Is There a Rationale for Antiplatelet Therapy in Acute Heart Failure?

Robert J. Mentz, MD; Valentina Lazzarini, MD; Mona Fiuzat, PharmD; Marco Metra, MD; Christopher M. O’Connor, MD; G. Michael Felker, MD, MHS

Current therapies for acute heart failure (AHF) mainly focus on the restoration of hemodynamic stability and fluid balance. Recent decades of therapeutic investigations in AHF have generally failed to improve patient outcomes. These data are in contrast to the ongoing improvements in survival in patients with chronic HF. This disconnect may be in part because of the better understanding of the pathophysiology of chronic HF, allowing for the development of targeted therapeutic strategies. Conversely, the specific mechanisms leading to the development of AHF and the associated adverse outcomes remain unclear. Hence, there is an ongoing need to identify and test novel therapeutic targets in AHF.

HF is associated with activation of the renin–angiotensin–aldosterone system, sympathetic nervous system, and mechanisms of inflammation and oxidative stress. Each of these pathways may directly influence the chronic progression of cardiac dysfunction and acute decompensation. In addition, these mediators may contribute indirectly through the activation of other pathophysiologic mechanisms, which have not been fully elucidated. One such potential mechanism is platelet activation. The activation of neurohormonal, inflammatory, and thrombotic pathways is known to be associated with enhanced platelet reactivity in AHF. However, whether increased platelet activity is simply a marker of this systemic imbalance or an actual contributor to acute decompensation is incompletely understood. Several pathophysiologic mechanisms that may explain a possible detrimental role of platelet activation on the myocardium have been described. Myocardial injury, as manifest clinically by elevations of cardiac troponin, may represent a connection between platelet activation and poor prognosis. If a causal role for platelet activation can be confirmed in the AHF setting, specific antiplatelet therapies might improve prognosis in this high-risk population. In this article, we summarize the data supporting the hypothesis of a beneficial effect of antiplatelet therapy in AHF. We focus on the pathophysiologic mechanisms of platelet activation possibly related to HF, present the relevant studies investigating antiplatelet therapy in HF, and highlight the unanswered questions and need for future study.

Evidence of Platelet Activation in HF

Platelet reactivity can be assessed by a variety of methods, including evaluation of aggregation capacity and levels of circulating factors expressed at the time of platelet activation. The optimal method to quantify the physiological and pathologic function of platelets has not been established. If HF patients, several markers have been investigated. Mean platelet volume is routinely measured by automated cell counters and is associated with thrombotic potential. Other markers include molecules that mediate platelet activation and interaction with other cells. On platelet activation, these molecules may be exposed on the platelet surface (eg, platelet/endothelial cell adhesion molecule-1, osteonectin), secreted in a soluble form (eg, β-thromboglobulin) or both (eg, P-selectin, CD-40 ligand). Soluble markers are more easily measured than platelet-bound markers, but the association between these markers is unclear. Routine use of these markers is not well established because of several limitations. First, most markers lack specificity as they are expressed not only by platelets but also by leukocytes or endothelial cells. Moreover, specimens are prone to collection and processing artifacts. Finally, the lack of standardized methods for analysis may limit reproducibility.

These limitations may explain, in part, why investigations exploring platelet activation in HF have yielded conflicting results. Studies investigating platelet markers in HF have been relatively small in size and heterogeneous with respect to design, marker assessment, and measurement techniques (Table 1). In these studies, a certain degree of baseline platelet activation seems to be present in patients with HF. Subjects with HF exhibit greater variability in these biomarkers compared with consistently low levels in healthy controls. Another consistent finding is that markers of platelet activation are elevated regardless of HF pathogenesis and previous treatment with aspirin. Of note, patients with HF have similar levels of platelet markers compared with patients with coronary disease without HF. The severity of HF and comorbid disease may be associated with the degree of platelet activation in HF.

The difference between the levels of platelet activation biomarkers in acute versus chronic HF is less clear. In general, survival in patients with chronic HF. This disconnect may be in part because of the better understanding of the pathophysiology of chronic HF, allowing for the development of targeted therapeutic strategies. Conversely, the specific mechanisms leading to the development of AHF and the associated adverse outcomes remain unclear. Hence, there is an ongoing need to identify and test novel therapeutic targets in AHF.

HF is associated with activation of the renin–angiotensin–aldosterone system, sympathetic nervous system, and mechanisms of inflammation and oxidative stress. Each of these pathways may directly influence the chronic progression of cardiac dysfunction and acute decompensation. In addition, these mediators may contribute indirectly through the activation of other pathophysiologic mechanisms, which have not been fully elucidated. One such potential mechanism is platelet activation. The activation of neurohormonal, inflammatory, and thrombotic pathways is known to be associated with enhanced platelet reactivity in AHF. However, whether increased platelet activity is simply a marker of this systemic imbalance or an actual contributor to acute decompensation is incompletely understood. Several pathophysiologic mechanisms that may explain a possible detrimental role of platelet activation on the myocardium have been described. Myocardial injury, as manifest clinically by elevations of cardiac troponin, may represent a connection between platelet activation and poor prognosis. If a causal role for platelet activation can be confirmed in the AHF setting, specific antiplatelet therapies might improve prognosis in this high-risk population. In this article, we summarize the data supporting the hypothesis of a beneficial effect of antiplatelet therapy in AHF. We focus on the pathophysiologic mechanisms of platelet activation possibly related to HF, present the relevant studies investigating antiplatelet therapy in HF, and highlight the unanswered questions and need for future study.

Evidence of Platelet Activation in HF

Platelet reactivity can be assessed by a variety of methods, including evaluation of aggregation capacity and levels of circulating factors expressed at the time of platelet activation. The optimal method to quantify the physiological and pathologic function of platelets has not been established. If HF patients, several markers have been investigated. Mean platelet volume is routinely measured by automated cell counters and is associated with thrombotic potential. Other markers include molecules that mediate platelet activation and interaction with other cells. On platelet activation, these molecules may be exposed on the platelet surface (eg, platelet/endothelial cell adhesion molecule-1, osteonectin), secreted in a soluble form (eg, β-thromboglobulin) or both (eg, P-selectin, CD-40 ligand). Soluble markers are more easily measured than platelet-bound markers, but the association between these markers is unclear. Routine use of these markers is not well established because of several limitations. First, most markers lack specificity as they are expressed not only by platelets but also by leukocytes or endothelial cells. Moreover, specimens are prone to collection and processing artifacts. Finally, the lack of standardized methods for analysis may limit reproducibility.

These limitations may explain, in part, why investigations exploring platelet activation in HF have yielded conflicting results. Studies investigating platelet markers in HF have been relatively small in size and heterogeneous with respect to design, marker assessment, and measurement techniques. In these studies, a certain degree of baseline platelet activation seems to be present in patients with HF. Subjects with HF exhibit greater variability in these biomarkers compared with consistently low levels in healthy controls. Another consistent finding is that markers of platelet activation are elevated regardless of HF pathogenesis and previous treatment with aspirin. Of note, patients with HF have similar levels of platelet markers compared with patients with coronary disease without HF. The severity of HF and comorbid disease may be associated with the degree of platelet activation in HF.

The difference between the levels of platelet activation biomarkers in acute versus chronic HF is less clear. In general,
markers of platelet activation are reduced with AHF therapies and further reductions occur during follow-up. These data support the hypothesis of a direct association between platelet activation and AHF decompensation. In contrast, conflicting data have been observed with regard to the association of platelet biomarkers with prognosis. Notably, the small size of these previous studies underscores the need for ongoing exploration of the biology of platelet activation in HF.

<table>
<thead>
<tr>
<th>Marker</th>
<th>Study</th>
<th>Group Comparison</th>
<th>Results</th>
<th>Association With Prognosis</th>
<th>Independent From Pathogenesis</th>
<th>Association With Severity</th>
<th>Effect of Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean platelet volume</td>
<td>Chung et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Acute vs chronic HF and healthy controls</td>
<td>Chronic HF&gt;healthy controls; no significant difference for acute HF</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Kandis et al&lt;sup&gt;10&lt;/sup&gt;</td>
<td>Acute vs chronic HF</td>
<td>Acute&gt;chronic HF</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Chung et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Chronic HF vs disease and healthy controls</td>
<td>Disease&gt;healthy controls, chronic HF=disease controls</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>n/a</td>
</tr>
<tr>
<td>P-selectin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P- and s-form</td>
<td>O’Connor et al&lt;sup&gt;13&lt;/sup&gt;</td>
<td>Acute HF vs healthy controls</td>
<td>Acute HF&gt;healthy controls</td>
<td>n/a</td>
<td>n/a</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Chung et al&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Chronic HF vs disease and healthy controls</td>
<td>Chronic HF&gt;healthy controls; no difference with disease controls</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Chung et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Acute vs chronic HF and healthy controls</td>
<td>Acute HF&gt;chronic HF&gt;healthy controls; decrease at follow-up for acute HF and no differences between groups for s-form</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>P-form</td>
<td>Gurbel et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Chronic HF vs healthy controls</td>
<td>Chronic HF&gt;healthy controls</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Stumpf et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Chronic or acute HF vs healthy controls, ischemic HF vs disease controls</td>
<td>HF&gt;healthy controls, ischemic HF&gt;disease controls</td>
<td>n/a</td>
<td>Yes</td>
<td>NYHA</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Milo et al&lt;sup&gt;12&lt;/sup&gt;</td>
<td>Acute vs chronic HF</td>
<td>Acute&gt;chronic HF; decrease at follow-up for acute HF</td>
<td>No</td>
<td>Yes</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>S-form</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Yin et al&lt;sup&gt;28&lt;/sup&gt;</td>
<td>Chronic HF vs healthy controls</td>
<td>Chronic HF&gt;healthy controls</td>
<td>Yes</td>
<td>n/a</td>
<td>NYHA, EF</td>
<td>n/a</td>
</tr>
<tr>
<td>CD-40 ligand</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P- and s-form</td>
<td>Stumpf et al&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Chronic or acute HF vs healthy controls, ischemic HF vs disease controls</td>
<td>HF&gt;healthy controls, (p-form); no differences for s-form</td>
<td>n/a</td>
<td>Yes</td>
<td>NYHA (p-form)</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Chung et al&lt;sup&gt;23&lt;/sup&gt;</td>
<td>Chronic HF vs disease and healthy controls</td>
<td>Chronic HF&lt;disease controls (total); no differences for p- and s-form</td>
<td>No</td>
<td>Borderline</td>
<td>P-form in LVEF&gt;35%</td>
<td>n/a</td>
</tr>
<tr>
<td>S-form</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ueland et al&lt;sup&gt;14&lt;/sup&gt;</td>
<td>Acute HF following MI vs chronic HF and healthy controls</td>
<td>Acute HF&gt;healthy controls, chronic HF&gt;healthy controls</td>
<td>Trend; n/a</td>
<td>n/a</td>
<td>Yes; NYHA; NYHA, EF</td>
<td>n/a</td>
</tr>
<tr>
<td>P-form</td>
<td>Chung et al&lt;sup&gt;11&lt;/sup&gt;</td>
<td>Acute HF vs chronic HF and healthy controls</td>
<td>No differences between groups; decrease at follow-up for acute HF</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
<td>n/a</td>
</tr>
<tr>
<td>PECAM–1</td>
<td>Serebruany et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Chronic HF vs healthy controls</td>
<td>Chronic HF&gt;healthy controls</td>
<td>n/a</td>
<td>Yes</td>
<td>n/a</td>
<td>No</td>
</tr>
<tr>
<td>Osteonectin</td>
<td>Serebruany et al&lt;sup&gt;25&lt;/sup&gt;</td>
<td>Chronic HF vs healthy controls</td>
<td>Chronic HF&gt;healthy controls</td>
<td>n/a</td>
<td>Yes</td>
<td>n/a</td>
<td>No</td>
</tr>
<tr>
<td>Thromboglobulin</td>
<td>Jafri et al&lt;sup&gt;29&lt;/sup&gt;</td>
<td>Chronic HF vs disease and healthy controls</td>
<td>Chronic HF&gt;healthy controls; chronic HF=disease controls</td>
<td>n/a</td>
<td>Yes</td>
<td>EF, NE levels</td>
<td>n/a</td>
</tr>
</tbody>
</table>

EF indicates ejection fraction; HF, heart failure; n/a, not assessed; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NE, norepinephrine; NYHA, New York Heart Association; PECAM, platelet/endothelial cell adhesion molecule; p-form, platelet-bound form; and s-form, soluble form.
Pathophysiology of Platelet Activation

Several mechanisms that are activated in chronic HF and further enhanced during acute decompensation may promote a prothrombotic state and may explain, in part, the observed increased platelet reactivity. Endothelial damage and dysfunction along with imbalances in nitric oxide production and increased expression of adhesion molecules may lead to enhanced platelet adhesion and activation. In addition, increased levels of angiotensin II and circulating catecholamines, oxidative stress, and inflammation contribute to the increased activity of platelets and the coagulation cascade. Although these mechanisms can lead to platelet activation, the extent to which this activation may play a direct role in the pathophysiology of AHF remains unclear.

One mechanism that may link platelet activation and adverse outcomes in AHF is myocardial injury. Myocardial injury, as shown by elevations in circulating cardiac troponin, occurs in the context of AHF even in the absence of overt ischemia. The reported prevalence of elevated troponin varies widely across studies, depending on the specific population, assay, and threshold used. Increased troponin levels on admission for AHF are associated with higher rates of in-hospital mortality, and postdischarge morbidity and mortality. The predictive value of increased troponin levels seems to be independent and additive to that of other biomarkers, such as natriuretic peptides. Therefore, mechanisms other than myocardial strain because of left ventricular volume overload seem to be involved in myocardial damage during AHF. However, the causes of troponin release during AHF are likely multifactorial and not completely understood.

The potential role of platelet activation as a link between HF decompensation and troponin elevation requires further investigation. Support for the association between increased troponin levels and platelet activation may be extrapolated from studies in ischemic heart disease. The degree of platelet activation has been associated with troponin levels in small studies of patients with non-ST-elevation acute coronary syndromes, as well as revascularization studies. Possible pathways through which platelet activation may contribute to the myocardial damage observed in AHF include vasoconstriction and the deposition of platelet aggregates, subsequently leading to microvascular damage and ischemia. In fact, the platelet response to agonists, such as ADP, involves not only platelet aggregation but also secretion of several vasoactive agents, such as serotonin and thromboxane A2. Animal models have demonstrated that these substances cause vasoconstriction and further promote platelet aggregation.

Role of Coagulation and Hemostasis

Although distinct from the pathophysiology of platelet activation in AHF, the coagulation cascade is relevant to the discussion of hemolytic perturbations during HF hospitalizations. AHF may increase the risk for thrombotic complications through each of the mechanisms of Virchow’s triad, including abnormalities in the vessel walls, blood flow, and blood constituents as recently reviewed. In contrast to the low risk for venous thromboembolism (VTE) in chronic HF patients, patients with severe medical illnesses, including AHF, are at high risk for VTE. Notably, the risk associated with HF seems to be highest in the early period after HF diagnosis with attenuation over time.

Despite the thrombotic risk associated with HF, multiple trials investigating the use of anticoagulation in chronic HF patients in sinus rhythm as well as extended VTE prophylaxis after hospitalization in medically ill cohorts (including those with AHF), have demonstrated marginal to no net clinical benefit. Thus, consensus documents have recommended against the broad use of anticoagulation in these patients and have reserved use for select patients based on the individualized risk–benefit ratio. In fact, the recent 2012 American College of Chest Physicians guidelines for hospitalized medical patients differ significantly from those of 2008, which recommended anticoagulant prophylaxis on the basis of HF alone, and now indicate that increased-risk and low-risk patients should be distinguished using a risk assessment tool with administration of anticoagulant restricted to those at increased risk. Thus, many HF patients that would have been recommended to receive anticoagulation by the 2008 guidelines no longer qualify by the most recent guidelines unless they have high risk features, such as active cancer, previous VTE, reduced mobility, and advanced age. The potential for significantly reduced mobility early during AHF hospitalization and the advanced age of the HF population represent several key characteristics that place this group at increased risk for VTE and highlight the need for further prospective study to increase the evidence base for these recommendations.

An ongoing trial on the basis of lessons learned from these earlier studies is investigating the use of a novel oral anticoagulant, betrixaban, in the subgroup of hospitalized patients at highest risk for VTE (eg, cardiac or respiratory failure with advanced age and severe immobility; ClinicalTrials.gov identifier: NCT01583218). This study may help answer whether there is a potential role for anticoagulation in addition to (or in place of) antiplatelet therapy during AHF.

Evidence for Efficacy of Antiplatelet Therapy

Limited data are available with regard to the use of antiplatelet therapy in patients with HF in sinus rhythm (Table 2). Therefore, whether antiplatelet therapy may be a useful strategy to improve prognosis in patients with AHF remains largely unexplored. Aspirin and clopidogrel are the most commonly investigated and used antiplatelet drugs. Aspirin’s mechanism of action involves the irreversible acetylation of the enzyme cyclooxygenase, which inhibits the production of thromboxane A2 and prostaglandin in platelets, and prostaglandin I2 in vascular cells. In platelets, cyclooxygenase inhibition leads to a reduction in aggregation, whereas in the vessels this causes a decrease in vasodilating properties. Concern has been raised with regard to the vascular effect of prostaglandin synthesis blockade that may be detrimental in patients with HF, by diminishing vasodilating properties of glomerular afferent arterioles, and leading to worsened kidney function and sodium retention. Evidence of an association between increased HF hospitalization and aspirin use in chronic HF patients was seen in the Warfarin–Aspirin Study in HF (WASH) and Warfarin and Antiplatelet Therapy
in Chronic Heart Failure (WATCH) trials,40,41 but the contemporary Warfarin–Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial did not support this association.42 As the largest trial of antithrombotic therapy in HF patients in sinus rhythm with rigorous methodology involving a double-blind, double-dummy study design, the lack of association between aspirin and HF hospitalizations in WARCEF should reduce concerns related to potential adverse effects of antiplatelet therapy on worsening HF.

Another matter of concern has been a possible adverse interaction of aspirin with angiotensin-converting enzyme (ACE) inhibitors,59 which was initially supported by post hoc analyses of large ACE-inhibitor trials.51,52 The hypothesized mechanism for worse outcomes involves aspirin's effects at the prostaglandin level with attenuation of ACE-inhibitor–mediated bradykinin benefits related to systemic arterial vasodilation and cardiac remodeling.53 However, these associations have generally been refuted by more recent studies.54–56 For instance, in the OPTIMIZE-HF (Organized Program to Initiate Lifesaving Treatment in Hospitalized Patients with Heart Failure) registry, aspirin use in combination with either an ACE inhibitor or an angiotensin receptor blocker was not associated with adverse events post discharge for AHF in patients with ischemic or nonischemic HF.56 Thus, contemporary studies derived from registry data and population-based cohorts57 have refuted earlier concerns related to a potential aspirin and ACE-inhibitor interaction that was seen in early clinical trials with strict entry criteria.

Uncertainties on aspirin use in HF patients and the availability of alternative methods to inhibit platelet aggregation led to the investigation of clopidogrel use in HF. Clopidogrel is a thienopyridine, which can irreversibly inhibit platelet P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet sur-
face receptors58 without effects on prostaglandin inhibition. AADP-dependent activation, blocking the platelet ADP receptor P2Y12. Clopidogrel decreases the expression of platelet su

### Table 2. Intervention Trials on Antiplatelet Therapy in Patients With Heart Failure and Reduced Ejection Fraction

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Design</th>
<th>Primary End Point</th>
<th>Size</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLUTO-CHF* (2003)</td>
<td>Randomized, single-blind trial on patients increased, platelet reactivity, comparing clopidogrel-aspirin and aspirin alone</td>
<td>Decrease in markers of platelet activation</td>
<td>50</td>
<td>Combined treatment significantly decreased platelet reactivity compared with aspirin alone</td>
</tr>
<tr>
<td>WASH (2004)</td>
<td>Randomized, open-label trial comparing no antithrombotic therapy, aspirin, and warfarin</td>
<td>Death, nonfatal MI, or nonfatal stroke</td>
<td>279</td>
<td>Underpowered because of slow enrollment. No significant difference for primary end point. All-cause and HF hospitalization higher in patients with aspirin</td>
</tr>
<tr>
<td>HELAS (2006)</td>
<td>Randomized double-blind trial. Patients with ischemic HF randomized to aspirin or warfarin. Patients with idiopathic dilated cardiomyopathy randomized to either warfarin or placebo</td>
<td>Any of nonfatal stroke, peripheral or pulmonary embolism, MI, rehospitalization, HF, or all-cause death</td>
<td>197</td>
<td>Underpowered study because of slow enrollment. No significant differences among groups</td>
</tr>
<tr>
<td>WATCH (2009)</td>
<td>Randomized trial comparing open-label warfarin and double-blind treatment with either aspirin or clopidogrel</td>
<td>Time to first event in a composite end point of death, nonfatal MI, or nonfatal stroke</td>
<td>1587</td>
<td>Underpowered because of slow enrollment. No significant differences for primary composite end point among the 3 groups. No difference in end points between aspirin and clopidogrel. Hospitalization for worsening HF more frequent in patients treated with aspirin vs warfarin. Lower risk of stroke and higher risk of hemorrhage in warfarin patients</td>
</tr>
<tr>
<td>WARCEF (2012)</td>
<td>Randomized, double-blind trial comparing aspirin or warfarin</td>
<td>Time to the first event in a composite end point of ischemic stroke, intracerebral hemorrhage, or all-cause death</td>
<td>2305</td>
<td>Underpowered because of slow enrollment. No difference in the rate of main composite end point. The hazard ratio changed over time, slightly favoring warfarin over aspirin by the fourth year of follow-up. Lower risk for ischemic stroke and higher risk of hemorrhage for warfarin. No evidence of higher HF hospitalization with aspirin</td>
</tr>
</tbody>
</table>

*Study included both reduced and preserved ejection fraction.

HELAS indicates Heart Failure Long-term Antithrombotic Study; HF, heart failure; MI, myocardial infarction; PLUTO-CHF, Plavix Use for Treatment of Congestive Heart Failure; WARCEF, Warfarin–Aspirin in Reduced Cardiac Ejection Fraction; WASH, Warfarin–Aspirin Study in Heart Failure; and WATCH, Warfarin and Antiplatelet Therapy in Chronic Heart Failure.
by the presence or absence of HF and treatment with clopidogrel. The survival of patients without HF was comparable between patients with or without clopidogrel, whereas a significant survival benefit of clopidogrel was observed in the patients with HF (Figure 1). Another, smaller study of patients hospitalized for AHF showed lower mortality rates in patients taking clopidogrel, or aspirin plus clopidogrel versus a control group not receiving antiplatelet therapy. Aspirin use alone was not associated with a difference in outcome. These findings support the hypothesis that platelet activation may play a key role in the poor prognosis of HF patients and suggest a possible therapeutic benefit with clopidogrel.

![Figure 1](image1.png)

**Figure 1.** Survival in patients with first-time myocardial infarction (MI), subdivided according to the presence or absence of heart failure (HF) and treatment with clopidogrel. Reprinted from Bonde et al, with permission from Elsevier.

![Figure 2](image2.png)

**Figure 2.** A framework for the relationship between acute heart failure, platelet activation, myocardial injury, and poor outcome. NO indicates nitric oxide; RAAS, renin-angiotensin-aldosterone system; and SNS, sympathetic nervous system.
The potential benefits of the more recently developed antiplatelet agents (prasugrel, ticagrelor) have not yet been tested in HF patients.

**Gaps and Future Directions**

Platelet activation is a largely unexplored potential therapeutic target for AHF. Figure 2 shows a possible framework for linking platelet activation, myocardial injury, and poor outcomes and offers potential areas that could be addressed by appropriately designed studies. A substantial challenge is the lack of a standardized, effective measurement of platelet activity. Second, further exploration is required to determine the degree of platelet activation that is present in AHF patients. The specificity of enhanced platelet activity for AHF patients as compared with stable chronic HF and other controls is unclear. The extent to which platelet activity may be related to myocardial damage and prognosis also requires further study. These issues are still unresolved mainly because of the lack of adequately powered, targeted studies. Large prospective observational studies of AHF patients, assessing the association among different platelet activity markers, natriuretic peptides, markers of myocardial damage, and prognosis could provide a significant first step in understanding the potential therapeutic benefit of antiplatelet agents in these patients. Stable chronic HF patients could serve as a control group. Such a study may also allow the identification of the most useful platelet markers, and higher risk patients’ subgroups to target in future intervention studies.

If the association among platelet activity, myocardial damage, and poor prognosis in AHF is confirmed, subsequent studies will need to clarify the impact of antiplatelet therapy on outcomes. The observational studies to date demonstrate the need for further empirical testing given the difficulties in adjustment for bias in nonrandomized populations. Previous prospective, randomized trials of antiplatelet therapies did not investigate the AHF population or directly compare antiplatelet therapies. A randomized controlled study may answer simpler solutions to complex problems. Consensus document arising from a European Society of Cardiology cardiovascular round-table think tank on acute heart failure, 12 May 2009. *Eur Heart J*. 2009;30:1101–1107.

**Conclusions**

Platelet activation may represent an unaddressed target of AHF therapy. There is evidence suggesting that platelet activation is present in the setting of AHF, which may contribute to the myocardial damage and may be related to patients’ poor outcome. Therefore, antiplatelet therapy may be beneficial if initiated in patients during an episode of AHF. However, current evidence is insufficient to support or refute the hypothesis of a direct role of platelet activation in the pathophysiology of AHF or a possible role for antiplatelet therapies. Overall, the studies performed to date have underlined the need for pursuing antiplatelet research in HF with adequately designed trials.

**Disclosures**

None.

**References**

1. Felker GM, Mentz RJ. Diuretics and ultrafiltration in acute decompen-
7. Michibayashi T. Platelet aggregation and vasocostriction related to plate-
8. Badimon L, Martínez-González J, Royo T, Lassila R, Badimon JI. A sud-
   tion in cardiogenic pulmonary edema secondary to ischemic versus non-
13. O’Connor CM, Gurbel PA, Serebruany VL. Usefulness of soluble and surface-
15. Golino P, Ashton JH, Buja LM, Rosolowsky M, Taylor AL, McNatt J, Campbell WB, Willerson JT. Local platelet activation causes vasoconstric-
19. Sharma G, Berger JS. Platelet activity and cardiovascular risk in appar-
20. Gurney D, Lip GY, Blann AD. A reliable plasma marker of platelet activa-


Key Words: acute heart failure ■ antiplatelet therapy ■ platelet activation
Is There a Rationale for Antiplatelet Therapy in Acute Heart Failure?
Robert J. Mentz, Valentina Lazzarini, Mona Fiuzat, Marco Metra, Christopher M. O'Connor and G. Michael Felker

Circ Heart Fail. 2013;6:869-876
doi: 10.1161/CIRCHEARTFAILURE.112.000381

Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circheartfailure.ahajournals.org/content/6/4/869

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Heart Failure can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Heart Failure is online at:
http://circheartfailure.ahajournals.org//subscriptions/