Platelets and heart failure

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Heart failure is associated with increased risk of venous thromboembolism, stroke, and sudden death. Platelet abnormalities have been well described in heart failure but the significance of platelets in contributing to the thromboembolic complications of heart failure remains uncertain. Furthermore, the role of antiplatelet agents in heart failure remains unclear. This review will focus on platelet activation and the role of platelet dysfunction in heart failure, with particular regard to pathophysiology and outcome. The effects of heart failure therapeutics on platelet function and antiplatelet therapy in heart failure will also be discussed.

KEYWORDS
Platelet activation;
Heart failure;
CD40L;
P-selectin;
Antiplatelet therapy

Introduction
Congestive heart failure (CHF) is a major global disease and is increasing in prevalence due to the increasing age of the general population and improved survival of patients with myocardial infarction. Despite significant advances in medical therapy, the mortality rate from severe CHF still remains over 60% within 5 years of diagnosis.1 CHF also has a significant impact on health-care costs, accounting for 2% of total UK National Health Service expenditure.2

It is well recognized that patients with CHF have increased risk of venous thromboembolism, stroke, and sudden death. For example, the incidence of stroke is ~4–5% in severe heart failure, when compared with 0.5% of the general population of the same age group.1 Sudden cardiac death may also have a similar thrombotic origin (i.e. intracardiac or intracoronary).2 These thrombosis-related complications in patients with CHF have been attributed to a prothrombotic state, the exact cause of which is not known.2

In 1856, Virchow described three components for the pathophysiology of thromboembolic disease—abnormal blood constituents, blood flow, and vessel wall. Although originally described for venous thrombosis, the concepts may nonetheless be applicable to occlusive arterial diseases. Various studies have generally concentrated on clotting factors, and markers of endothelial damage/dysfunction in heart failure, but not on platelets per se.3 Furthermore, a role for aspirin, which is the commonest prescribed antiplatelet agent, in patients with CHF has been debated, given recent clinical data.4-6

The aim of this review is to provide an overview of the pathophysiology of platelet activation and thrombogenesis in heart failure specifically, and to summarize present and future antiplatelet therapeutic options for heart failure.

Search strategy

Evidence that platelets are activated in heart failure
Platelet abnormalities in CHF have been well described (Table 1). For example, heart failure patients have increased whole blood aggregation,7 platelet-derived adhesion molecules,8 CHF patients also have higher mean platelet volume9 and soluble (and platelet-bound) P-selectin, regardless of the aetiology.10,11 sCD40L was also shown to be increased in acute and chronic heart failure when compared with healthy controls and was shown to be correlated to NYHA and ejection fraction.12

Prognostic data on platelet markers in heart failure patients are limited. Indeed, platelet aggregation and flow cytometry abnormalities in stable heart failure patients do not appear to predict cardiovascular events.10,13 A study by Yin et al.,14 which included a high proportion of valvular disease in their patients with heart failure, found soluble P-selectin levels to be an independent significant predictor of cardiovascular events.

Although many studies have shown increased platelet activation in heart failure, none have specifically studied...
patients with isolated idiopathic cardiomyopathy, those without any vascular risk factors or subjects devoid of therapeutic agents. The study by Stumpf et al. \textsuperscript{15} did have a group of ischaemic heart disease patients for comparison, but they were mainly patients with known ischaemic heart disease admitted with non-cardiac chest pain. Clearly, the significance of platelet activation in heart failure, especially in relation to prognosis, requires further study.

**Mechanisms of platelet activation in heart failure**

**Haemodynamic and vascular factors**

Mehta and Mehta\textsuperscript{16} first reported in 1979 that patients with heart failure had significantly more circulating platelet aggregates than normal volunteers. During sodium nitroprusside infusion, the number of circulating platelet aggregates declined to normal levels and in vitro platelet aggregation responses to epinephrine and adenosine diphosphate were also significantly suppressed. The associated 30% decline in systemic vascular resistance and a 28% increase in cardiac output suggested that an increase in vascular resistance in heart failure may cause an increase in circulating platelet aggregates (Figure 1).

Dilated cardiac chambers, poor contractility, regional wall abnormalities, and concomitant atrial fibrillation may all predispose to thromboembolism by facilitating stasis of intracardiac blood flow.\textsuperscript{17,18} Plasma levels of fibrinopeptide A and thrombin–antithrombin III complex are all increased in heart failure, and correlate positively with left ventricular end-systolic volume and negatively with the fractional shortening of the left ventricle.\textsuperscript{19}

Increased plasma levels of coagulation markers in those patients with lower ejection fractions suggests that a low cardiac output may promote a prothrombotic or hypercoagulable state.\textsuperscript{18} Indeed, patients with left ventricular dysfunction and aneurysm formation have significantly higher fibrin D-dimer (an index of thrombogenesis), fibrinogen (a coagulation factor), and von Willebrand factor (vWF, a marker of endothelial damage/dysfunction) levels, compared with those with normal cardiac function or healthy controls, in keeping with a prothrombotic state.\textsuperscript{20} Also, plasma viscosity, fibrinogen, vWF, and soluble P-selectin (a marker of platelet activation) are all elevated in patients with CHF compared with healthy controls, with plasma viscosity and fibrinogen levels being

<table>
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<tr>
<td>Varo et al.\textsuperscript{71}</td>
<td>195 patients who had assigned to the placebo arm of the OPUS-TIMI116 trials and who had reached end-points of death, MI, or CHF was matched with one control in 10 months follow-up</td>
<td>sCD40L</td>
<td>Patients reached endpoints had significantly higher median (25th, 75th percentiles) sCD40L levels than did controls (P &lt; 0.002). sCD40L above median levels were associated with higher risk for death, MI, and the composite death/MI, or death/MI/CHF (HR 1.9 (P &lt; 0.05), 1.9 (P &lt; 0.001), 1.9 (P &lt; 0.001), and 1.8 (P &lt; 0.01), respectively)</td>
</tr>
<tr>
<td>Gibbs et al.\textsuperscript{24}</td>
<td>120 patients CHF vs. 120 healthy controls</td>
<td>Plasma viscosity, sP-sel, vWF, and fibrinogen</td>
<td>Higher levels of plasma viscosity, sP-sel, vWF, and fibrinogen in CHF patients than controls</td>
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<td>O’Connor et al.\textsuperscript{11}</td>
<td>22 CHF patients vs. 14 healthy controls</td>
<td>sP-sel and platelet P-sel</td>
<td>Patients with CHF had significantly elevated sP-sel and P-sel expression</td>
</tr>
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<td>Chin et al.\textsuperscript{72}</td>
<td>120 CHF patients and follow-up for 2 years. Endpoints include all-cause mortality and cardiovascular hospitalizations</td>
<td>TF, IL-6, sP-sel</td>
<td>Predictors of endpoints were high (≥ median) TF (P = 0.011), and IL-6 (P = 0.007) but not P-sel</td>
</tr>
<tr>
<td>Yin et al.\textsuperscript{14}</td>
<td>74 CHF patients vs. 19 healthy controls. Median follow-up of 240 days. Endpoints include cardiac death, heart transplantation, and hospitalization for heart failure</td>
<td>sP-sel</td>
<td>sP-sel was independent predictor of CHF and there were negative correlations between left ventricular EF and sCAMS</td>
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<td>Stumpf et al.\textsuperscript{15}</td>
<td>50 CHF (40 in-patients) vs. 10 with CAD but no heart failure vs. 15 healthy controls</td>
<td>Platelet-bound CD40L, CD62P</td>
<td>Levels of platelet-bound CD40L, CD62P higher in both disease groups than controls. Platelet-CD40L levels were higher in CHF than CAD patients</td>
</tr>
<tr>
<td>Ueland et al.\textsuperscript{12}</td>
<td>236 patients with acute HF following MI vs. 116 CHF vs. 30 healthy controls</td>
<td>sCD40L</td>
<td>Higher levels of sCD40L in acute HF and CHF than healthy controls. No difference in sCD40L between ischaemic and idiopathic dilated cardiomyopathy patients</td>
</tr>
</tbody>
</table>

CI, confidential intervals; HR, hazard ratio; MI, myocardial infarction; OPUS-TIMI-116, orbofiban in patients with unstable coronary syndromes-thrombolysis in myocardial infarction-116 study; P-sel, P-selectin; TF, tissue factor.
higher in patients with more severe symptoms, although soluble P-selectin was not correlated to ejection fraction.21 The sympathetic nervous system is activated in CHF and can be related to prognosis. Jafri et al.19 reported that patients with severe heart failure and high plasma norepinephrine concentration or low ejection fraction were more likely to have activation of platelets (higher plasma platelet factor 4, beta-thromboglobulin) and coagulation system (as indicated by higher plasma antithrombin III complexes, fibrinopeptide A, and D-dimers). The increased levels of circulating norepinephrine in CHF may also lead to decrease in platelet alpha2 adrenoreceptors.22

Epinephrine increases platelet deposition on severely damaged vessel wall or immobilized collagen in experimental study.23 The catecholamine-potentiating effect on platelet activation appears to be mediated by the α2-adrenoceptor stimulation, as it is blunted by exposure to selective antagonists, such as yohimbine, and is cyclo-oxygenase independent as it is unaffected by aspirin treatment. Blocking fibrinogen binding (i.e. glycoprotein IIb/IIIa antagonist) prevents catecholamine-induced platelet aggregation.24

Infusion of angiotensin II into healthy subjects increases plasma β-thromboglobulin, platelet surface expression of P-selectin, and platelet fibrinogen binding, whereas platelet aggregation is unaltered.25 Nonetheless, the actions of angiotensin on the heart are also complex. For example, angiotensins II and III increase cardiac contractility in some animals and in human myocardium in vitro, especially under hypoxic conditions.26 However, peripheral constriction and sodium retention stimulated by angiotensin II aggravates heart failure. Angiotensin II can also induce myocardial necrosis, fibrosis, and hypertrophy in animal studies.27 Furthermore, it increases nuclear factor-kappa B (NF-kB)-mediated myocardial expression of proinflammatory cytokines and chemokines.28

Pre-treatment of vascular muscle cells with angiotensin II enhances IL-18-induced NF-kB activation, thus increasing cytokine gene and mRNA expression and perpetuating a vicious circle involving the IL-18 signalling pathway.29 In contrast, ACE-inhibitor use attenuates angiotensin II-induced atherosclerosis and vascular inflammation.30 The progression of heart failure is also associated with cardiac angiotensin II formation, which is positively correlated to increasing end-systolic wall stress.31 In relation to platelets, angiotensin II causes thrombin-induced dose-dependent elevations of intraplatelet free calcium and increases platelet aggregation in essential hypertension.32 These lead to stimulation of the coagulation system, with increased plasma thrombin–antithrombin complex and prothrombin fragment F1+2 levels. Increased plasma concentrations of angiotensin II and endothelin, which correlate with plasma vWF, also suggests that haemostatic abnormalities may be in part due to neuroendocrine activation in heart failure.33 Furthermore, in vitro and ex vivo studies with angiotensin II receptor antagonists inhibit platelet adhesion and aggregation by nitric oxide release.34

Nitric oxide and cytokines
The actions of nitric oxide on the cardiovascular system are complex, and a detailed treatise is beyond the scope of this article. Platelet-derived nitric oxide inhibits platelet aggregation via constitutive nitric oxide synthase (eNOS). Acute inhibition of endogenous nitric oxide production in humans
causes rapid platelet activation in vivo, which is reversed by exogenous nitric oxide. Reduced vascular availability of nitric oxide is also associated with increased platelet activation, and is a risk factor for silent cerebral infarction in patients with atrial fibrillation. When platelet eNOS becomes uncoupled from its cofactor, tetrahydrobiopterin, it is associated with diminished platelet-derived nitric oxide production and increased superoxide O$_2^-$ production.

In in vivo studies, increased platelet O$_2^-$ production correlates significantly with plasma TNF-α levels; however, in heart failure patients, TNF-α dose-dependently induces platelet O$_2^-$ production and is inhibited by aspirin and NADPH (reduced nicotinamide adenose dinucleotide phosphate) oxidase inhibitors suggesting that enhanced platelet O$_2^-$ production is mediated by TNF-α via activation of arachidonic acid and NADPH oxidase pathways. There is also evidence to suggest that TNF-α may suppress eNOS and activate another isomorf of NO synthase (iNOS) in patients with CHF in proportion to the severity of heart failure, and TNF-α may contribute to the enhanced systemic and local production of nitric oxide.

Platelets can possibly induce pathology in heart failure via C-C chemokines secretion. For example, macrophage chemoattractant protein-1 (MCP-1), macrophage chemotactic protein-1 (MIP-1α), and RANTES (regulated on activation normally T-cell expressed and secreted) are potent chemoattractants of monocytes and lymphocytes that can modulate other cell functions. C-C chemokines are increased in CHF and are inversely correlated to left ventricular ejection fraction and cardiac index, and positively correlated to NYHA classification. Activated platelets stimulate MCP-1 production in monocytes through enhanced RANTES secretion and direct platelet–monocyte contact, being mediated by platelet surface P-selectin. Raised MCP-1 levels from CHF patients may have enhancing effects on spontaneous reactive oxygen species generation in monocytes, which may be involved in apoptosis of cardiomyocytes. The increased reactive oxygen radicals generation in monocytes may further enhance the synthesis of MCP-1 through an autocrine mechanism, possibly representing a vicious circle operating in CHF.

Effect of heart failure therapeutics on platelets

Diuretics

Most of the heart failure therapies have some anti-platelet properties. For example, diuretics such as hydrochlorothiazide, furosemide, spironolactone, and indapamide augment the synthesis of prostaglandins D2, E2, and I2, probably through facilitated reorientation of endoperoxide biotransformation. Apart from hydrochlorothiazide, they can also suppress thromboxane A2 production. Although spironolactone and indapamide can enhance lipoxigenase formation of hydroxyeicosatetraenoic acid, indapamide inhibits the second wave of platelet aggregation induced by adenosine diphosphate and collagen in platelet-rich plasma by 50%. In vitro, low doses of thrombin can inhibit platelet aggregation by 70%, via blocking calcium mobilization rather than by inhibiting the arachidonic acid pathway. In contrast, hydrochlorothiazide and frusemide have no significant effect on platelet aggregation (Table 2).

Beta-blockers

The antiplatelet properties of β-blocker are much less significant (Table 2). In vitro, propanolol and carvedilol

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<th>Study</th>
<th>Patient populations</th>
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<th>Findings</th>
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<tbody>
<tr>
<td>Mehta and Mehta$^{16}$</td>
<td>11 patients with CHF vs. 10 healthy controls</td>
<td>Platelet aggregates</td>
<td>↑ platelet aggregates</td>
</tr>
<tr>
<td>Jafri et al.$^{19}$</td>
<td>70 CHF vs. 41 patients with CAD but no heart failure vs. 36 healthy controls</td>
<td>PF4 β-TG D-dimers TAT</td>
<td>↑ platelet-aggregates related to vascular resistance</td>
</tr>
<tr>
<td>Sbarouni et al.$^{33}$</td>
<td>21 CHF patients</td>
<td>Plasma and blood viscosity, fibrinopeptide A, D-dimers, vWF</td>
<td>Levels of β-TG, D-dimers, and TAT but not PF4 significantly higher in CHF than controls. D-dimers levels were higher in CHF than CAD group</td>
</tr>
<tr>
<td>Yamamoto et al.$^{18}$</td>
<td>13 patients with hypertrophic cardiomyopathy vs. 17 with dilated cardiomyopathy vs. 20 healthy controls</td>
<td>PF4, β-TG, fibrinopeptide A, TAT, D-dimers, and plasmin-alpha 2-plasmin inhibitor complex</td>
<td>Fibrinopeptide A and TAT in both disease groups were significantly higher than controls and they are correlated with the left ventricular end-diastolic volume</td>
</tr>
<tr>
<td>Serebruany et al.$^{8}$</td>
<td>37 severe CHF patients vs. 14 healthy controls</td>
<td>PECAM-1 osteonectin</td>
<td>Levels of PECAM-1 and osteonectin higher in CHF patients than controls</td>
</tr>
<tr>
<td>Serebruany et al.$^{7}$</td>
<td>100 CHF patients</td>
<td>Whole blood aggregation, platelet contractile force, expression of GP IIb/IIIa and P-selectin</td>
<td>↑ whole blood aggregation, correlated with the closure time and the GP IIb/IIIa and P-selectin expression</td>
</tr>
<tr>
<td>Erne et al.$^{9}$</td>
<td>Nine patients with CHF and 50 with MI</td>
<td>MPV</td>
<td>Mean MPV significantly higher in patients with acute MI and CHF when compared with controls</td>
</tr>
</tbody>
</table>

β-TG, β-thromboglobulin; CAD, coronary artery disease; MPV, mean platelet volume; PECAM-1, platelet/endothelial cell adhesion molecule-1; P-sel, P-selectin; PF4, platelet factor 4; TAT, thrombin-antithrombin III complex; vWF, von Willebrand factor.
reduce platelet aggregation induced by epinephrine and ADP, whereas atenolol increases fibrinogen binding in response to agonists but reduces β-thromboglobulin in hypertensive subjects. In other work, β-blockers (bisoprolol or carvedilol) failed to affect vWF and P-selectin levels in patients with heart failure.

ACE-blocking agents

All ACE-blocking agents probably can inhibit platelet activation induced by angiotensin II, but there appears to be little consistency in the study findings in CHF (Table 3), possibly due to some underpowered studies with small sample sizes (e.g. n = 10), or relatively short-term treatment durations (e.g. platelet indices were measured only 12 h after treatment). It may also be possible that ACE-inhibitors have a relative indirect action on platelets via altering the levels of angiotensin, whereas angiotensin receptor antagonists directly block the platelet angiotensin receptors.

Treatment with ACE-inhibitors decreases levels of β-thromboglobulin in hypertensive patients, while lisinopril reduces soluble P-selectin levels in patients with CHF. Captorpl and fosinopril decrease thromboxane B2 concentrations, with no significant change in adenosine diphosphate, epinephrine, or thrombin-stimulated platelet aggregation when compared with baseline levels or between different ACE-inhibitors. In other studies, enalapril, fosinopril, and captopril reduce platelet aggregation in hypertensive patients. Treatment with captopril in patients with recent myocardial infarction also reduces the expression of glycoprotein IIb/IIIa receptors by 30%.

Small studies on hypertensive humans report no change in ADP-induced aggregation or platelet factor 4 by captopril, quinapril, or enalapril.

Losartan suppresses thrombin-induced calcium transients and thromboxane release in a dose-dependent manner in platelets, thus counteracting ex vivo platelet activation possibly via blockade of thromboxane A2 receptor-dependent signalling rather than acting at the AT1 receptor itself. Angiotensin-receptor blockade also reduces megakaryocyte size and ploidy bleeding time. However, these drugs do not have any significant effect on plasma soluble P-selectin, plasminogen activator-1, and vWF in hypertensive patients. Meanwhile, irbesartan has similar effects on platelet inhibition in both animals and human studies.

Further evidence from animal studies suggests that combination of ACE- and aldosterone inhibition completely abolishes platelet activation suggesting that a more complete blockade of the renin–angiotensin–aldosterone system may offer even better platelet inhibition.

Antiplatelet therapy in heart failure

The benefit of antiplatelet agents in patients at risk of ischaemic events is well recognized in the ATTC (Antithrombotic Therapy Trialists’ Collaboration) meta-analysis. In a recent analysis, Masoudi et al. showed that from a population of 24,012 patients with coronary artery disease and heart failure, aspirin remained associated with a lower risk of death or all-cause re-admission or re-admission for heart failure. However, there was no convincing evidence

Table 3 Effects of various cardiovascular drug treatments on platelet function

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<th>Diuretics</th>
<th>Study</th>
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<tr>
<td>Furosemide</td>
<td>Kribben et al.</td>
<td>Inhibit ADP, but not adrenaline-induced platelet aggregation ex vivo and in vitro</td>
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<td>Hydrochlorothiazide</td>
<td>Grose et al.</td>
<td>No effect on platelet aggregation</td>
</tr>
<tr>
<td>Indapamide</td>
<td>Rendu et al.</td>
<td>Inhibit platelet aggregation by blocking calcium mobilization</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>Schafer et al.</td>
<td>Combination of ACE-inhibitor and spironolactone completely abolished platelet activation in animal studies</td>
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<td>β-Blockers</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>Knight et al.</td>
<td>Increased fibrinogen binding in response to platelet agonists</td>
</tr>
<tr>
<td>Atenolol</td>
<td>Gleeup et al.</td>
<td>Reduce beta-thromboglobulin</td>
</tr>
<tr>
<td>Carvedilol/Propanolol</td>
<td>Gasser et al.</td>
<td>Reduce platelet aggregation induced by epinephrine and ADP</td>
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<tr>
<td>Bisoprolol/Carvedilol</td>
<td>Gibbs et al.</td>
<td>P-selectin and von Willebrand factor not affected by treatment in CHF patients</td>
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<tr>
<td>ACE-inhibitors and angiotensin receptor blockers</td>
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<tr>
<td>Captopril</td>
<td>Someya et al.</td>
<td>Reduce platelet aggregation</td>
</tr>
<tr>
<td>Captopril</td>
<td>Persson et al.</td>
<td>No change in platelet aggregation</td>
</tr>
<tr>
<td>Captopril</td>
<td>Birkebaek et al.</td>
<td>No change in platelet aggregation and PF4</td>
</tr>
<tr>
<td>Captopril Enalapril</td>
<td>Moser et al.</td>
<td>No change in platelet aggregation in all three drugs. Both fosinopril and captopril decreased T x B2 formation, whereas enalapril increased it</td>
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<tr>
<td>Fosinopril</td>
<td>Gupta et al.</td>
<td>No change in platelet aggregation and PF4</td>
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<tr>
<td>Fosinopril</td>
<td>Keidar et al.</td>
<td>Reduce platelet aggregation</td>
</tr>
<tr>
<td>Enalapril Losartan</td>
<td>Li-Saw-Hee et al.</td>
<td>No change in platelet aggregation, PF4</td>
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<tr>
<td>Losartan</td>
<td>Panthansali et al.</td>
<td>Decreased megakaryocyte size and ploidy bleeding time</td>
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<tr>
<td>Losartan Candesartan</td>
<td>Nunez et al.</td>
<td>Inhibition of platelet activation with losartan. No effect on platelet activation inhibition with candesartan and mild inhibitory effect with valsartan</td>
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<tr>
<td>Valsartan</td>
<td></td>
<td></td>
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<tr>
<td>Losartan</td>
<td>Schwemmer et al.</td>
<td>Inhibits platelet activation in healthy subjects stimulated with T x A2 analogue</td>
</tr>
<tr>
<td>Losartan</td>
<td>Li et al.</td>
<td>Reduce platelet activation in dose-dependent manner in healthy subjects’ platelets stimulated with T x A2</td>
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T x A2, thromboxane A2; T x B2, thromboxane B2.
for routine use of anti-platelet agent in CHF patients from the two recent trials, the WASH (Warfarin/Aspirin Study in Heart failure)\(^4\) and WATCH (Warfarin and Antiplatelet therapy in Chronic Heart Failure)\(^5\) trials (Table 4).

In the small, pilot WASH\(^4\) study, there was no difference in mortality between placebo, aspirin, and warfarin. Similarly, in the WATCH\(^5\) study, there was no difference in mortality between aspirin, clopidogrel, and warfarin, although this may be underpowered as the trial ended early due to poor recruitment. Meta-analysis of the two studies suggests a weak trend in favour of a lower mortality with warfarin compared with aspirin (at least on an intention to treat analysis) (odds ratio 0.91 (0.67–1.22)). Importantly, aspirin was shown to substantially increase hospitalizations for CHF in a meta-analysis of both studies [odds ratio 0.64 (0.48–0.85)].\(^6\) This again reiterates the potential mechanistic interaction between aspirin and ACE-inhibitors, and that clopidogrel may provide an alternative anti-platelet agent in CHF patients, especially in those who have recurrent decompensation and re-admissions for heart failure.

Guazzi et al.\(^6\) measured maximal exercise oxygen uptake (VO\(_{2}\)max) in patients with CHF, and demonstrated an adverse effect when ACE-inhibitors were combined with aspirin, but not with ACE-inhibitors alone. Similarly,

### Table 4 Effects of antiplatelet therapy in heart failure

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<td>WASH(^4)</td>
<td>279 CHF patients randomized to placebo, aspirin (300 mg), and warfarin (target INR 2.5)</td>
<td>No difference in the primary endpoints of death, non-fatal myocardial infarction, or non-fatal stroke between the three arms (26, 32, and 26% in patients on placebo, aspirin and warfarin, respectively). Patients on warfarin had fewer hospitalizations for heart failure than those on aspirin (48, 47, and 64% patients on placebo, aspirin, and warfarin, respectively, (P = 0.044)).</td>
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<tr>
<td>WATCH(^5)</td>
<td>1587 CHF patients randomized to aspirin (162 mg), clopidogrel (75 mg), and warfarin (target INR 2.5)</td>
<td>No significant difference in the composite endpoint of death/myocardial infarction/stroke between the three groups (20.5 vs. 21 vs. 19.8% for aspirin, clopidogrel, and warfarin, respectively). Patients on warfarin had less hospitalization (16.1 vs. 22.2 vs. 18.3%, (P = 0.01) for heart failure but significantly higher bleeding than the anti-platelet groups (5.56 vs. 3.6 vs. 2.48% with warfarin, aspirin, and clopidogrel, respectively, (P &lt; 0.01)).</td>
</tr>
<tr>
<td>Guazzi et al.(^6)</td>
<td>325 mg aspirin was given to 26 patients with dilated cardiomyopathy for 8 weeks, 18 patients (Group 1) already on enalapril 20 mg, and 8 were not (Group 2). Exercise testing was performed at baseline and at 8 weeks.</td>
<td>Group 1: Reduced carbon dioxide ((P &lt; 0.01), VO(_{2})p ((P &lt; 0.02)), tidal volume levels ((P &lt; 0.02)). Group 2: No significant change on these parameters</td>
</tr>
<tr>
<td>Kindavater et al.(^6)</td>
<td>18 patients with CHF were randomized to aspirin 325 mg or clopidogrel 75 mg for 2 weeks, and the treatments were swapped over and for another 2 weeks. Cycle ergometry was performed at weeks 2 and 4.</td>
<td>Significant increase in the mean VO(<em>{2}) max in patients on clopidogrel compared with aspirin (VO(</em>{2}) max 1200 ± 342 vs. 1114 ± 345 mL O(_2)/min, (P = 0.033))</td>
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<tr>
<td>PLUTO-CHR(^6)</td>
<td>50 CHF patients randomized to aspirin 325 mg (A, (n = 25)) and aspirin 325 mg + clopidogrel 75 mg (A+C) for 1 month</td>
<td>Group A: No changes in platelet parameters. Group C+A: ADP and epinephrine-induced platelet aggregation were inhibited ((P = 0.0001) and (P = 0.0016), respectively); differences in closure time ((P = 0.04)), expression of PECAM-1 ((P = 0.009)), GP Ib ((P = 0.006), and CD 151 ((P = 0.0026)) vs. Group A</td>
</tr>
<tr>
<td>PURSUIT(^5)</td>
<td>9419 patients with non-ST-elevation acute coronary syndrome randomized to placebo ((n = 861)) and eptifibatide treatment ((n = 8558))</td>
<td>Primary endpoint of death or non-fatal MI at 30-day CHF: Placebo 23.5%, Eptifibatide 23.5% (OR 1.11, (P = 0.51)). Without CHF: Placebo 14.8%, Eptifibatide 13.3% (OR 1.13, (P = 0.04)).</td>
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<tr>
<td>HELAS(^6)</td>
<td>197 CHF patients (ejection fraction &lt; 35%): (i) patients with ischaemic heart disease ((n = 115)) were randomized to receive either aspirin 325 mg (IHD-A) or warfarin (IHD-W); (ii) patients with dilated cardiomyopathy ((n = 82)) were randomized to receive either warfarin (DCM-W) or placebo (DCM-P)</td>
<td>The primary endpoint (non-fatal stroke, peripheral or pulmonary embolism, myocardial re-infarction, re-hospitalization, exacerbation of heart failure, or death from any cause) was 14.9 events per 100 patient years for IHD-A, 15.7 events per 100 patient years for IHD-W, 8.9 events per 100 patient years for DCM-W, and 14.8 events per 100 patient years for DCM-P patients</td>
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PECAM-1, Platelet/Endothelial Cell Adhesion Molecule-1; PLUTO-CHR, Plavix Use for Treatment Of Congestive Heart Failure; PURSUIT, Platelet lib/Illa in Unstable Angina: Receptor Suppression Using Integrilin Therapy; OR, odds ratio; VO\(_{2}\)p, peak exercise oxygen uptake; WASH, Warfarin/Aspirin Study in Heart failure; WATCH, Warfarin and Antiplatelet Therapy in Chronic Heart Failure; HELAS, Heart failure Long-term Antithrombotic Study.
Kindsvater et al.\textsuperscript{65} also showed that VO\textsubscript{2} max in patients with CHF who receive clopidogrel in conjunction with an ACE-inhibitor was greater than that with aspirin combined with an ACE-inhibitor.

In the PLUTO-CHF (Plavix Use for Treatment Of Congestive Heart Failure) trial,\textsuperscript{66} patients receiving both aspirin and clopidogrel had significantly greater inhibition of platelet activity than those who received aspirin alone. Although earlier studies of patients with non-ST-elevation myocardial infarction and unstable angina reported benefits from glycoprotein IIb/IIIa inhibitor use, a retrospective analysis of the PURSUIT (Platelet IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) trial\textsuperscript{67} showed no incremental benefit from the use of eptifibatide compared with standard treatment in patients with non-ST-segment elevation acute coronary syndrome and CHF.

The recent HELAS (Heart failure Long-term Antithrombotic Study) trial\textsuperscript{68} was probably too small and underpowered for any conclusions on antithrombotic therapy benefits in heart failure. Embolic events were relatively rare (2.2 events per 100 patient years) compared with death or hospitalization for heart failure, and only five strokes were recorded, with no peripheral or pulmonary thromboembolism and two myocardial infarction events. There were 9.6 deaths per 100 patient years for the entire population, predominantly due to worsening heart failure. Thus, the precise role for antiplatelet agents in heart failure management strategies is yet to be determined.

In the updated Cochrane systematic review of trials of antiplatelet agents vs. control or anticoagulation for heart failure in sinus rhythm\textsuperscript{69} found no evidence from long-term randomized trials to recommend routine use of aspirin to prevent thromboembolism in patients with heart failure in sinus rhythm, and a possible interaction with ACE-inhibitors by aspirin may reduce its efficacy. When compared with aspirin, there was some evidence to indicate superior effects from oral anticoagulation in relation to hospitalizations, among patients with heart failure in sinus rhythm. The corresponding updated Cochrane systematic review on anticoagulation for heart failure in sinus rhythm\textsuperscript{70} found a reduction in mortality and cardiovascular events with anti-coagulants compared with control, but concluded that this evidence needed to be interpreted with caution.

Conclusion

Although platelets are well recognized to play a role in the thrombosis-related complications in CHF, it is not clear whether they are the main mechanism for the increased thromboembolism or they merely coexist as bystander, being related to the associated vascular disease. Perhaps studies of idiopathic cardiomyopathy without any concomitant vascular risk factor, perhaps with suitable 'disease control' groups may provide additional insights into the significance of platelet activation in heart failure. The possible confounding effects on platelet function assessments by drugs commonly used in heart failure patients (e.g. ACE-inhibitors, beta-blockers, statins etc.) may make long-term prospective studies difficult to conduct in treatment naïve patients.

Indeed, the significance of current therapeutic heart failure treatments in reducing stroke and thromboembolic complications in CHF is under debate. For example, there is no randomized trial evidence to support the routine use of antiplatelet agents in all systolic heart failure patients. Some data even suggest that aspirin may potentially attenuate the beneficial effects of ACE-inhibitors and therefore, alternative antithrombotic agents in CHF may be warranted.

A greater appreciation of the underlying platelet pathophysiology in CHF would inform our development of new therapeutic agents and aid our management strategies in this common and growing clinical problem.

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References


Clinical vignette
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Intracoronary thrombus in a 26-year-old man

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A 26-year-old smoker with no other cardiovascular risk factor presented with acute anterior ST-segment elevation myocardial infarction. He had smoked cannabis one day prior to admission. Coronary angiography showed no evidence of coronary atherosclerosis but a large coronary thrombus in the proximal and mid portion of left anterior descending coronary artery (LAD), partially obstructing flow (Panel A). Multiple attempts of thrombus aspiration using an aspiration catheter (Export, Medtronic, Minneapolis, MN, USA) were unsuccessful. Despite intracoronary administration of 20 mg of r-tPA over 15 min, standard dose of intravenous unfractionated heparin and abciximab, as well as 300 mg clopidogrel loading dose on top of aspirin, angiography performed 12 h later confirmed persistent LAD filling defect (Panel B). Thrombus removal with an aspiration catheter was again ineffective. Direct thrombus extraction was performed by introducing a filter protection device (SpiderRX 4 mm, ev3, Plymouth, MN, USA) into the mid-LAD beyond the thrombus (Panel C). The open device was then gently pulled back so that the thrombus could be entirely trapped within the filter and then removed using a retrieval sheath. Final angiogram showed complete thrombus removal and no evidence of distal embolization (Panel D). The filter contained a large thrombus (Panels E and F). Toxicological screening for amphetamines and cocaine as well as thrombophilia work-up were negative.