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Review

Prognostic and therapeutic implications of vascular disease in patients with atrial fibrillation

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ABSTRACT

Atrial fibrillation (AF) is associated with a 5-fold increase in the risk of ischemic stroke, and AF-related stroke patients have a higher mortality and greater morbidity than patients with non-AF related stroke. AF and vascular disease share a close relationship, with the concomitant presence of both disease states leading to a dramatic rise in future cardiovascular events. Indeed, the presence of peripheral artery disease independently predicts stroke in patients with AF.

Myocardial infarction (MI) is another well-established risk factor for the development of AF; however, the role of pre-existing AF in MI is less well evidenced, with recent studies showing that this population more frequently develops coronary ischaemic events and has a higher risk of mortality than sinus rhythm patients. Finally, complex aortic plaque is associated with heightened thromboembolic risk in AF patients.

Recent data from clinical trials with non-vitamin K antagonist oral anticoagulants (NOACs) provided new insights on the prognostic implications of vascular disease coexistence in AF patients, and randomised trials testing a combination of NOAC with antiplatelet agents are ongoing. This review article provides an overview of recent data linking adverse outcomes in concomitant AF and vascular disease and the clinical trial evidence for possible therapeutic targets.

1. Introduction

Atrial fibrillation (AF) is associated with a 5-fold increase in the risk of stroke, and AF-related stroke patients have a higher mortality and greater morbidity than patients with non-AF related stroke [1]. Indeed, central to the improved management of patients with AF has been the need for early detection of AF, correct risk stratification and use of appropriate thromboprophylaxis [2]. The use of oral anticoagulant therapy (OAC), whether with the Vitamin K antagonists (VKAs, *e.g.* warfarin) or the non-VKA oral anticoagulants (NOACs), results in a marked reduction in ischemic stroke and mortality [3–6]. However, despite such treatment a high proportion of AF patients experience cardiac complications, such as myocardial infarction (MI) [7]. This enhanced risk of cardiovascular events is conferred by the common coexistence in AF patients of several cardiovascular risk factors, including hypertension, diabetes mellitus, heart failure (HF) and peripheral artery disease (PAD) [8].

AF and vascular disease share a close relationship, with the concomitant presence of both disease states leading to an increased risk of cardiovascular disease, both ischemic stroke and MI [9,10]. At this regard, 'vascular disease' which includes "prior MI, PAD, or complex aortic plaque has been included in clinical risk stratification scores such as the CHA_2DS_2-VASc score [11]. This review aims to assess the following: 1) the relationship between AF and vascular disease and their prognostic implications; 2) therapeutic strategies for patients with coexistent AF and vascular disease.

2. Atrial fibrillation and vascular disease

Over recent years the association of AF with PAD has gained much attention. PAD independently predicts stroke in patients with AF and consequently is included as a component of the CHA_2DS_2-VASc score [11]. Indeed, AF coexisting with PAD also leads to frequent adverse cardiovascular outcomes [12]. This has led to the suggestion of routinely screening for the presence of AF in patients with PAD and vice versa [13–15]. Although beneficial, OAC for stroke prophylaxis in AF does not remove the consequences of having AF with concomitant PAD [16,17].

An important issue is the early detection of PAD in AF patients, as a significant proportion of patients may still have not developed

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symptoms of overt PAD, but may already suffer from asymptomatic PAD. Ankle-brachial index (ABI) is the recommended tool to screen patients for the presence of asymptomatic PAD [18]; an ABI ≤ 0.90 has a high specificity and accuracy in detecting PAD with a ≥50% degree of stenosis [19]. Abnormal ABI, even in absence of symptoms, is associated with poor cardiovascular prognosis, and there is also evidence that patients with a low resting ABI have a poorer functional status and a more rapid functional decline over time [20]. Thus, the detection of asymptomatic PAD may allow early intervention strategies to reduce cardiovascular risk.

In a study by Violi et al., 21% of patients with non-valvular AF had significant asymptomatic PAD (defined by an ABI ≤ 0.9) [21], associated with an increased risk of cardiovascular events [22]. Furthermore, in those 428 patients with ABI ≤ 0.9 there was a higher incidence of hypertension, diabetes and transient ischaemic stroke. The incorporation of ABI into the CHA_2DS_2VASc score increases the prevalence of vascular disease thus reclassifying the risk profile of a significant proportion of AF patients who would otherwise be considered as 'low-risk' [21]. Thus, the inclusion of low ABI as part of the 'vascular disease' definition may help to identify a wider population of AF patients that merit anticoagulation.

Wasmer et al. further highlighted the potential prognostic importance of AF in patients with PAD in a 42,000-patient prospective study [23]. Within this population, 5622 patients were recorded as having PAD and in a multivariate Cox regression analysis, PAD was an independent predictor of death (HR 1.46; 95% CI 1.39–1.52, $p < 0.001$), ischaemic stroke (HR 1.63; 95% CI 1.44–1.85) and amputation (HR 1.14 CI 1.07–1.21) in patients with AF [23].

'Real world' data of patients with PAD and concomitant AF shows a higher occurrence of MI, stroke, major bleeding and all cause death when compared to patients in sinus rhythm [24]. Despite a shorter duration of follow up in this population *vs.* the sinus rhythm cohort (208 *vs.* 1556 patient-years) the presence of PAD in the AF population showed a significantly worse outcome. In support of this, registry data from Denmark further highlighted the prognostic implications of AF with concomitant PAD [25]. Of the 87,202 AF patients included, 2503 had concomitant vascular disease, whereby the risk of stroke/thromboembolism was higher in patients with PAD than in those with MI (HR 1.93 95%CI 1.7–2.19 *vs.* 1.12 95%CI 1.04–1.21, respectively). This highlights the importance of PAD assessment in stroke risk stratification for AF patients, whereby PAD specifically increases the risk of "large artery stroke" *vs.* cryptogenic stroke in this specific patient population [26].

More recent prospective data from "high risk" heart failure (HF) patients with AF and PAD confirmed the increased annual rates of ischaemic stroke (adjusted HR 1.34 95%CI 1.08–1.65) and all cause death (adjusted HR 1.47 95%CI 1.35–1.59) when compared to AF populations without PAD [27]. With heart failure also independently associated with thromboembolic risk the added effect of PAD would put such AF patients at a heightened risk of major adverse cardiovascular events [28]. Patient with HF with preserved ejection fraction have shown similar findings [29].

Further observational data of randomized controlled trials has shown that individuals with atherosclerotic PAD are more likely to experience systemic embolic events if AF is present [30]. Of approximately 38,000 patients across 4 clinical trials with lower and upper limb ischaemia, the HR for all-cause mortality was 4.33 (95% CI 3.29–5.7). Although a post-hoc analysis, such findings are in concordance with the population-based data [21,27]. From a different perspective, patients with AF who undergo surgical intervention for PAD have a higher mortality and need for above the knee amputation [31]. This is linked to the higher risk of arterial embolization in patents with AF causing a higher severity of limb ischaemia [32].

Evidence to the contrary was provided from the Multi Ethnic Study of Atherosclerosis (MESA) study where patients with PAD had a higher incident of stroke but this was not mediated by the presence of AF (HR 1.7 95% CI 1.1–1.25) [33]. Of note, the study population with PAD had a mean age of only 67 and one could argue that the higher risk population for AF related stroke or indeed those most commonly seen in clinical practice may have been underrepresented. The small number of AF cases that occurred before stroke may have limited the statistical power to detect the mediating effect of AF on stroke.

Other studies have suggested no interaction between the presence of AF and worse clinical outcomes in patients with PAD [34]. Such studies still support the adverse role of AF and PAD as independent risk factors for stroke, heart failure hospitalization and death but do not conclude that the presence of AF per se in patients with PAD leads to a substantially worse clinical outcome [35]. Therefore, the treatment of patients with PAD and AF must aim to reduce thrombotic risk but also aim to improve the overall prognosis and adverse clinical outcomes that are associated with having both conditions.

3. Treatment of patients with PAD and AF

Antiplatelet therapy is effective for reducing the mortality and morbidity of PAD patients [18], whereas OAC therapy with warfarin is not beneficial and is potentially harmful because of an increased risk of major bleeding [36]. By contrast, the use of anticoagulant drugs in the form of NOACs or warfarin is recommended in patients with a AF apart from those deemed to be at low risk for AF related stroke.

Data from the EurObservational research programme pilot survey (EORP) highlight the correlation between higher all cause death and AF in patients with PAD, with this risk being lowered with the use of cardiovascular prevention drugs (most notably angiotensin converting enzyme inhibitors) (p = .0008) [37]. The combination of a VKA (warfarin) and aspirin in patients with PAD resulted in a higher rate of bleeding without reducing the rate of cardiovascular events [36].

Until recently, little data have been available on the treatment of patients with PAD and AF. In the RE-LY trial, 38.4% (n = 6952) of patients received either aspirin or clopidogrel or both antiplatelets concomitantly during the study. A single antiplatelet drug combined with a NOAC increased the risk of bleeding by 60–80% compared with using OAC only, and a dual antiplatelet drug combined with an oral anticoagulant increases this risk by 130% compared with an oral anticoagulant alone [38]. Post hoc analysis of the ROCKET AF trial showed that of the 839 patients with concomitant PAD, 40% were treated with antiplatelet therapy (*i.e.* aspirin) – such combination therapy with rivaroxaban increased the risk of major and clinically significant non-major bleeding compared to warfarin (HR 1.4, 95% CI 1.06–1.86) [39], with no significant difference in embolic events (stroke and systemic embolism) [39]. Nevertheless, one must be cautious with such subgroup analyses especially as the sample size by which such observations were drawn may prohibit a true difference to be drawn (n = 839).

A sub analysis of patients with PAD in the ARISTOTLE trial found that in this subgroup of 884 patients, the risk of stroke was similar regardless of whether patients were assigned to apixaban or warfarin when adjusted for patient characteristics (HR 1.73, 95%CI 1.22–2.45, p = .0002) [40]. These findings are in line with the previously mentioned ROCKET AF post hoc analysis by which patients with PAD did not have a superior benefit of NOAC over warfarin for prevention of stroke or clinically overt bleeding (HR 1.61 95%CI 1.13–2.30). This is unsurprising given the relatively small numbers of patients with PAD involved in the post hoc analysis. Furthermore, approximately one third of patients with PAD were on concomitant antiplatelet therapy thus increasing the risk of bleeding.

In summary, there is no general agreement on the most effective and safe management of patients with AF and concomitant PAD, which should be on an individual basis. Those who warrant OAC (which should be a NOAC unless contraindicated) based on their CHA_2DS_2VASc score should not be denied such therapy in the presence of antiplatelet therapy for PAD as the latter does not offer appropriate