed important flaws in the conduct and reporting of these studies, although the compliance of authors with PRISMA or MOOSE recommendations increased slightly from around 40% in 2012 to 60% in 2018 [35]. Abushouk et al. evaluated 352 systematic reviews published in high-impact journals and found that 71% (95% CI: 65.7–75.4) had critically low methodological quality according to the AMSTAR-2 tool [38]. In this tool, seven domains are strongly associated with the validity of the systematic review, as deviations of their compliance can directly affect the conclusions of the study [26]. Similar to other reviews [39,41], we found that these critical domain items were scarcely fulfilled by NMA authors, the 'list of studies with complete reasons for exclusion' and 'provision of comprehensive search strategies' being the least reported items. The absence of this information hampers understanding of the eligibility criteria of the systematic review, may introduce several biases of data selection and make research reproducibility difficult. [42]. Although the assessment of risk of bias in individual primary studies was fairly reported by over 60% of NMAs (using validated tools), a critical evaluation of the impact of these biases on the meta-analytical results and interpretation of findings was provided by only a third of these studies. The absence or poor discussion of the influence of the risk of bias on the NMA findings may suggest the intention to hide information that would compromise the integrity of the results and their translation into clinical practice [43].

We also found that only one third of NMAs had a prior record of the report, with protocol deviation justifications available as recommended by AMSTAR-2 in <10% of studies [26]. Li and collaborators [41] described an even lower rate of only 5% of systematic reviews and meta-analyses from high-impact journals in the field of heart failure complying with this item. This domain was already foreseen in the 2007 AMSTAR version [44], although the prior registration or publication of a protocol was not yet a common practice for systematic reviews.

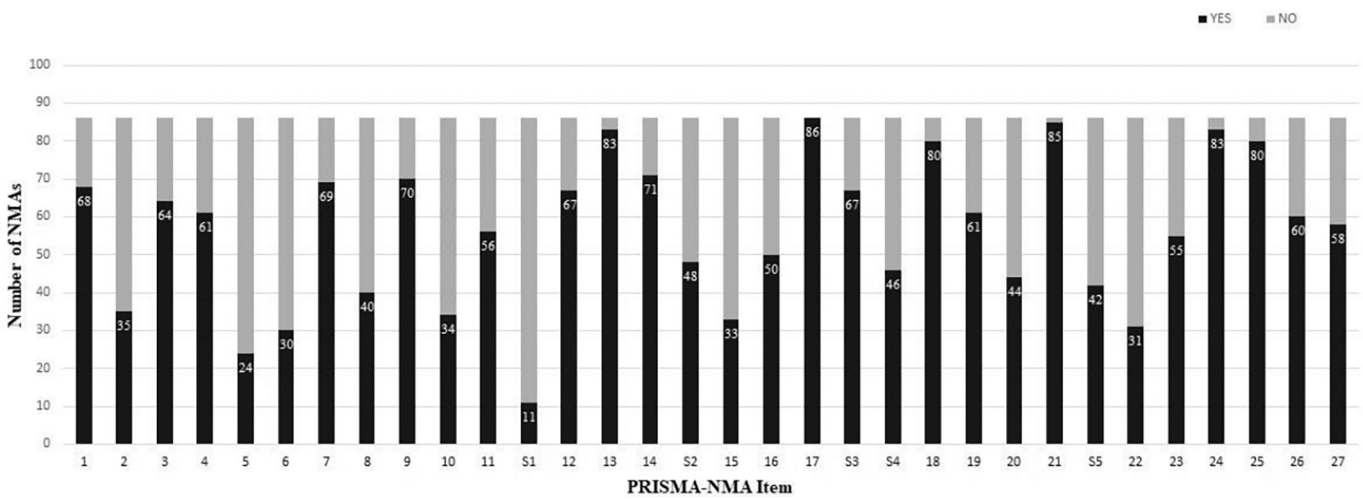


**Fig. 3.** Compliance with PRISMA-NMA items.
PRISMA-NMA items:
1. Identification of the report as a systematic review incorporating an NMA.
2. Structured summary (background, methods, results, discussion/conclusions, other).
3. Rationale for the review in the context of what is already known.
4. Explicit statement of questions being addressed (PICOS).

Prospective registrations of studies in the field of health aim to reduce bias in the conduct and dissemination of research, increase transparency and help prevent unintentional duplication, thus reducing research waste. Within the scope of systematic reviews (with or without statistical analysis), the prospective record gains additional importance, as these studies usually play an even greater role in evidence-based decision-making, in clinical practice and health policy [45]. PROSPERO was launched in 2011 as the first prospective register for systematic reviews (Centre for Reviews and Dissemination – CRD, University of York), yet other platforms such as the Registry of Systematic Reviews/Meta-Analyses in Research Registry, INPLASY (International Platform of Registered Systematic Review and Meta-analysis Protocols), and the Open Science Framework Registries and protocols.io (which represent generic registers open to any study type) are currently available [45].

The PRISMA-NMA checklist containing specific items for NMAs, such as network geometry assessment, inconsistency assessment, network diagram presentation, network geometry summary and network exploration inconsistency, was developed as an extension of the PRISMA tool aiming to further guide studies' conduct and reporting [25]. However, previous literature [15,46–49] highlights that the geometry of the treatment network is still underreported. Although we found that a network plot and a brief description of network geometry were fairly available in the evaluated NMAs, the complete network geometry was the least reported figure, available in <15% of studies. Reporting of this item can guide the interpretation of the study's findings, as it identifies whether direct and indirect evidence is available (e.g., closed geometry such as triangle or square) or if there are incomplete connections in the network (i.e., loose ends) [11,50]. Furthermore, the network's geometry may reflect the wider clinical context of the evidence and may be shaped by rational choices for treatment comparators or by specific biases [50]. Around half of studies lack a description of the data on network inconsistency including model fit measures, model comparisons and node analyses [25]. These findings are similar to those of other research on the methodological quality of 42 NMAs published by Cochrane, where only 26.2% described the geometry of network, 64.3% presented the network plot and 33.3% fully assessed inconsistency [46]. Considering that PRISMA-NMA was published in June 2015 and most of the NMAs evaluated in our overview were available after this date ($n = 48$, 80%), the poor compliance with most mandatory standards for conduct and reporting of these studies is hardly justified. Although reporting rankeograms, ranking orders or SUCRA of the evaluated interventions is not a mandatory item in NMAs, this may be an important element to assist in the selection of a technology in a given setting [11]. Bafeta and colleagues described that around 60% of Bayesian-approach NMAs provided the rank of interventions [49]. However, of these, only 17% additionally reported data uncertainty (e.g., confidence/credible intervals for the ranks). The uncertainty of classification of interventions should always be evaluated by researchers and healthcare professionals because the difference between interventions may be small and not clinically relevant [49].

Our study has some limitations. We did not assess the overlap of systematic reviews as it was not the primary goal of this overview; yet, given the number of published NMAs and included primary studies, important evidence of publication overlap may exist. We included only NMAs of drug interventions and cardiac surgical procedures, but NMAs of other technologies and clinical approaches are also available, and our results cannot be immediately translated to other scenarios. A simple quantitative score of PRISMA-NMA checklists – without assigning different weights to the items – was used to exploratorily rate the NMAs; potential differences in the importance of recommendations may exist. Further investigations can be conducted to identify other factors related to poor reporting in this field. NMAs that evaluated the use of antithrombotics in cardiac surgical procedures proved to be very heterogeneous, not allowing them to be analysed together.

## 5. Conclusion

The global increase of mortality and morbidity associated with cardiovascular diseases warrants the prioritization of strategies to manage these conditions, including the conduct of evidence-based syntheses such as NMAs. The number of these publications summarizing the comparative findings of the efficacy and safety profile of antithrombotics in heart diseases has increased exponentially in the past decade. However, although they represent a systematic and low-cost approach to ground decision-making, the methodological (AMSTAR-2) and reporting quality is still suboptimal, with overall low compliance with PRISMA-NMA recommendations. This may reflect fragile and inconsistent clinical practices due to misleading conclusions from critically low-quality NMAs. Journal editors and peer reviewers from this field, as well as researchers and funding bodies, should ensure that these

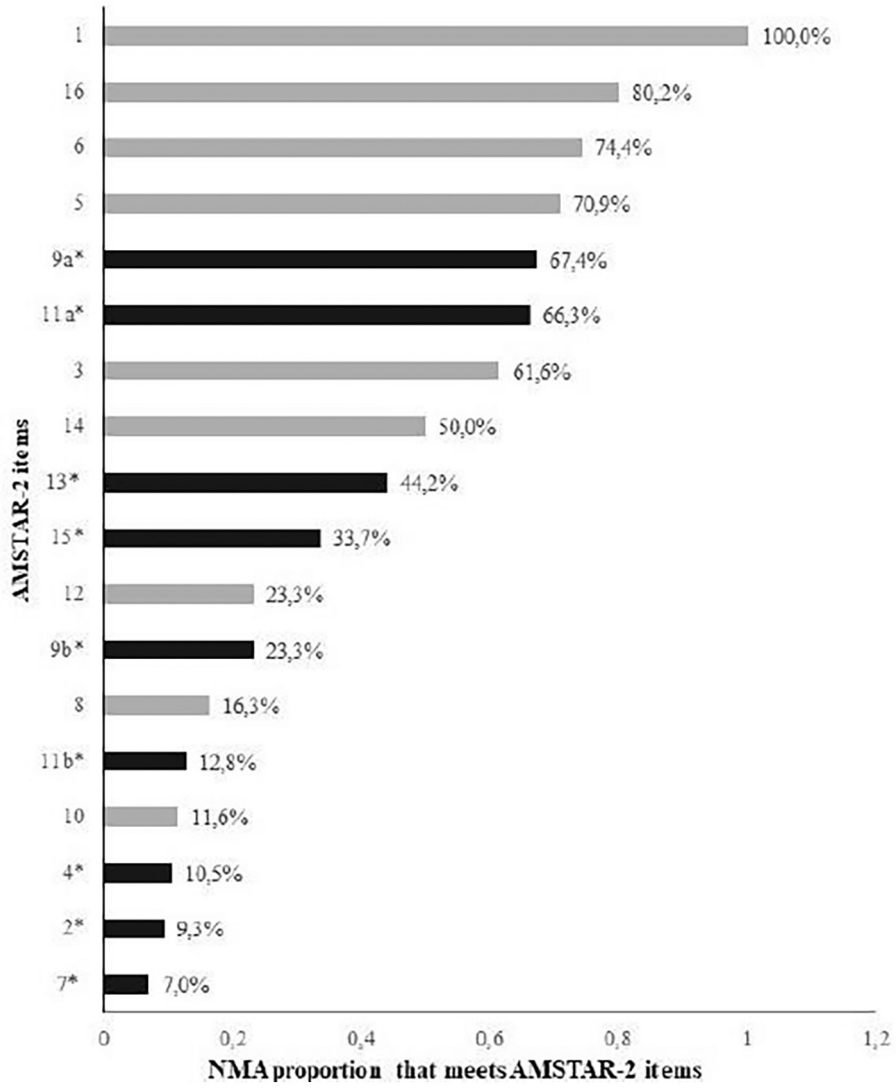


**Fig. 4.** Proportion of NMAs meeting AMSTAR-2 items.
* Critical domains.
AMSTAR 2 items:
1. Components of PICO.
2. Explicit prior statement of the methods (protocol).
3. Selection of the study designs.
4. Comprehensive literature search strategy.
5. Study selection in duplicate.
6. Data extraction in duplicate.
7. List of excluded studies and justify the exclusions.
8. Description of included studies in detail.
a. Satisfactory technique for assessing the risk of bias (RoB) in RCTs included in the review.
b. Satisfactory technique for assessing the risk of bias (RoB) in NRS included in the review.
9. Sources of funding for the included studies.
a. Appropriate methods for statistical combination of results (when an RCT meta-analysis was performed).
b. Appropriate methods for statistical combination of results (when an NRSI meta-analysis was performed).
10. Potential impact of RoB in individual studies on the results of the meta-analysis (when meta-analysis was performed).
11. Consideration of RoB in individual studies when interpreting/discussing review results.
Satisfactory explanation and discussion of any observed heterogeneity in the review results.
12. Adequate investigation of publication bias, and discussion of its likely impact on the results of the review.
13. Potential sources of conflict of interest, including any funding they received for conducting the review.

conduct and reporting guidelines are strictly followed before publication and evidence dissemination.

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None.

5. Review protocol with the registration number and where it can be accessed.
6. Eligibility criteria and justifications.
7. All information sources in the search and date last searched.
8. Full electronic search strategy for at least one database.
9. State the process for selecting studies.
10. Method of extracting data from reports and processes for confirmation with investigators.
11. List of all variables for which data was collected.
S1. Methods used to explore the geometry of the treatment network under study and potential biases.
12. Methods used for assessing risk of bias of individual studies.
13. State the principal summary measures.
14. Methods of handling data and combining results of studies for each NMA.
S2. Statistical methods used to evaluate the agreement of direct and indirect evidence.
15. Assessment of risk of bias that may affect the cumulative evidence.
16. Methods of additional analyses if done, indicating which were pre-specified.
17. Numbers of studies screened, assessed for eligibility, and included in the review (flow diagram).
S3. Network graph of the included studies.
S4. Brief overview of characteristics of the treatment network.
18. Characteristics of the data extracted and provide the citations.
19. Data on risk of bias.
20. Summarized data for each intervention group and effect estimates and confidence intervals.
21. Results of each meta-analysis done, including confidence/credible intervals.
S5. Results from investigations of inconsistency.
22. Results of any assessment of risk of bias across studies.
23. Results of additional analyses, if done.
24. Main findings, including the strength of evidence for each main outcome.
25. Discussion of limitations.
26. General interpretation of the results, and implications for future research.
27. Sources of funding for the systematic review and professional conflicts of interest.

## Declaration of Competing Interest

The authors have declared that no competing interests exist.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2023.05.036.

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