
# Blood coagulation disorders in heart failure: from basic science to clinical perspectives

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**Review Article**

# Blood coagulation disorders in heart failure: from basic science to clinical perspectives

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**Highlights:**

- Thrombotic complications in heart failure patients are an underappreciated problem
- We reviewed data regarding coagulation disorders in acute and chronic heart failure
- We discussed scenarios where antiplatelet and anticoagulant therapy can be tailored
- We provided top 10 pearls in coagulation disorders management in heart failure

**Abstract**

Heart failure (HF) is a clinical syndrome divided into three subtypes, based on the left ventricular ejection fraction. Every subtype has specific clinical

characteristics and concomitant diseases, substantially increasing risk of thromboembolic complications such as stroke, peripheral embolism and pulmonary embolism. Despite the annual prevalence of 1% and devastating clinical consequences, thromboembolic complications are not typically recognised as the leading problem in HF patients, representing an underappreciated clinical challenge. Although the currently available data do not support routine anticoagulation in patients with HF and sinus rhythm, initial reports suggest that such strategy might be beneficial in a subset of patients at especially high thromboembolic risk. Considering the existing evidence gap, we aimed to review the currently available data regarding coagulation disorders in acute and chronic HF based on the insight from preclinical and clinical studies, summarize the evidence regarding anticoagulation in HF in special case scenarios and outline future research directions to establish the optimal patient-tailored strategies for antiplatelet and anticoagulant therapy in HF. In summary, we highlight the top 10 pearls in the management of patients with HF and no other specific indications for oral anticoagulation therapy. Further studies are urgently needed to shed light on the pathophysiological role of platelet activation in HF and to evaluate whether antiplatelet or antithrombotic therapy could be beneficial in HF patients.



**Keywords:** anticoagulation, antiplatelet, heart failure, thrombosis, tailored therapy

## 1. Introduction

Heart failure (HF) is a clinical syndrome caused by a structural or functional disorder of the heart which results in elevated intracardiac pressures and/or inadequate cardiac output during exercise or rest [1] [REF], with the worldwide prevalence of 1-2% [2]. HF is divided into three subtypes, based on the left ventricular ejection fraction (LVEF): (i) HF with reduced ejection fraction (HFrEF), (ii) HF with mildly reduced ejection fraction (HFmrEF) and (iii) HF with preserved ejection fraction (HFpEF) [1]. Every subtype has specific clinical characteristics and most common concomitant diseases, including variable risk of thromboembolic complications. It also must be acknowledged that some experts consider LVEF in HF patients as a continuum of left ventricular systolic dysfunction rather than distinct clinical phenotypes of specific subpopulations [1] [REF].

Although thromboembolic complications are not typically recognised as the leading problem in HF patients, HF is associated with substantial coagulation disorders [3]. For example, the incidence of stroke is higher in the first month following HF diagnosis or decompensation and decreases within 6 months following the acute event [4]. The prothrombotic phenotype in HF patients might be due to (i) systemic inflammatory response induced by chronic hypoxia, (ii) increased concentrations of prothrombotic molecules, and (iii) arterial and venous endothelial dysfunction. Thus, increased risk of thromboembolic complications is a hallmark of HF and represents an underappreciated clinical challenge. Whereas thromboembolism prophylaxis with low-molecular weight heparin is recommended in hospitalised patients with acute HF (AHF) in absence of contraindications, and in patients treated with long-term mechanic circulatory support [1], the guidelines regarding the routine antithrombotic and/or anticoagulant treatment in patients with HF are

controversial. Data from meta-analyses suggests patients with HF and sinus rhythm (SR), treated with warfarin, have doubled the risk of major bleeding, however without significant increase in intracranial haemorrhage [5]. Nevertheless the authors observed significant reductions in stroke risk, but finally lacked beneficial effects in all-cause mortality [5]. However, no such data are available for direct oral anticoagulants (DOACs). The only study which evaluated the efficacy and safety of a DOAC (low-dose rivaroxaban twice daily) in patients with HFrEF, coronary artery disease (CAD) and SR did not show any benefit in terms of the composite endpoint of death, stroke, or myocardial infarction (MI), compared with placebo [6]. However, a *post-hoc* analysis of this study demonstrated that patients treated with rivaroxaban had 32% lower incidence of the primary neurological endpoint (all-cause stroke or transient ischaemic attack), compared with placebo, without an increased rate of fatal bleeding or bleeding into a critical space [4]. Hence, although the currently available data do not support routine anticoagulation in patients with HF and SR, initial reports suggest that such strategy might be beneficial in a subset of patients at especially high thromboembolic risk. Considering the existing evidence gap, we aimed to review the currently available data regarding coagulation disorders in acute and chronic HF (CHF) based on the insight from preclinical and clinical studies, summarize the evidence regarding anticoagulation in HF in special case scenarios and outline future research directions to establish the optimal patient-tailored strategies for antiplatelet and anticoagulant therapy in HF. Here we summarize the known mechanisms underlying coagulation disorders in HF - **Figure 1**.

## 2. Platelet activation in acute and chronic heart failure

HF is associated with an increased risk of thromboembolism regardless of the presence of atrial fibrillation (AF) [7]. These coagulation disorders might be

partly explained by the Virchow's triad components (stasis of blood in peripheral circulation and heart chambers, hypercoagulability, endothelial dysfunction). However, the precise mechanisms underlying thrombosis in patients with HF and SR remain to be determined [8].

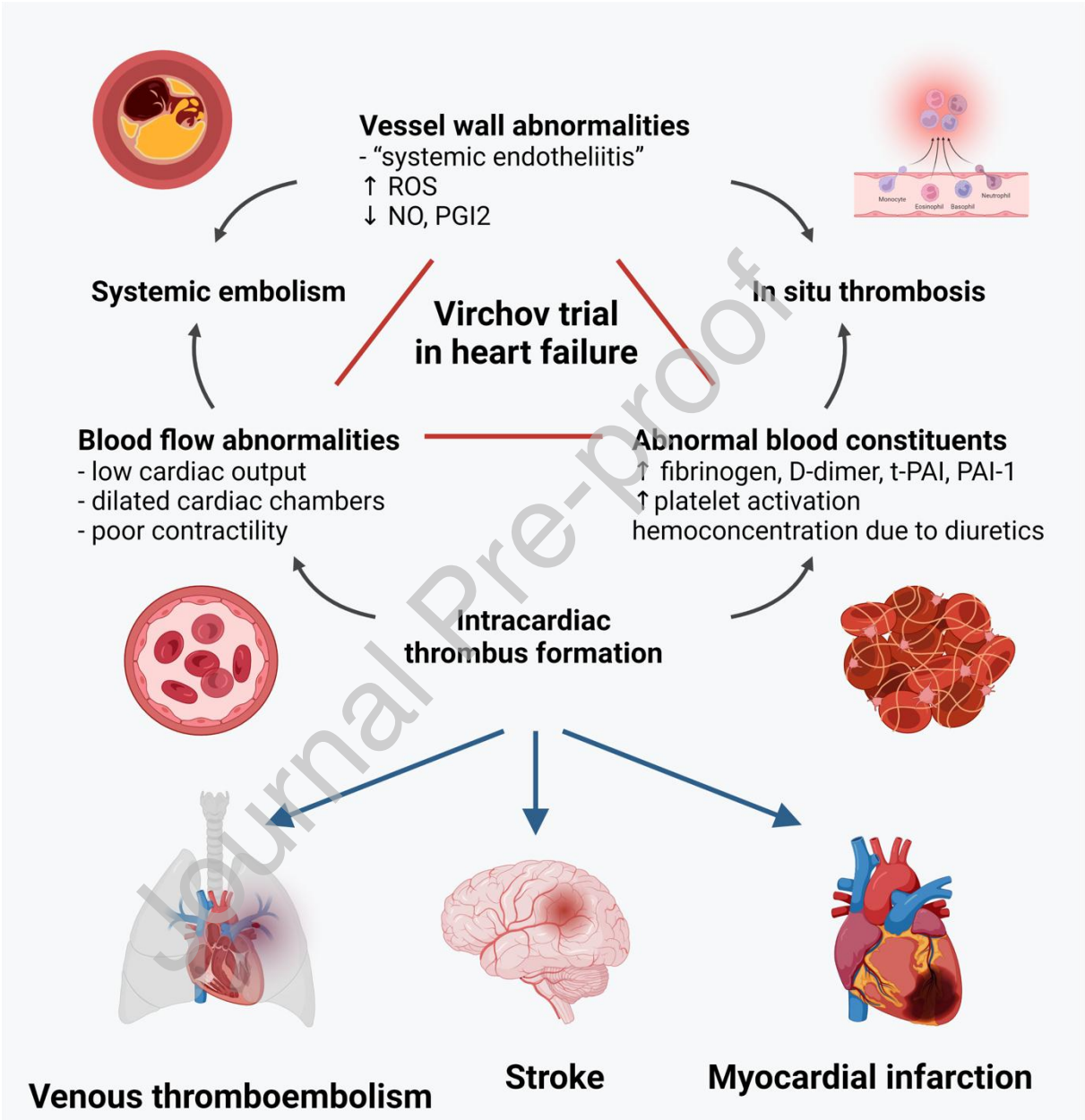


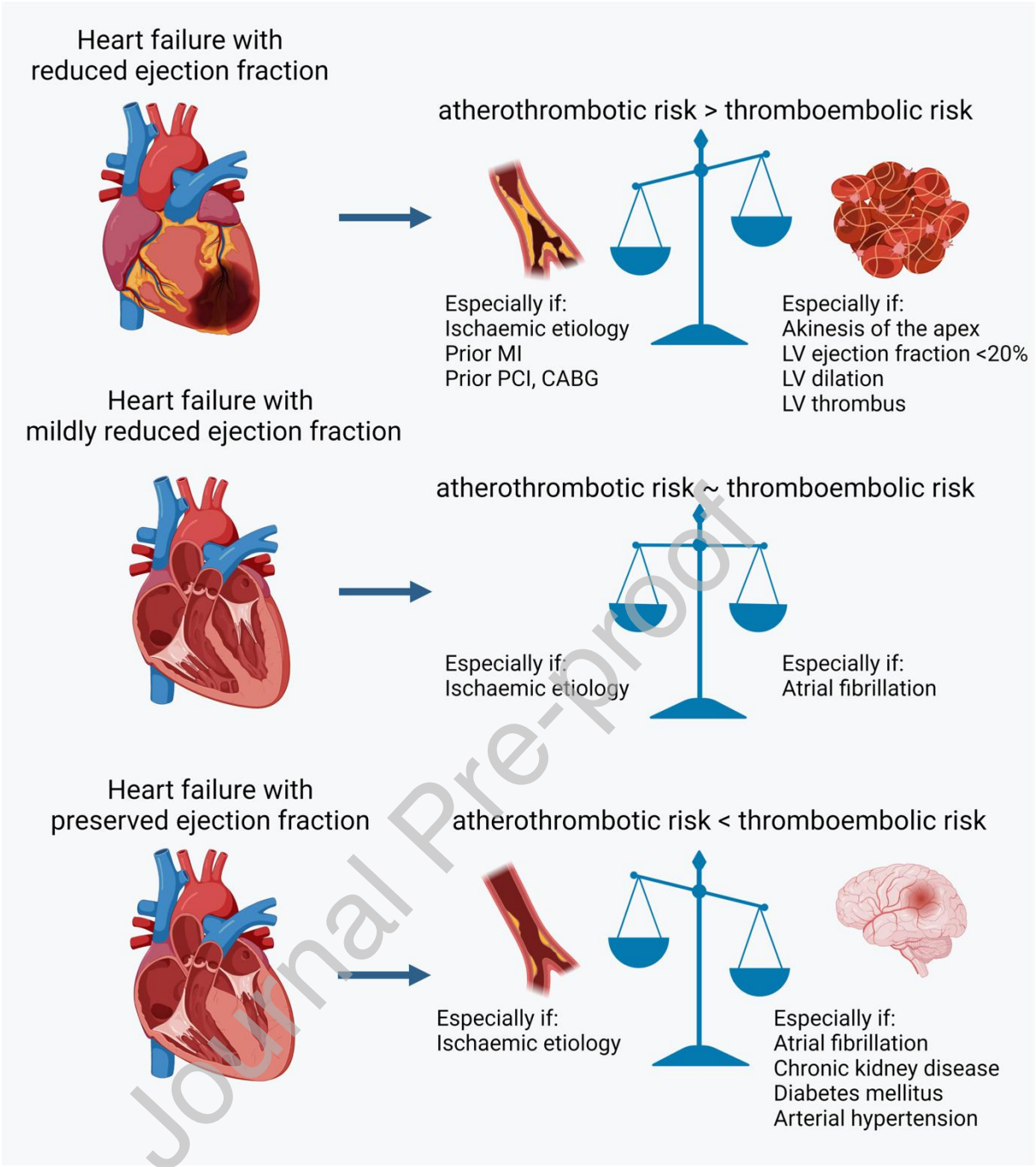

**Figure 1**. Mechanisms underlying coagulation disorders in acute heart failure. Abbreviations: NO – nitric oxide; PAI-1 – plasminogen activator inhibitor-1; PGI2 – prostaglandin I2; ROS – reactive oxygen species; t-PA – tissue plasminogen activator

Preclinical studies showed dysregulation of platelet signalling pathways in HF, leading to platelet hyperreactivity [9]. In HF patients, elevated levels of platelet activation such as soluble P-selectin have been observed, compared to healthy controls [7]. Adhesion proteins and platelet activation markers (CD63, CD40 ligand and P-selectin) were overexpressed in AHF, compared to CHF [7,10]. The expression levels of these markers were reduced following initiation of treatment in patients with decompensated HF [11]. Moreover, platelet-leucocytes interactions, known to correlate with platelet activation and adverse events, were also increased in HF patients [12].

The mechanisms underlying platelet dysregulation in HF still need to be understood. For these reasons, platelets remain an unchallenged target in HF: few studies have attempted to investigate the role of antiplatelet and antithrombotic therapies in this setting and they all failed to demonstrate a significant clinical benefit [13–16].

## 3. Coagulation disorders in heart failure subtypes

The pathophysiology of coagulation disorders in different CHF subtypes is summarized in **Visual Take Home Graphic**.






**Visual Take Home Graphic**. Pathophysiology of coagulation disorders in different heart failure subtypes. Abbreviations: CABG – coronary artery bypass grafting; LV – left ventricle; MI – myocardial infarction; PCI – percutaneous coronary intervention.

Increased thromboembolic risk in patients with HFrEF was demonstrated in numerous studies, as indicated by (i) prothrombotic plasma profile, (ii) higher rate of thromboembolic complications, (iii) risk of left ventricle (LV) thrombus. HFrEF patients have substantially increased thromboembolic risk due to unfavourable fibrin clot properties, compared to healthy controls [17]. Thromboembolic complications in patients with HFrEF include stroke, peripheral embolism and pulmonary embolism. In the randomized controlled Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT), patients with HFrEF experienced thromboembolism at an annual rate of 1.0%, with the higher risk associated with lower LVEF [18]. Based on the retrospective analysis of the Studies of Left Ventricular Dysfunction (SOLVD), a decline in LVEF was associated with thromboembolic risk in women, with a relative risk of 1.53 with every 10% decrease of LVEF [19]. Similarly, in the Survival and Ventricular Enlargement trial the authors showed an 18% increase in stroke risk for every 5% reduction in the LVEF [20]. LV thrombus is another possible complication of HFrEF, present in 2.1 to 7.0% of patients. The predisposing factors include severe systolic dysfunction, ischaemic HF aetiology and akinesis of the apex and anterior wall [21,22]. Patients with an LV thrombus have 4-fold higher risk of thromboembolism and 2-fold higher risk of long-term mortality and anticoagulation is a standard-of-care in these patients [1,22].

Regarding HFmrEF, Practice Innovation and Clinical Excellence (PINNACLE) Registry showed that these patients were more likely to have AF, type 2 diabetes, and chronic kidney disease (CKD) and to have a history of tobacco use, compared to HFrEF [23]. The authors also found that patients with HFmrEF had distinct atherothrombotic profile, including history of CAD, prior MI or percutaneous coronary interventions [23]. Interestingly, due to this specific clinical profile of patients with HFmrEF, the authors hypothesized that

the antithrombotic therapy with rivaroxaban, which did not improve outcomes in patients with HFrEF, might be beneficial in HFmrEF patients [6,23].

Thromboembolic risk in HFpEF patients is associated with a higher prevalence of AF, compared to other HF subtypes [24]. In addition, patients with HFpEF have many other cardiovascular and non-cardiovascular comorbidities that indirectly increase the risk of thrombotic complications, such as CKD, arterial hypertension and type 2 diabetes.

Despite substantially higher risk of thromboembolic complications, currently no evidence supports the routine anticoagulation in patients with HF and SR [8,24]. Nevertheless, no specific randomized clinical trials have been conducted in the subgroups of patients at very high risk thromboembolic risk, such as patients with HFrEF <20% and/ or akinesis of the apex. There are only few observational, retrospective data concerning this topic of interest and demonstrating promising results in the resolution of left ventricular thrombus (REF). More robust data regarding the potentially lower rates of stroke or other thromboembolic events due to anticoagulation in this challenging patient subgroup is urgently needed.



## 4. Anticoagulation for heart failure in special pathophysiological settings

### *4.1. Patients with heart failure with and without atrial fibrillation*

The risks of systemic thromboembolism and ischaemic stroke are common in HFrEF due to impaired LV systolic function. Moreover, these events are associated with devastating clinical consequences, regardless of the presence or absence of AF [25].

Contemporary data show that 47.5% of first-time strokes in HFrEF patients are either severely disabling or fatal [4]. While the efficacy of

anticoagulants in HF for concurrent comorbidities such as AF is well-established, data on the routine use of anticoagulants in patients with chronic HF and SR have been conflicting. For example, pioneer data derived from the WATCH trial, conducted among HFrEF patients in SR, showed that warfarin use was not superior to aspirin or clopidogrel regarding reduction in the primary outcome of death, nonfatal MI, or nonfatal stroke [15]. In this trial, warfarin use was associated with fewer nonfatal stroke events, while this was offset by the higher number of major haemorrhage and central nervous system bleeding events. Similar findings were found in the WARCEF trial demonstrating that reduced risk of ischaemic stroke with warfarin in patients with HFrEF and SR was outweighed by an increased risk of major bleeding [16]. Due to the increasing prevalence in the use of DOACs for thromboembolism prevention, it remains unclear whether the use of DOACs in the setting of HF and SR would provide a more favourable risk-benefit profile compared to VKA.

The seminal COMPASS trial was executed to determine if the addition of low-dose DOAC (2.5 mg of rivaroxaban twice daily) to aspirin in patients with stable atherosclerotic disease would mitigate the risks of MACE with an acceptable margin of bleeding events, compared to aspirin alone. This trial showed that the combined use of low-dose rivaroxaban and aspirin was associated with a 24% relative risk reduction of adverse cardiovascular outcomes, however, this effect was countered by the 70% increase in the relative risk of major bleeding events [26]. Subanalysis of this large trial showed that the effect of concomitant use of rivaroxaban and aspirin achieved a similar reduction in MACE among both HF and non-HF patients, however, the magnitude of treatment benefit was higher among patients with HF [27]. The observed benefit was similar among patients with LVEF <40% and those with ≥40% while the excess bleeding was not different in patients with and without HF. The authors observed the 36% increase in the relative risk for major

bleeding among patients with HF in SR treated with rivaroxaban, however, this increase was not statistically significant.

The issue of anticoagulation in patients with exacerbated HF, concomitant CAD, and without AF was investigated in the COMMANDER HF trial, enrolling 5022 patients [6]. The results of this trial were disappointing, as the "vascular dose" of rivaroxaban (2.5 mg twice daily from the COMPASS trial) added to the standard of care failed to reduce rates of death, MI, or stroke, compared to placebo. The *post-hoc* analysis of this trial showed that thromboembolic events are frequent in this population and that rivaroxaban significantly reduced the rate of thromboembolism (about 20% of relative risk reduction), however, these events were not the principal drivers of mortality and morbidity in this population, thus were unaffected by rivaroxaban [28]. While current European and US guidelines recommend the use of OACs in patients with HFrEF and concomitant AF and/or mechanical valves, no recommendations are made in HF patients with SR due to the lack of benefit on morbidity and mortality [1,29][REF]. However, low-dose rivaroxaban alongside aspirin is an option for patients with high-risk chronic coronary syndrome and without high bleeding risk, including in HF.

Altogether, current data do not support the prophylactic use of OAC in patients with HFrEF and SR, in the absence of left ventricular thrombus. However, addition of low-dose rivaroxaban might be considered in selected cases, for example among HF patients in SR that also have established CAD and/or peripheral artery disease and are at low risk of bleeding but high risk of recurrent ischaemic events [1].

### *4.2. Patients with heart failure and left ventricular thrombus*

The formation of LV thrombus is a consequence of depressed LV systolic function due to various aetiologies such as a large anterior or apical MI with an extensive scar or aneurysm formation, non-ischemic dilated cardiomyopathy, and/or chronic severe HFrEF. The thrombus formation in the LV is precipitated by relative blood stasis in hypokinetic cardiac chambers, while prothrombotic blood phenotype is one of the characteristics of patients with HFrEF *per se* [30]. Therefore, at least two components of Virchow's triad of thrombogenesis are operative in HFrEF, often complemented with the component of endothelial injury. However, there is no robust randomized data informing clinical practice on the use of anticoagulants in patients with HF and LV thrombus that have no other indications for the anticoagulation. There is a substantial prevalence of LV thrombus in HF, but the incidence of thromboembolic events remains low thus questioning the practice of routine systemic anticoagulation in this setting [31]. Latest guidelines recommend to consider systemic anticoagulation in HF patients with intraventricular thrombus, regardless of the underlying rhythm [1]. On the other hand, US guidelines acknowledge the low benefit of anticoagulation in patients with HFrEF and SR among patients with severely depressed systolic function and evidence of intracardiac thrombi [29]. International guidelines focused on stroke prevention and acute ST-elevation MI management generally recommend 3 to 6 months of OAC with warfarin among patients with visible intracardiac thrombus, or until the thrombus is resolved [32,33].

No randomized data exist concerning the efficacy and safety of DOACs vs. warfarin in the treatment of LV thrombus, although observational data and meta-analyses suggest non-inferiority or even superiority of DOACs vs. warfarin with respect to thrombus resolution and safety profile [34,35]. Contrary to this, there are data showing the inferiority of DOACs in preventing stroke or

systemic embolism in patients with LV thrombus, compared to warfarin [36]. A recent state-of-the-art review on LV thrombus recommended the use of VKA with a goal international normalised ratio (INR) 2-3 in LV thrombus, and DOAC should be used if VKA cannot be tolerated [37].

In conclusion, no specific guidelines and trials exist on the use of anticoagulation in the setting of HF and concomitant LV thrombus in the absence of other prothrombotic conditions, and most of such practices are based on extrapolation of data from other settings such as ACS. Nevertheless, it is common practice to start anticoagulation treatment after diagnosis of LV thrombus and continue for 3 to 6 months or until the thrombus resolution is confirmed by cardiac imaging. Due to the unresolved question of whether DOACs are equivalent or better than warfarin in treating LV thrombus, the choice of anticoagulation agent in this setting remains the question of scientific debate and should be selected on an individual case-by-case basis, but guidelines generally continue to endorse VKA as first choice.

### *4.3. Patients treated With Mechanical Circulatory Support and Left Ventricular Assist Device*

Patients treated with mechanical circulatory support (MCS), for example extracorporeal membrane oxygenation (ECMO) or a left ventricular assist device (LVAD) are at particular risk of thrombosis for a number of reasons.

*Mechanical Circulatory Support*

The thrombotic response can be initiated by blood coming into contact with an artificial surface via activation of the intrinsic pathway and by adherence of platelets and leucocytes which then release prothrombotic factors locally [38].

Non-physiological levels of shear stress can similarly trigger thrombosis. This can predominantly activate the coagulation cascade and/or platelets depending on the specific conditions [39]. It is therefore rational to consider antithrombotic therapy during MCS. However, as well as an elevated risk of thrombosis, patients receiving MCS also have an increased incidence of bleeding events, some associated directly with the MCS technology but also a seemingly unrelated elevated background risk [40]. Balancing these risks is challenging but continues to favour a high-intensity of prophylactic treatment [41]. Current recommendations for long-term MCS suggest initiating post-operative parenteral anticoagulation, typically with UFH, as long as bleeding is controlled.

*Left Ventricular Assist Device*

In the case of LVAD, once the patient is clinically stable, oral anticoagulation for the duration of circulatory support is recommended. The agent of choice remains a VKA such as warfarin, with a target INR of 2.0 to 3.0. Largely due to a paucity of data, treatment with a DOAC is not recommended in patients with LVAD [42]. Alongside anticoagulation, routine low-dose aspirin is recommended to reduce thrombotic complications [43]. In some cases of particularly high thrombotic risk or when implanting certain devices such as the HeartWare® system (though now discontinued), it has been recommended to confirm good response to aspirin and optionally add a second antiplatelet drug such as dipyridamole or clopidogrel [44].

In the case of ECMO, it has been questioned whether with current-generation equipment, including heparin-coated circuits, therapeutic levels of anticoagulation are necessary. A systematic review of 34 studies including 201 patients suggested that anticoagulant-free ECMO had similar rate of circuit and patient thrombosis as continuous systemic anticoagulation. Nevertheless, this

review was limited by a retrospective design, inconsistent reporting of outcomes and a relatively small sample size [40]. In daily clinical practice, systemic anticoagulation remains a standard-of-care in patients treated with ECMO. Several small-scale studies of lower-intensity regimens of anticoagulation are underway (e.g. RATE, NCT04536272; SAFE-ECMO, NCT04997265).

### 4.4. Patients after heart transplantation

HF patients who have undergone cardiac transplantation represent another challenging group regarding the optimal antithrombotic strategies. Transplant-specific reasons such as increased long-term risk of malignancy, infection, and chronic kidney disease due to immunosuppression contributes to bleeding risk, whilst the pro-inflammatory milieu of acute or chronic rejection increases the risk of thrombosis [45].

Antithrombotic therapy may be complicated by metabolic interactions of drugs such as VKAs, NOACs and ticagrelor with the calcineurin inhibitors ciclosporin and tacrolimus [46]. Cardiac transplant recipients may have less response to aspirin than other groups, and in those transplant patients with evidence of vasculopathy compared to those without [47].

There are no data supporting the routine use of antithrombotic therapy after cardiac transplantation. The cornerstones of management are to continue long-term antithrombotic therapy if this was indicated pre-transplant (e.g. for chronic coronary syndromes, representing a raised baseline ischaemic risk due to CAD itself) and to treat post-transplant thrombotic events as they arise. A common complication of cardiac transplantation is cardiac allograft vasculopathy (CAV), a manifestation of chronic rejection mediated by platelet, immune and endothelial activation [48]. Antiplatelet therapy might reduce the

development or sequelae of CAV. Studies which examined whether aspirin might impact on development of CAV after cardiac transplantation did not provide solid evidence for any beneficial effect of such therapy [49].

There is no evidence that routine therapeutic anticoagulation without a clear indication after heart transplantation is beneficial. While OAC is indicated in case of AF or VTE, there is only limited regarding the choice of OAC. The use of a NOAC may lead to less bleeding than VKA, consistent with general findings [50]. Whether these drugs provide the same degree of thrombotic protection in patients with heart transplant remains unexplored.

## 5. Recommendations for anticoagulation in heart failure and future studies

In this article we aimed to review the available literature to summarize the current management of anticoagulation in patients with HF. We want to emphasize that HF should be recognized as a risk factor for thromboembolic events, of which stroke is one of the most severe. In summary, we highlight the top 10 pearls in the management of patients with HF and no other specific indications for OAC therapy (**Table 1)**.

HF is associated with an increased risk of thromboembolism regardless of the presence of AF. Both platelet activation and coagulation system abnormalities may be responsible for the increased risk of major thromboembolic events in patients with HF. Although recent antithrombotic and antiplatelet clinical trials failed to demonstrate significant clinical benefits of OACs in comparison to aspirin or placebo in the overall population of HF patients, a *post-hoc* analysis of the COMMANDER-HF study demonstrated a significantly lower incidence of the primary neurological endpoint in HFrEF patients treated with rivaroxaban, without an increased rate of major bleeding.

Although routine anticoagulation in patients with HF and SR cannot be recommended, it remains important to actively search for AF and other indications for OACs in patients with HF, to accelerate diagnosis and optimize treatment of thromboembolic risk factors.

Patients with HFrEF experience thromboembolism at the annual rate of 1.0%. A decrease in LVEF positively correlates with an increase in thromboembolic risk, with the highest risk in patients with LVEF <20% and akinesis of the apex and apical LV segments, predisposing for LV thrombus formation. Patients with an LV thrombus have 4-fold higher risk of thromboembolism and 2-fold higher risk of long-term mortality and should be considered for anticoagulation. Moreover, observational data indicate that the use of clinical scores such as $CHA_2DS_2$-VASc might help to estimate the thromboembolic risk among patients with HF (HFrEF and HFmrEF) and SR. On the other hand, HFpEF is mosaic of various patient populations and their clinical characteristics, which carry an additional risk for both thrombosis and bleeding. Therefore, choosing the optimal pharmacotherapy and potential benefits of OACs are far more challenging. The most common comorbidities which are described in detail in separate subparagraphs should be taken into account when assessing the global thromboembolic risk in HFpEF patients.

On the other hand, thromboembolic prophylaxis, e.g. with LMWH, is recommended in patients with AHF who do not have specific indications for anticoagulation and with no contraindications to anticoagulation therapy, to reduce the risk of VTE and PE. However, the benefits of long-term anticoagulation following an AHF episode have not been demonstrated.

Although not routinely recommended, anticoagulation might be beneficial in specific clinical scenarios, frequently met in general practice such as ACS, AF, after TAVI, during MCS/ ECMO or after heart transplantation. In these subpopulations, the optimal antithrombotic/antiplatelet therapy should be

tailored to the individual patient, based on the medical history and thromboembolic risk.

**Lay summary:**

Heart failure (HF) is a clinical syndrome divided into three subtypes, based on the left ventricular systolic function. Every subtype has specific clinical characteristics and concomitant diseases, substantially increasing risk of thromboembolic complications such as stroke, peripheral embolism and pulmonary embolism. Despite the annual prevalence of 1% and devastating clinical consequences, thromboembolic complications are not typically recognised as the leading problem in HF patients, representing an underappreciated clinical challenge. Although the currently available data do not support routine anticoagulation in patients with HF and no atrial arrhythmia, initial reports suggest that such strategy might be beneficial in a subset of patients at especially high risk of thrombotic complications. Considering the existing evidence gap, we aimed to review the currently available data regarding coagulation problems in stable and unstable HF patients based on the insight from preclinical and clinical studies, summarize the evidence regarding anticoagulation in HF in specific patient groups and outline future research directions to establish the optimal strategies for antiplatelet and anticoagulant therapy in HF, tailored to the needs of an individual patient. In summary, we highlight the top 10 pearls in the management of patients with HF and no other specific indications for oral anticoagulation therapy.

**Proposed social media text:**

Thrombotic complications in heart failure patients - an underappreciated challenge ! The authors discussed data regarding coagulation disorders in acute

and chronic heart failure, scenarios where antiplatelet and anticoagulant therapy can be tailored & provided top 10 pearls in coagulation disorders management in heart failure.

Aleksander Siniarski: Research support and consulting fees from Adamed, AstraZeneca, Gedeon Richter

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Hanne Ehrlinder: Nothing to declare

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Rui Azevedo Guerreiro: Nothing to declare

William A.E. Parker: Research support and consulting fees from AstraZeneca



**Declaration of Competing Interest**

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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**@Aleksandra –** there is a mistake in **reference 5** in names. Please change it accordingly by Mendeley or EndNote. Moreover Reviewver 3 mentioned that **ref 14** has some issued with names, please double check that ;-)

**Figure legends:**

**Figure 1**. Mechanisms underlying coagulation disorders in acute heart failure. Abbreviations: NO – nitric oxide; PAI-1 – plasminogen activator inhibitor-1; PGI2 – prostaglandin I2; ROS – reactive oxygen species; t-PA – tissue plasminogen activator

**Figure 2**.

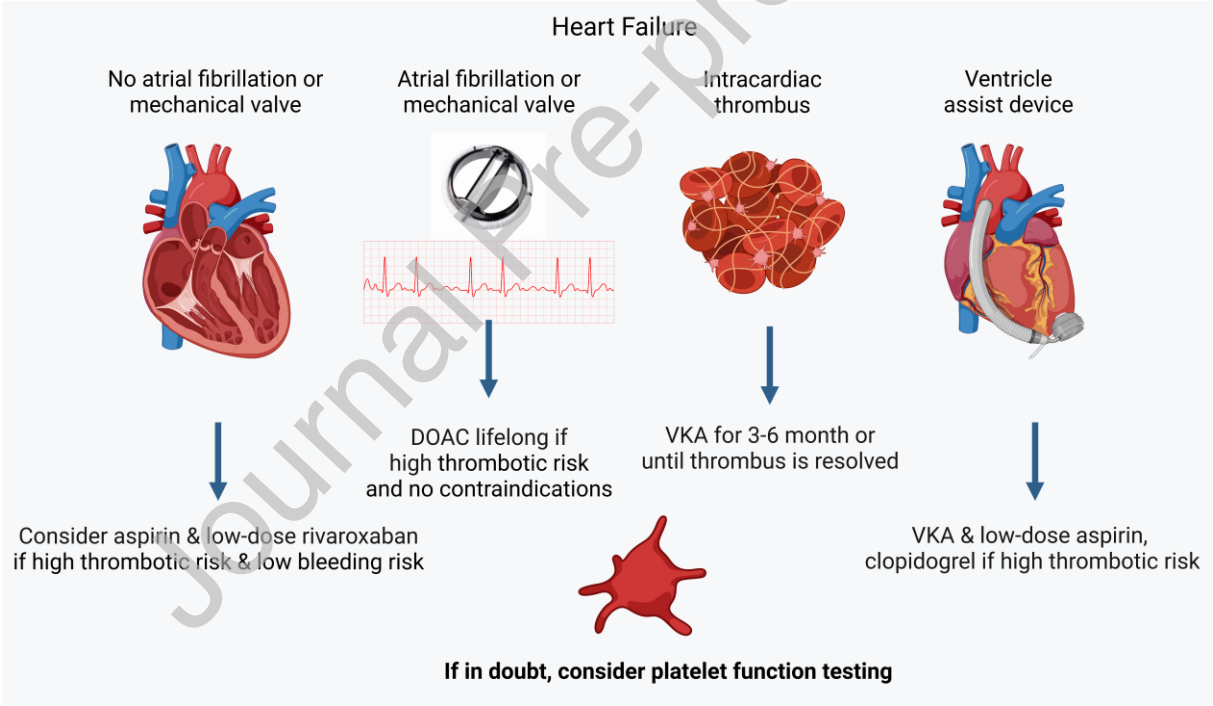

**Table 1. Top 10 pearls in the management of patients with HF and no other indications for oral anticoagulation.**

1. The heart failure (HF) population is at high risk for thromboembolic events.
2. Recent clinical trials failed to demonstrate significant benefits of antithrombotic therapy in the overall HF population without an alternative indication.
3. Atrial fibrillation (AF) in patients with HF and should be meticulously ruled out and if exists (if there are no contraindications) should be treated with proper anticoagulation regimen.
4. In HF with reduced ejection fraction (EF), a decrease in EF positively correlates with an increase in thromboembolic risk.
5. Acute HF patients should be considered for prophylactic anticoagulation during the hospitalization to prevent venous thromboembolism. The benefits of long-term anticoagulation following an acute episode have not been demonstrated.
6. Left ventricle thrombus is associated with around 4-fold increase risk in thromboembolism and 2-fold higher risk of mortality. Anticoagulation is recommended in this setting. Most current guidelines continue to favour vitamin K antagonists over non-vitamin K antagonist OACs, but more studies are urgently needed in this area.
7. HF with preserved EF ejection fraction is often associated with a mosaic of clinical comorbidities, which should be taken into account when assessing the global thromboembolic risk.
8. HF patients should receive antiplatelet therapy if there is an additional indication, such as prior myocardial infarction or coronary revascularization. Assessment of both ischaemic and bleeding risk should be performed in HF patients requiring antiplatelet therapy to

determine the correct intensity of treatment.

9. Patients treated with mechanical circulatory support or heart transplantation represent particular challenges and the optimal antithrombotic regimen should be tailored to the individual patient after considering ischaemic and bleeding risks.
10. HF is a dynamic condition and indications for antithrombotic treatment may change over time. Frequent re-evaluation is key to optimizing outcomes.

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