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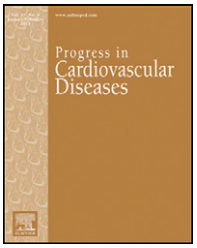

Preventing Thrombosis to Improve Outcomes in Heart Failure Patients

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ABSTRACT

Heart failure (HF) is associated with an increased risk of thrombotic events, particularly if this condition is accompanied by atrial fibrillation (AF). Many HF patients have background coronary artery disease (CAD) making them prone to coronary thrombosis resulting in myocardial infarction or sudden death. Oral anticoagulation is essential in the vast majority of HF patients with AF with non-vitamin K based anticoagulants being a suitable alternative to warfarin. In contrast, aspirin alone does not provide adequate stroke prevention in such patients. In HF without AF, oral anticoagulation should not be routinely used, and antiplatelet agents should be prescribed in patients with background CAD. This review provides an overview of prothrombotic factors and antithrombotic management of patients with HF.

Heart failure (HF) has been associated with increased risk of thrombotic events that affected a third of HF patients.[1] Poor mobility and multiple co-morbidities predispose to occurrence of venous thromboembolism (VTE).[2,3] The risks are particularly high in patients with acute HF decompensation who require hospital admission with VTE reported in up to half of such patients, unless VTE prophylaxis is given.[2,3] Many HF patients have background coronary artery disease (CAD) making them prone to coronary thrombosis resulting in myocardial infarction or sudden cardiac death (SCD).[4] Patients with HF are also at increased risk of ischemic stroke, which has been reported to occur in 2% of such patients within the first year of presentation.[5] In fact, about 20% of patients with ischemic stroke have impaired left ventricular (LV) systolic function.[6]

The risk of stroke and systemic VTE is especially high in patients with concomitant atrial fibrillation (AF), which is extremely common in subjects with HF irrespectively of LV ejection fraction (LVEF). Literature suggests that up to 40% of HF patients may experience the arrhythmia.[7,8] In patients with HF and preserved LVEF, AF was associated with approximately 3-fold higher risk of ischemic stroke compared to those with no history of the arrhythmia.[9] In patients with HF with reduced LVEF (HFrEF),the presence of AF carries a 2-fold increased risk of ischemic stroke and systemic VTE compared to those in normal sinus rhythm (NSR).[10] All major clinical guidelines on management of AF recognize HF as a major risk factor for stroke.[11,12]

Moreover, the true rate of AF can be underestimated due to possibility of 'silent' AF. A retrospective analysis of multicentre trials of cardiac resynchronization therapy in HF demonstrated the presence of AF episodes in a third of patients and it was frequently 'silent'.[13] The study also showed that even short (e.g., 10 min) paroxysms of 'silent' AF might have significant clinical consequences, being associated with 2-fold increased risk of deaths or hospital admission for HF.

The prothrombotic state in heart failure

Congestive HF and AF share a number of common pathophysiological processes producing a multifactorial prothrombotic milieu.

Statement of Conflict of Interest see page 390.

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Abbreviations and Acronyms

AF = atrial fibrillation

CAD = coronary artery disease

HF = heart failure

HFrEF = heart failure with reduced ejection fraction

LA = left atrium or atrial

LAA = left atrial appendage

LV = left ventricle or ventricular

LVEF = left ventricular ejection fraction

NSR = normal sinus rhythm

NYHA = New York Heart Association

NVAF = non-valvular atrial fibrillation

SCD = sudden cardiac death

VTE = venous thromboembolism

First, both HF and AF are characterized by impaired cardiac and/or systemic hemodynamics predisposing to blood stasis. In AF atrial stasis is caused by lack of synchronous contractility of atrial cardiomyocytes, resulting in absence of efficient atrial systole. The stasis is most prominent within the left atrial (LA) appendage (LAA), which has no 'through flow' and where the blood flow ultimately depends on efficient synchronous contraction of the appendage cardiomyocytes. It is not surprising that the LAA is the most frequent site of thrombus formation in AF[14]; LA dilation has been shown to be independently associated with increased risk for stroke even after adjustment for other recognized stroke risk factors.[15,16] The right atrial appendage is less prone to thrombus generation as it is smaller and shallower than its left sided counterpart. Intracardiac blood stasis in AF is reflected by increased levels of brain natriuretic peptides despite preserved LVcontractility.[17]

Blood stasis in AF is not solely restricted to the atria and AF does contribute to systemic stasis as absence of atrial systole disturbs LV diastolic filling and cardiac stroke volume. The impact is even more prominent when it occurs in the presence of other conditions predisposing to local or systemic blood stasis.

Flow congestion in HF is clearly noticeable within the failing LV especially if patients have severe regional wall motion abnormalities in the apical area (e.g., in post myocardial infarction aneurism). Severe deterioration in systolic LV function leads to peripheral congestion and severe blood stasis.

In fact, HF frequently co-exists with AF, with 13% to 40% of HF patients having AF irrespectively of LVEF.[7,8] Atrial fibrillation potentiates intracardiac and extracardiac blood stasis in patients with HF, thus predisposing to stroke and systemic VTE. Occurrence of AF in HF further deteriorates already impaired systemic perfusion as effective atrial contraction in sinus rhythm contributes up to 25% of the cardiac output.[18,19]

Second, patients with HF have prominent endothelial dysfunction, irrespectively of HF aetiology.[20] The presence of endothelial dysfunction in HF bears increased mortality and risk of hospital re-admissions. Endothelial dysfunction parallels and predisposes to chronic proinflammatory state and increased oxidative stress, which promotes thrombogenesis.[21,22] Presence of congestive HF further augments endothelial dysfunction already evident in HF.[21–23] Small areas of endothelial denudation and thrombus formation have been described in atrial fibrillation complicated by cerebral embolism.

Third, the final component of Virchow's triad in HF is evident by an imbalance in pro- and antithrombotic factors with clear prothrombotic shift overall. Patients with HF have increased levels of plasma fibrinogen, fibrinopeptide A and fibrin D-dimer.[21,24,25] Furthermore, the presence of endothelial dysfunction in HF has profound implication on production of hemostatic and fibrinolytic factors in HF with net effect favoring prothrombotic changes[20,26]

Thrombosis prevention in heart failure with atrial fibrillation

In almost 100,000 patients admitted with HF and enrolled in Get With The Guidelines-HF program, AF was independently associated with poor outcome.[27] Current guidelines on management of patients with AF suggest administration of oral anticoagulation in virtually all HF patients without contraindications.[28,29] Indeed, HF per se puts patents in the category of CHA_2DS_2-VASc score ≥1, where oral anticoagulation is advisable with majority of patients having at least one other risk factor thus making oral anticoagulation mandated (i.e., score ≥2). As a result oral anticoagulation should be routinely used in HF with concomitant AF.[28,30]

All patients started on oral anticoagulation with warfarin or other vitamin K antagonists must have regular monitoring of international normalised ratio (INR), with target recommended INR value of 2.0–3.0 in non-valvular AF (NVAF).[31,32] Anticoagulation with warfarin brings many challenges, given the high inter- and intra-patient variability in INRs, requiring regular anticoagulation monitoring. A high time in therapeutic range (TTR, ie. >70%) is needed to ensure the best outcomes in efficacy and safety[33–35]; TTRs can be influenced by multiple clinical risk factors, which have been incorporated into the SAMe-TT_2R_2 score to help identify those patients who are likely to do well on warfarin.[36–38]

Real world data indicate that oral anticoagulation in AF is often underutilized, with fear of perceived risk of bleeding complications being the most common reason of not prescribing of the indicated treatment.[26] Although oral anticoagulants should be avoided in patients with genuine high risk of bleeding (e.g., coagulopathy) such patients are uncommon. To avoid inadequate stroke prevention in HF accompanied by AF, all such patients should have bleeding risk quantification using the recommended HAS-BLED score.[28,39,11] In subjects with HAS-BLED score ≥3, risks and benefits of oral anticoagulation should be individually considered and if started the therapy needs to be regularly reviewed to ensure its safety.

Although aspirin is frequently used in patients with HF and NSR, it does not provide adequate protection against stroke or systemic VTE in people with AF. In those few patients where oral anticoagulants are genuinely contraindicated due to high risk of bleeding, aspirin bears similar risk of bleeding to warfarin without providing effective prevention of VTE events; and it should be avoided unless the patient has CAD.