Atrial Fibrillation and Vascular Disease — A Bad Combination

Jonas Bjerring Olesen, MD; Gunnar Hilmar Gislason, MD, PhD;
Christian Torp-Pedersen, MD, DMSc; Gregory Y. H. Lip, MD

Department of Cardiology (Olesen, Gislason, Torp-Pedersen), Copenhagen University Hospital Gentofte, Hellerup, Denmark; University of Birmingham Centre for Cardiovascular Sciences (Lip), City Hospital, Birmingham, United Kingdom

ABSTRACT

This article provides an overview of (i) the risk of stroke associated with vascular disease (acute coronary syndromes and peripheral artery disease) in patients with atrial fibrillation, (ii) the frequent coexistence of vascular disease in patients with atrial fibrillation and, (iii) the cardiovascular risk associated with the coexisting of the two diseases. The literature on this topic is relatively sparse, and we discuss results from both clinical trials and observational studies.

There is a clear indication of an increased stroke risk associated with vascular disease in patients with atrial fibrillation. Indeed, patients with atrial fibrillation often had coexisting vascular disease (around 18%), and the combination of the two diseases substantially increases the risk of future cardiovascular events. The increased risk associated with peripheral artery disease in atrial fibrillation is even more pronounced.

Patients with atrial fibrillation and stable vascular disease should be treated with oral anticoagulation only, although when these patients present with acute coronary syndrome and/or undergo coronary stenting, concomitant treatment with antiplatelet drugs is indicated. To guide antithrombotic management in patients with atrial fibrillation, several stroke and bleeding risk prediction schemes have been developed.

Introduction

Atrial fibrillation (AF) and vascular disease are closely associated, and the coexistence of the 2 diseases increases the risk of future cardiovascular events dramatically. AF and atherothrombosis share many etiological risk factors, and given their common coexistence, the optimal management of these patients is of great interest.¹ Because vascular disease increases the complications associated with AF, new risk evaluations in such patients for future cardiovascular events may improve their management strategy.¹

In this brief overview, the term “vascular disease” will be used to include a number of conditions, including acute coronary syndromes and peripheral artery disease.

Vascular Disease and Stroke Risk in Atrial Fibrillation

Thromboembolic stroke is one of the most feared complications associated with AF, and there has been some

debate as to whether vascular disease increases the risk of thromboembolism in AF.

The presence of peripheral artery disease confers a poor prognosis in AF, with high rates of mortality, cardiovascular events, and stroke.^{2–4} In the nationwide cohort study by Lin et al,⁵ peripheral artery disease was an independent predictor of stroke among nonanticoagulated AF patients, with an associated odds ratio of 1.8 (95% confidence interval, 1.2–2.8). Vascular disease, including peripheral artery disease, was also a risk factor of subsequent stroke in AF patients age <65 years in the Loire Valley Atrial Fibrillation Project,⁶ and peripheral artery disease was an independent predictor of stroke and death in the Danish Diet, Cancer, and Health Study.⁷ Rasmussen et al found an incidence rate of stroke at 1-year follow-up of 10.9 per 100 person-years in patients with new-onset AF and peripheral artery disease, vs a rate of 4.6 in new-onset AF patients without vascular disease.⁷ The results are summarized in Table 1.

What about coronary artery disease? Even though Ezekowitz et al reported an increased risk of stroke associated with symptomatic angina pectoris,⁸ uncomplicated coronary artery disease may be less of a stroke risk factor per se.^{9,10} However, there are extensive reports of increased risk of stroke associated with myocardial infarction in AF patients.^{11–13} Van Walraven et al also analyzed data from 6 small clinical trials and found that myocardial infarction was significantly associated with stroke.¹² In AF patients,

Table 1. Vascular Disease and Stroke Risk in Atrial Fibrillation

Study/Risk Factor	Stroke Rate Per 100 Person-Years		Adjusted Stroke Risk Associated With Vascular Disease	
	No Risk Factor	With Risk Factor	RR/HR/OR (95% CI)	P Value
Aronow (1989) ¹³				
Myocardial infarction			4.84	<0.01
Aronow (1998) ⁵⁵				
Myocardial infarction			0.87 (0.60-1.26)	0.46
Ezekowitz (1995) ⁸				
Active angina pectoris			1.7-fold	0.01
Myocardial infarction			1.4-fold	0.13
Frost (2000) ⁴				
Myocardial infarction (men)			1.2 (1.1-1.4)	
Myocardial infarction (women)			1.1 (0.9-1.3)	
Peripheral vascular disease (men)			1.3 (1.0-1.7)	
Peripheral vascular disease (women)			1.3 (1.0-1.6)	
Goto (2008) ³				
Vascular disease		2.43		
Lin (2011) ⁵				
Myocardial infarction			1.42 (0.9-2.23)	0.13
Peripheral artery disease			1.81 (0.91-2.23)	0.006
Coronary artery disease			1.07 (0.83-1.36)	0.6
Lip (2010) ³⁶				
Vascular disease	1.5	3.6	2.27 (0.94-5.46)	0.06
Olesen (2011) ³³				
Vascular disease	0.66 (0.57-0.76)	1.47 (1.01-2.12)	2.22 (1.49-3.30)	<0.0001
Olesen (2011) ⁶				
Vascular disease	0.34 (0.15-0.76)	1.78 (0.89-3.55)	2.19 (1.22-3.92)	0.17
Petersen (1990) ¹¹				
Myocardial infarction			4.3	0.003/0.04
Rasmussen (2011) ⁷				
Vascular disease	1.6 (1.4-1.8)	3.4 (2.5-4.5)	0.97 (0.70-1.34)	
Myocardial infarction		3.0 (2.2-4.2)	1.01 (0.71-1.44)	
Peripheral artery disease		4.6 (2.8-7.6)	0.87 (0.52-1.46)	
van Walraven (2003) ¹²				
Myocardial infarction or angina	1.4	5.6		0.002
Abbreviations: CI, confidence interval; HR, hazard ratio; OR, odds ratio; RR, relative risk.				

the observed rate of stroke was 5.6 per 100 person-years in patients with a history of myocardial infarction or angina pectoris and only 1.4 in patients without a history of myocardial infarction or angina pectoris.¹² In alignment, Aronow et al found that a history of myocardial infarction was associated with an odds ratio of 4.8 for thromboembolic stroke.¹³ The NICE (National Institute for Health and Clinical Excellence) guidelines systematic review did conclude that prior myocardial infarction was a stroke risk factor in AF.¹⁴

In the 2006, the American College of Cardiology/American Heart Association/European Society of Cardiology established guidelines, coronary artery disease was listed as a “weaker or less well validated” stroke risk factor, but the more recent 2010 European Society of Cardiology guidelines include vascular disease (defined as prior myocardial infarction, peripheral artery disease, or complex aortic plaque) as part of their comprehensive stroke risk assessment.¹⁵

Of note, large contemporary clinical trials in AF have also included vascular disease, whether coronary artery disease or peripheral artery disease, as a stroke risk factor.^{16–19}

Atrial Fibrillation and Vascular Disease

Although the possible association between vascular disease and stroke in AF is debated, the association between vascular disease and AF is more unambiguous.¹ Vascular disease has been found to increase the risk of AF,^{3,20} and AF has likewise been shown to be a major risk factor for vascular disease and cardiovascular death.^{2,3,21–26} Furthermore, the 2 diseases share a number of risk factors (eg, increasing age, obesity, diabetes, heart failure, and hypertension), and the 2 diseases often coexist.^{1,20,27}

Vascular Disease in Atrial Fibrillation

Recent large clinical trials in AF patients with at least 1 risk factor for stroke have reported a pronounced prevalence of vascular disease in these patients.

In the ACTIVE W trial (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events), 17% of the participants had a history of myocardial infarction and 4% had peripheral artery disease,¹⁶ whereas in the ACTIVE A trial, 14% of the participants had a history of myocardial infarction and 3% had peripheral artery disease.²⁸ In ACTIVE W and ACTIVE A, the annual risk of myocardial infarction was <1%, whereas the annual risk of cardiovascular death (any death that was clearly not due to a nonvascular cause) was 3% in ACTIVE W and 5% in ACTIVE A.^{16,28}

In the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy), patients were age ≥ 65 years, and associated coronary artery disease could be included. Of note, 17% of the study cohort had a history of myocardial infarction. During follow-up, the annual risk of myocardial infarction and cardiovascular death was 0.6% and 3%, respectively, with warfarin, and 0.8% and 2%, respectively; with dabigatran—a numerical difference that was not statistically significant.^{19,29} This has led to the debate as to whether dabigatran increased the risk of myocardial infarction or that warfarin was protective against myocardial infarction.³⁰

Similar annual risks were reported from the AVERROES trial (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in AF Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment); the risks were <1% for myocardial infarction and 3% for cardiovascular death.¹⁸ The ATHENA trial (A Placebo-Controlled, Double-Blind, Parallel Arm Trial to Assess the Efficacy of Dronedarone 400 mg b.i.d. for the Prevention of Cardiovascular Hospitalization or Death from Any Cause in Patients with Atrial Fibrillation/Atrial Flutter) included 30% of patients with coronary artery disease, and during 21 ± 5 months of follow-up, 3% died from a cardiovascular cause and 3% were hospitalized with acute coronary syndrome.³¹

The prevalence of vascular disease in these clinical trials resembles the prevalence found in real-world observational studies. For example, Olesen et al found a prevalence of 18% in the Danish AF population.^{32,33} In the EuroHeart Survey of hospitalized AF patients, 17.6% had a history of acute myocardial infarction and 7.6% had peripheral vascular disease.³⁴ Van Walraven et al found that in AF patients included in 6 small clinical trials, 19.7% had a history of myocardial infarction or angina pectoris.¹²

Vascular Disease in Atrial Fibrillation Is Bad

In the REACH registry (REduction of Atherothrombosis for Continued Health), Goto et al found that the prevalence of AF was 12.5% in patients with coronary artery disease and 11.5% in patients with peripheral artery disease,³ compared to a prevalence of 2.3% in the general population.³⁵ In patients with atherosclerosis, the risk of cardiovascular events (including cardiovascular death, myocardial infarction, stroke, and hospitalization for an atherothrombotic event) was higher in patients with concomitant AF (17.9% vs 12.1% at 1-year follow-up), and the risk associated with peripheral artery disease plus AF was higher than the risk associated with coronary artery disease plus AF (27.1% vs 19.7%).³

Conway and Lip found that in patients with peripheral artery disease, AF was associated with a 2.5-fold increased risk of in-hospital death.² In addition, Friberg et al found that AF was a more severe risk factor of cardiovascular death in women than in men, and among women AF was actually associated with a higher risk of cardiovascular death than a history of myocardial infarction.²⁵ In the multivariate analysis, myocardial infarction was approximately associated with a 3.5-fold increased risk of cardiovascular death.²⁵

In AF patients, both stroke and bleeding prediction schemes have been developed,^{36–39} and perhaps it is time for a novel vascular event prediction scheme among these high-risk patients. In the large clinical trials, subsequent myocardial infarction occurred approximately half as frequently as stroke,^{16,18,19} but in the Framingham Heart Study, coronary heart disease is a much more frequent cause of death than stroke.²⁶

Antithrombotic Therapy in Atrial Fibrillation Plus Vascular Disease

The most effective antithrombotic treatment for stroke prevention in AF patients with intermediate to high risk of stroke is oral anticoagulation,^{15,16,40–44} with warfarin currently being the most frequently prescribed drug. In

AF patients who are prescribed anticoagulation drugs for stroke thromboprophylaxis, warfarin might also provide a protective effect against myocardial infarction, an effect that has not been found with nonwarfarin anticoagulants or anticoagulation equivalents.^{18,19,30} The suggested protective effect of warfarin on the risk of myocardial infarction is not restricted to AF patients, and previous studies in patients with previous myocardial infarction have found warfarin to confer a better protection against reinfarction than aspirin.⁴⁵ However, in this study, patients on warfarin were at increased risk of bleeding compared to aspirin.⁴⁵

In the article by van Walraven et al,⁴⁶ among AF patients the risk of vascular events increased with increasing age (≥ 65 years), and the absolute benefit of oral anticoagulation therapy compared to control/placebo also increased with increasing age, whereas the absolute benefit of antiplatelet therapy declined. A similar pattern was seen for stroke,⁴⁶ but the magnitude of absolute benefit was less compared to that seen for vascular events. This reaffirms that in patients with AF, oral anticoagulation not only has a marked benefit regarding stroke, but also on all-cause mortality and vascular mortality.^{40,47} In the recent RE-LY

trial, dabigatran, use of the oral direct thrombin inhibitor, at a 150-mg dose twice daily, resulted in a significant reduction in vascular mortality and a borderline reduction in all-cause mortality when compared to warfarin.¹⁹

AF patients with a history of stable vascular disease should be treated with warfarin only (ie, aspirin should not be added because of an excessive risk of bleeding).^{17,48,49} However, when AF patients present with acute coronary syndrome and/or undergo coronary stenting, oral anticoagulation alone does not protect sufficiently against new vascular events and stent thrombosis, and concomitant treatment with antiplatelet drugs is indicated,^{50,51} although combination therapy substantially increases the risk of bleeding.⁵²

In the consensus document from the European Society of Cardiology Working Group on Thrombosis, endorsed by the European Heart Rhythm Association and the European Association of Percutaneous Cardiovascular Interventions (which includes a systematic review of the published literature), specific antithrombotic treatment regimes were suggested according to bleeding risk, clinical setting, and type of stent (Table 2).⁵¹ Current European guidelines generally recommend the use of bare metal

Table 2. Recommended Antithrombotic Strategies Following Coronary Artery Stenting in Patients With Atrial Fibrillation at Moderate-to-High Thromboembolic Risk in Whom Oral Anticoagulation Therapy Is Required

Hemorrhagic Risk	Clinical Setting	Stent Implanted	Recommendations
Low/intermediate risk	Elective	Bare metal	1 month: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/d + clopidogrel 75 mg/d
			Up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/d ^a
			Lifelong: warfarin (INR 2.0–3.0) alone
	Elective	Drug-eluting	3 (–olimus ^b group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/d + clopidogrel 75 mg/d
			Up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/d ^a
			Lifelong: warfarin (INR 2.0–3.0) alone
High risk	ACS	Bare metal/ drug-eluting	6 months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/d + clopidogrel 75 mg/d
			Up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/d ^a
			Lifelong: warfarin (INR 2.0–3.0) alone
	Elective	Bare metal ^c	2 to 4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/d + clopidogrel 75 mg/d
			Lifelong: warfarin (INR 2.0–3.0) alone
	ACS	Bare metal ^c	4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤ 100 mg/d + clopidogrel 75 mg/d
			Up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/d ^a
			Lifelong: warfarin (INR 2.0–3.0) alone

Abbreviations: ACS, acute coronary syndrome; INR, international normalized ratio. Reproduced from Lip et al⁵¹ and Ghattas et al.⁵³ ^aCombination of warfarin (INR 2.0–3.0) + aspirin ≤ 100 mg/day (with proton pump inhibitors if indicated) may be considered as an alternative. ^bSirolimus, everolimus, and tricolimus. ^cDrug-eluting stents should be avoided as far as possible, but if used, consideration of more prolonged (3–6 months) triple antithrombotic therapy is necessary.

stents in anticoagulated AF patients, and these patients should be treated with triple therapy (ie, warfarin + aspirin + clopidogrel) following stenting. There should be approximately 1 month of triple therapy, unless the risk of bleeding is low or intermediate and the patients presented with acute coronary syndrome, in which case triple therapy should be maintained for 6 months.^{51,53}

Recent reports in the United States suggest an excessive use of stenting of occluded coronary arteries in stable patients.⁵⁴ If these reports stand, many patients with concomitant AF and vascular disease are unnecessarily stented and thereafter treated with antithrombotic triple therapy, a treatment that substantially increases the risk of serious bleeding.^{49,52} In AF patients, Hansen et al found a 3.7-fold increased risk of bleeding associated with triple therapy compared to warfarin only,⁴⁹ and in patients with acute myocardial infarction, Sorensen et al found a 4.1-fold increased risk of bleeding associated with triple therapy compared to aspirin only.⁵²

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