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One Weapon, Two Blows in the War Against the Thrombus

Running Title: Antithrombotics: sometimes one is enough

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Old habits die hard, as do old clinical precepts. The war against the thrombus in clinical practice has long been based on the twin paradigms of white vs. red thrombi and Virchow's triad. Platelet-predominant white thrombi form in high-flow arterial streams. Red thrombi, rich in fibrin and trapped erythrocytes, form in low-pressure environments in the venous circulation and atria [1]. Virchow's triad offers a 3-way breakdown of the predisposition to thrombosis into abnormalities affecting the vessel wall, blood flow, and/or blood constituents [2].

Originally described in venous thromboembolism (VTE), the scope of Virchow's triad has expanded with the recognition that it can be usefully applied to both atrial fibrillation (Afib) and arteriopathy. For arterial thrombi, the foremost determinant is endothelial injury/dysfunction associated with atherosclerosis, hypertension, inflammation, or trauma; but turbulent blood flow at bifurcations or stenotic regions and platelet hyperactivity also contribute. For venous thrombi, cognate risk factors are vascular injury (trauma, surgery, vasculitis, sepsis); venous stasis; and hypercoagulable states, whether genetic (e.g., Factor V Leiden mutation) or acquired (e.g., supplemental estrogen). Susceptibility to intracardiac thrombus is increased in Afib by atrial endothelial dysfunction; stasis of blood, particularly in the atrial appendages; and local inflammation coupled with a systemic prothrombotic state [3]. Stroke risk in Afib is widely estimated with the CHADS2 or CHA2DS2Vasc scores; the clinical modifiers represented therein likely operate, at a mechanistic level, through Virchow's triad [2] [4].

The white/red thrombus paradigm provides the rationale for pharmacological management of thrombosis. Antiplatelet agents are the mainstay of therapy for coronary/peripheral artery disease, whereas the coagulation pathway is the target in VTE and Afib. In Afib, for example, aspirin lowers the risk of ischaemic stroke by 21%, while vitamin K antagonists (VKA) achieve a 67% reduction - unfortunately at the cost of doubling the intracranial haemorrhage.
Among other drawbacks, dosage requirements for VKA show substantial inter- and intra-individual variation, influenced by age, genetic variants in \emph{CYP2C9} and \emph{VKORC1}, diet, gut flora, drug interactions, and liver function \cite{4}. Despite regular monitoring, time spent in the narrow therapeutic range is \textasciitilde60\% \cite{5}. Dual antiplatelet therapy predictably fails to alter plasma indices of thrombogenesis, but was established by the ACTIVE trials as an acceptable middle course. Stroke risk was 40\% lower with VKA than aspirin plus clopidogrel, which in turn offered 27\% reduction over aspirin alone \cite{1}\cite{6}.

The question then arises: if the red/ white thrombus dichotomy is so clear-cut, why does aspirin confer even a modest reduction in the stroke risk in Afib, and why should addition of clopidogrel offer incremental benefit? One plausible albeit orthodox response invokes the common association of Afib with vascular disease and its risk factors, such as hypertension. The reduction in vascular events observed with aspirin use in known arteriopathy is in the same range (20-30\%) as that in Afib. The implication is that the recognised benefit of aspirin in vascular disease accounts for much of its apparent benefit in Afib \cite{1}.

By the same token, anticoagulation might be expected to have limited role in vascular disease. Whether the remit of VKA can be extended becomes particularly relevant in the common scenario of dual pathology: coexisting Afib and vascular disease. Diabetes and hypertension, key risk factors for vascular disease, are also CHADS2 modifiers, and vascular disease \textit{per se} - including myocardial infarction (MI), peripheral artery disease, and complex aortic plaque - increases thromboembolic risk in Afib, as reflected in the upgrading of CHADS2 to the CHA2DS2Vasc score \cite{4}. These patients often need anticoagulation and adding antiplatelet agents augments their bleeding risk. Could VKA confer sufficient protection from vascular events to be used as sole therapy in this population?

In the setting of recent acute coronary syndrome (ACS) and/or percutaneous coronary intervention, the answer is probably no. VKA monotherapy is relatively effective in
preventing secondary events unless stenting is involved, in which case - even when combined with aspirin - it is inferior to regimes incorporating a P2Y$_{12}$-receptor inhibitor (clopidogrel, prasugrel, ticlodipine, ticagrelor) [4]. The current recommendation is aspirin plus P2Y$_{12}$-receptor inhibitor for 12 months; adherence may be particularly important following deployment of drug-eluting stents owing to delayed re-endothelialisation. Yet omission of anticoagulation also appears suboptimal, increasing mortality (hazard ratio 3.43) and major cardiac events in a study of 426 patients with Afib and recent stenting [7]. An argument exists for triple therapy - aspirin, P2Y$_{12}$ inhibitor, VKA - but potential benefits may be offset by up to 16% annual incidence of haemorrhage [8]. An alternative strategy involves conjunctive use of VKA and P2Y$_{12}$-receptor inhibitor, which, in a trial of 573 patients, attenuated bleeding risk vs triple therapy (hazard ratio 0.36) without increasing major cardiovascular events [9]. Although the WOEST trial was underpowered to exclude excess stent thrombosis, a subsequent registry study supported the non-inferiority of VKA plus clopidogrel vs. triple therapy. Dropping the aspirin appears, then, to hold promise after recent ACS/ revascularisation.

Posing a distinct challenge are patients with Afib and stable coronary artery disease (in whom ≥12 months have elapsed after ACS/ revascularisation, or there is no history of either). Anticoagulation remains optimal, but the risk/ benefit ratio of add-on antiplatelet therapy alters owing to the now-minimal threat of stent thrombosis and declining - although persistent - concerns over plaque instability. The 2011 AHA/ACCF guidelines recommend VKA plus aspirin [10]. A recent study of 8,700 patients with Afib and stable coronary disease, however, found no difference in MI/ coronary death or thromboembolic risk between VKA monotherapy, VKA plus aspirin, or VKA plus clopidogrel [11].

In this issue of the *Journal*, Lamberts et al. investigate the burden, impact, and optimal management of Afib in >37,000 Registry patients with both vascular disease and heart failure.
The mean CHA2DS2-Vasc score of 5 confirms a high-risk stratum; mean HAS-BLED score was 2.1, underscoring the need to achieve a delicate balance.

Besides being observational and retrospective in design, registry studies have limited available clinical details; we do not know how Afib was picked up in these patients. Given real-world variations in practice, this may have ranged from 12-lead ECG prompted by symptomatic deterioration to the more pro-active approach of periodic ambulatory rhythm monitoring. While the 29,660 patients without an Afib diagnosis enjoyed improved survival, undiagnosed silent Afib is a concern in this population, leading clinicians to seek surrogate markers such as left atrial dimensions. Even assuming, however, that some of these patients had paroxysmal Afib, VKA afforded no advantage over antiplatelet therapy in lowering thromboembolic risk (hazard ratio 1.06, CI 0.86-1.31). This is heartening; it implies that the burden of silent Afib in these patients may not be sufficient to warrant anticoagulation. The WARCEF trial also found no difference in all-cause mortality between VKA and aspirin in 2,305 patients with left ventricular systolic dysfunction and sinus rhythm, but this may have been because the benefits of VKA in reducing ischaemic stroke were offset by increase in major haemorrhage among older patients [13].

Lamberts et al. subdivided their Afib sample into prevalent (pre-existing) and incident (new onset) categories, but found similar thromboembolic risk. VKA was more effective than antiplatelet therapy in attenuating this risk; combining the two afforded no advantage but did increase bleeding. This was no surprise; antiplatelet agents are included as additional protection against coronary events, not thromboembolism. But then came the pivotal finding: adding antiplatelet to VKA therapy offered no incremental benefit in reducing the risk of MI/coronary death. Nor was there any significant difference between VKA and VKA plus antiplatelet therapy in the combined outcome of thromboembolism and MI (HR 1.00 [CI 0.89-1.14]) [12].
Despite the large sample in this study, reported confidence intervals are often wide, suggesting underpowering. Nevertheless, it adds to accumulating evidence that optimal risk/benefit balance in some patients with Afib and vascular disease may be achieved by VKA alone. In a clinical setting, decision-making will be mutual and individualised, taking into account not only CHA2DS2-VASc and HAS-BLED scores but also coronary anatomy and, in heart failure patients, the extent of viable at-risk myocardium.

Returning to the red/white clot paradigm, however, the apparent efficacy of VKA in preventing coronary events requires some explaining. If we assume the distinction in thrombotic process is absolute, then the answer may lie in the pleiotropic properties of many drugs. Statin therapy, for example, may affect the reported 22% reduction in VTE risk by modulating endothelial function, inflammatory responses, and thrombogenesis [2]. Similarly, VKA have beneficial effects on myocardial contractility, oxygen consumption, platelet adhesiveness, and inflammatory reactions [14].

Yet it may also be time to replace our perception of a white/red thrombus dichotomy with a continuous spectrum. Carotid plaques and adverse cardiovascular events are more prevalent among VTE patients with idiopathic disease than those with transient acquired risk factors. At a mechanistic level, cytokine release, leukocyte recruitment, platelet activation, and fibrin turnover are common to both arterial and venous thrombosis. Antiplatelet therapy has been shown to reduce the incidence of VTE, just as warfarin can forestall coronary events [2; 4].

One weapon can deal two blows in the war against the thrombus, which is good news for reducing iatrogenic bleeding. In patients with stable coronary disease, heart failure, and Afib, VKA can sometimes be that weapon. The impact of this finding may diminish in years to come as VKA use in nonvalvular Afib declines in favour of alternatives that selectively inhibit factor Xa (rivaroxaban, apixaban and edoxaban) and thrombin (dabigatran). As direct-acting oral anticoagulants reduce the rate of intracranial haemorrhage by 50%, the risk/
benefit ratio will shift and demand revisiting of the issues [5]. Still relevant will be the recognition underpinning the current spate of antithrombotic studies: that optimal management of patients with apparent dual pathology is best guided by observational and empirical data, to complement the oversimplified precepts of old.

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References


