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The effect of anticoagulants on clinical outcomes of mortality, stroke, myocardial infarction, pulmonary embolism, and major bleeding for patients with heart failure in sinus rhythm.

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Title page

Title

The effect of anticoagulants on clinical outcomes of mortality, stroke, myocardial infarction, pulmonary embolism, and major bleeding for patients with heart failure in sinus rhythm.

Commentary on:

Shantsila E, Kozieł M, Lip GYH. Anticoagulation versus placebo for heart failure in sinus rhythm. Cochrane Database of Systematic Reviews 2021, Issue 5. Art. No.: CD003336. DOI: 10.1002/14651858.CD003336.pub4.

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Conflicts of interest statement

The authors declare no conflicts of interest.

Abstract

One to two percent of the population in developed countries are affected by chronic heart failure and this increases to greater than 10% in those over 70 years old. Heart failure (HF) predisposes patients to thromboembolic events. Anticoagulants are often used to prevent thromboembolic events in specific patient populations, such as those with atrial fibrillation. Currently, no guidance exists on the long-term use of anticoagulants for patients with HF in sinus rhythm. This article critically appraises a systematic review which assesses whether the long-term use of oral anticoagulants reduces total mortality and stroke in patients with HF in sinus rhythm.

Keywords

Anticoagulation therapy; Heart failure; Systematic review; Randomised control trial; Critical appraisal; Drug therapy

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Key Points

- There was no evidence of benefit for outcomes of all cause death, cardiovascular death, myocardial infarction, and pulmonary embolism with routine use of warfarin and rivaroxaban for people with heart failure in sinus rhythm.
- Rivaroxaban may reduce the risk of stroke in people with heart failure in sinus rhythm.
- Warfarin and rivaroxaban probably increase the risk of major bleeding events compared to placebo or no treatment in patients with heart failure in sinus rhythm.
- Future research should focus on establishing the thrombosis risk and bleeding risk for different severities of heart failure according to the New York Heart Association (NYHA) functional classifications (classes 1 to 4).

Introduction

One to two percent of the population in developed countries are affected by chronic heart failure and this increases to greater than 10% in those over 70 years-old (Mosterd and Hoes 2007). Heart failure (HF) is a syndrome caused by abnormalities in the structure or functioning of the heart which results in impairment of ventricular filling or the ejection of blood (Inamdar and Inamdar 2016). Heart failure results in decreased cardiac output and increased intracardiac pressures (Li and Zhang 2017). Heart failure predisposes patients to thromboembolic events (blood clot that forms in a blood vessel) (Hai et al. 2016). The cumulative incidence of these events is 1.44% at 30 days, 4.45% at 1 year and 10.48% at 5 years (Smilowitz et al. 2019). These events contribute to high hospital admission rates, high morbidity as well as increased risk of mortality (Søgaard et al. 2014; Vaqar and Graber 2022).

Anticoagulants are often used to prevent thromboembolic events in specific patient populations, such as those with atrial fibrillation (Vaqar and Graber 2022). Anticoagulants such as warfarin and rivaroxaban have been administered in clinical trials for the prevention of thromboembolic events (in patients with heart failure) (Cokkinos et al. 2006; Mehra et al. 2019). Both these medications act on the clotting cascade to prevent clot formation (Mehra et al. 2019). Warfarin is a vitamin K antagonist; vitamin K is required to synthesise clotting factors, hence preventing clot formation (Ezekowitz et al.

2010). Rivaroxaban acts further down the cascade and is a direct inhibitor of factor Xa (Mehra et al. 2019). Factor Xa activates prothrombin to thrombin which facilitates clot formation (Brown et al. 2013). At present, there is no guidance on the use of anticoagulants (longer-term) for patients with chronic heart failure in sinus rhythm (rhythm of heart) (Shantsila et al. 2021). A Cochrane systematic review was conducted by Shantsila et al, to provide a synthesis of existing evidence to assess the potential risk-benefit of using oral anticoagulants in people with heart failure in sinus rhythm (Shantsila et al. 2021). The review intended to determine whether the long-term use of oral anticoagulants reduces total mortality and stroke in people with heart failure in sinus rhythm (Shantsila et al. 2021).

Aim of commentary

This commentary aims to critically appraise the methods used within the review by Shantsila et al, (2021) and expand upon the findings in the context of clinical practice.

Methods

The Cochrane systematic review comprised a search of three databases from inception to March 2020: The Cochrane Central Register of Controlled Trial, MEDLINE (Ovid) and Embase (Ovid). No restrictions on publication type, or language were applied to the search strategy. In addition, reference lists of included studies were checked for additional trials. Trials comparing oral anticoagulation with placebo or no treatment, were eligible if they included adult patients (>18 years) with diagnosis of heart failure (clinical or assessment of the leR ventricular systolic function). Trials were included if anticoagulants included vitamin K antagonists (e.g., warfarin) or non-vitamin K antagonist oral anticoagulants (e.g., dabigatran, apixaban, rivaroxaban, or edoxaban). Cross-over trials, cluster randomised trails, and trials including co-interventions or short-term treatment (<1 month) were excluded. Studies were also excluded if they included participants without heart failure and the data was not analysed and reported separately. Trials whereby participants had co-morbidities that included atrial fibrillation (at randomisation) were also excluded.

Screening of titles, abstracts and full texts articles were independently undertaken by two review authors, with any disagreements resolved by a third author. Data extraction was undertaken by one author with the exception of outcome data (extracted independently by two authors). The risk of bias was independently assessed by two authors using the Cochrane Risk of Bias tool (Higgins et al. 2011). An overall assessment of evidence quality for each outcome (rating of certainty) was conducted using the Grading of Recommendations Assessment, Development and Evaluation (GRADE). The primary outcomes of interest were stroke and all-cause death. The secondary outcomes of interest were cardiovascular death (including sudden death), myocardial infarction, pulmonary embolism, peripheral arterial embolism, and major bleeding events (defined as fatal bleeding; symptomatic bleeding in a critical area or organ). A meta-analysis was undertaken if there was more than one study using a fixed effects model with odds ratios to combine the outcomes across multiple studies.

Results

The Cochrane systematic review included three RCT's of oral anticoagulation (warfarin or rivaroxaban) compared to no treatment or placebo in a total of 5498 patients with heart failure (Cleland et al. 2004; Cokkinos et al. 2006; Mehra et al. 2019).

Two studies compared warfarin to placebo or no treatment in 324 participants (Cleland et al. 2004; Cokkinos et al. 2006). These studies reported four outcomes: all-cause death, cardiovascular death, myocardial infarction, and major bleeding events. Warfarin was found to significantly increase the risk of major bleeding events compared to placebo or no treatment in both studies (n= 324, odds ratio: 5.98, 95% CI 1.71 to 20.93). That said, the evidence was of low-certainty due to high heterogeneity (80%) across the studies, and imprecision due to the small sample size and low event rates. There was no evidence of difference that warfarin had any effect on all-cause death compared to placebo or no treatment (n= 324, odds ratio: 0.66, 95% CI 0.36 to 1.18. Low certainty evidence). Similarly, there was also unclear evidence that warfarin had any effect on cardiovascular death compared to placebo or no treatment (n= 324, odds ratio: 0.98, 95% CI 0.58 to 1.65. Certainty of evidence not graded).

There was no evidence of difference that warfarin had any effect on the risk of myocardial infarction compared to no treatment or placebo in both studies (n= 324, odds ratio: 0.64, 95% CI 0.20 to 2.08. Certainty of evidence not graded). At single study level, a risk of bias assessment identified one study as having 'some concerns' of bias (Cokkinos et al. 2006) while the other study was judged at 'high risk' of bias (Cleland et al. 2004).

One study compared rivaroxaban to placebo in 5022 participants (Mehra et al. 2019). Six outcomes were reported by this study: All cause death, stroke, cardiovascular death, myocardial infarction, pulmonary embolism, and major bleeding incidents. When compared to placebo, rivaroxaban was found to reduce the risk of stroke in patients with heart failure (n= 5022, odds ratio: 0.67, 95%CI 0.47 to 0.95. Moderate certainty evidence). However, rivaroxaban was also found to increase the risk of major bleeding events compared to placebo (n= 5022, odds ratio: 1.65, 95% CI 1.17 to 2.33. Moderate certainty evidence). The outcomes of stroke and major bleeding events were deemed moderate certainty of evidence because of the limitation that there were very low event rates. There was no evidence of difference that rivaroxaban had any effect on the risk of all-cause death (n= 5022, odds ratio: 0.99, 95% CI 0.87 to 1.13: high-certainty evidence). Similarly, there was no evidence of difference that rivaroxaban had any effect on cardiovascular death compared to placebo (n= 5022, odds ratio: 1.00, 95% CI 0.86 to 1.15. Certainty of evidence not graded). There was also no evidence of difference that rivaroxaban had any effect on the risk of myocardial infarction or pulmonary embolism compared to placebo (n= 5022, odds ratio: 0.83, 95% CI 0.63 to 1.09; and odds ratio: 1.23, 95% CI 0.51 to 2.97, respectively. Certainty of evidence not graded). At single study level, a risk of bias assessment judged the study as having 'some concerns' of bias (Mehra et al. 2019).

Table 1. Critical appraisal using the Joanna Briggs Institute (JBI) critical appraisal tool for systematic reviews.

Criteria	Shatsila et al, (Shantsila et al. 2021)
1. Is the review question clearly and explicitly stated?	Yes-To determine whether long-term oral anticoagulation reduces total deaths and stroke in people with heart failure in sinus rhythm.

2. Were the inclusion criteria appropriate for the review question?	Yes- RCT comparing oral anticoagulants with placebo or no treatment in adults with HF, with treatment duration of at least one month. Inclusion decisions were made in duplicate, and any disagreements resolved between review authors.
3. Was the search strategy appropriate?	Yes - Full description of the search strategy. Relevant key terms and Mesh terms used.
4. Were the sources and resources used to search for studies adequate?	Yes- The following databases were used: Cochrane central register of controlled trials, Epub Ahead of print and other non-indexed citations, MEDLINE Daily, and Medline Ovid and Embase Ovid. All databases were searched from inception until time of study.
5. Were the criteria for appraising studies appropriate?	Yes- the Cochrane Handbook for Systematic Reviews of Interventions used its criteria for reviewing bias (RoB tool).
6. Was critical appraisal conducted by two or more reviewers independently?	Yes, critical appraisal was conducted by two reviewers independently (RoB tool).
7. Were there methods to minimize errors in data extraction?	Yes-Two review authors independently extracted outcome data from the included studies. The authors resolved disagreements by consensus. One review author transferred data into the Review Manager 5 file. Authors double-checked that data was entered correctly by comparing the data presented in the review with the data extraction form. A second review author spot-checked study characteristics for accuracy against the trial report.
8. Were the methods used to combine studies appropriate?	Yes- meta-analyses was undertaken only when this was meaningful, i.e., if the treatments, participants, and the underlying clinical question were similar enough for pooling to make sense. A fixed-effect model, as the previous updates of the analysis indicated a relatively small number of eligible trials, and we assumed the same intervention effect.
9. Was the likelihood of publication bias assessed?	Yes- publication bias was assessed within the GRADE assessment.
Total criteria achieved/	9/9

Commentary

Using the Joanna Briggs Institute Critical appraisal tool for systematic reviews, all 9 criteria were judged to be satisfactory for this review (seen in table 1). Consequently, it was deemed that this Cochrane systematic review is likely to provide an accurate and comprehensive summary of the results from available studies, addressing the question of interest.

Within clinical practise, implementing anticoagulants in individuals at increased risk of thromboembolic events is important because of the need to avoid stroke and pulmonary embolisms (which can increase mortality and morbidity) (Shantsila and Lip 2014). The review found no evidence of difference between rivaroxaban and warfarin compared to no treatment or placebo in reducing the risk of all-cause death, cardiovascular death, myocardial infarction. Moreover, the findings highlight that oral anticoagulation therapy may increase the risk of major bleeding, presenting a significant concern to patient safety (in the absence of benefit for most patients). This may be less of a concern when using rivaroxaban (compared to warfarin) as all-cause death showed no evidence of difference between intervention and placebo, implying that any major bleeding risk may not translate to increased death.

The review identified one positive effect on an outcome of oral anticoagulation therapy in that rivaroxaban was found to reduce the risk of stroke in heart failure patients. This reduction in risk is important as heart failure typically situates patients within a pro-thrombotic state with greater risk of stroke (Hiatt and Lentz 2002). Post-mortem studies on patients with heart failure identified an association with incidence of pulmonary embolism (Roberts et al. 1987). That said, the development of patient pro-thrombotic state seems to be dependent on the severity of heart failure (Shantsila et al. 2021; Shantsila and Lip 2014). Clinicians contemplating anticoagulation therapy (i.e., rivaroxaban) for preventing stroke, should consider that the benefit of risk reduction against risks of major bleeding may only be evident in patients with severe heart failure (New York Heart Association (NYHA) class III or IV) (Echemann et al. 2000). In addition, clinicians should consider that the risk of stroke is not consistent over time but is typically highest in the first month following diagnosis of heart failure (Kim and Kim 2018; Lip et al. 2012).

In terms of clinical policy, it may not be feasible to prescribe anticoagulation medication for longer-term use in patients with non-severe heart failure due to major bleeding risks (despite the increased risk of stroke) (Shantsila et al. 2021). However, in severe heart failure (NYHA functional class III to IV) the trade-off between bleeding risk and stroke risk might be offset and could prove to be beneficial (Shantsila et al. 2021). There is stepwise increase in stroke risk dependent on the NYHA

functional class association, and this should be considered prior to prescribing anticoagulation medication (Barkhudaryan et al. 2021). What this could indicate for future practice is characterizing heart failure patients and using appropriate bleeding risk scores to risk stratify and place only the highest risk on oral rivaroxaban (Edmiston and Lewis 2018). While this commentary cannot recommend the routine use of oral anticoagulation for general heart failure patients based on current evidence (particularly patients with NYHA functional class I to II), it does indicate a consideration on an individual case basis for heart failure patients (Shantsila et al. 2021).

Limitations of the three RCT's reported by this review identified a need for high quality studies to establish the effect oral anticoagulation has on bleeding, and whether it is beneficial for people with severe heart failure (NYHA functional class III or IV) (Shantsila et al. 2021). These studies could improve the certainty of evidence relating to treatment effects and adverse events associated with anticoagulation therapy. Future research should also focus on excluding any confounding variables such as heart failure and thrombosis, particularly as stroke is commonly associated with multiple morbidities such as coronary disease, atrial fibrillation and diabetes (Kim and Kim 2018).

CPD reflective questions

- What are the key limitations of the systematic review discussed in this commentary and what needs to be considered when applying the evidence to practice?
- What thromboembolic factors should be considered prior to anticoagulant intervention for patients with heart failure?
- What is the risk of uncontrolled thromboembolism and what benefit can be achieved by controlling this?

Declaration

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