Atherothrombosis and atrial fibrillation: Important and often overlapping clinical syndromes

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The prevalence of atrial fibrillation (AF) in the United States is approximately 6 million patients but may exceed 12 million by the year 2050 (1). More than 17 million patients have coronary artery disease (CAD), and over 6 and 8 million Americans, respectively, have suffered a stroke or have peripheral arterial disease (2). The prevalence of AF in patients with established atherothrombosis (11.7%) or risk factors for atherothrombosis (6.2%) is substantially higher compared with the general population (2.3%) (3, 4). Given the high proportion of patients with atherothrombosis and AF, it is important that physicians are aware of the clinical implications and management of these overlapping syndromes.

Overlapping pathogenesis

Atherothrombosis involves interplay between an individual’s genetic risk, cardiovascular risk factors, inflammation, and platelet-mediated thrombosis (5). The thrombogenic state of AF extends beyond the risk for thromboembolism from stasis in the left atrium (6). AF and atherothrombosis have similar mechanisms for thrombogenesis (6).

Inflammation is a driving force in the progression from atherosclerosis to atherothrombosis (7). C-reactive protein (CRP) is a well-established marker used to assess the level of inflammation in atherosclerosis (8). AF is also associated with inflammation (9). The renin-angiotensin-aldosterone system appears to play a role in the thrombogenic state of AF, though some studies are conflicting (6, 23, 24). The length of dysrhythmia may influence the extent of platelet activation and aggregation (25). Markers of inflammation, mainly interleukin-6 (IL-6) and CRP, are associated with an increased thromboembolic risk (18, 26–28). It is difficult to differentiate if these markers are due to AF or underlying co-morbidities (26).

Despite progress in understanding the pathogenesis of the thrombotic state of AF, biomarkers that adequately predict the thrombotic risk of patients with AF are lacking (29). Biomarkers are needed to risk stratify patients, select appropriate antithrombotic therapy, and assess the response to current and future therapies for the treatment of AF.

Overlapping patient populations and outcomes

The clinical syndromes overlap due to several co-morbidities that are risk factors for both diseases. Age is a well-known risk factor for atherothrombosis (2). AF increases incrementally with age, which may be due in part to left atrial enlargement increasing with age (30, 31).

Obesity is a global epidemic and will affect an estimated 700 million people world-wide by 2015 (2). Obesity is a strong predictor of atherothrombosis, and coexists with several cardiovascular risk factors (2, 32). Obesity increases the prevalence of AF by 50% and is proportional to body mass index (33). In the Women’s Health Study, a linear relationship was found between body mass
Management of patients with atherothrombosis and AF

A clinical dilemma arises in patients who have atherothrombosis and AF. Atherothrombotic patients require long-term antipatelet therapy (3). AF patients typically need oral anticoagulation with vitamin K antagonists (VKA) (37). Guidelines for management of patients with AF and atherothrombosis are lacking (38). The paucity of evidence has led to a wide variability in the antithrombotic regimens used to treat AF (39). This uncertainty is magnified in patients who have an indication for triple therapy (i.e. dual antiplatelet therapy and VKA). An analysis of 86,304 ACS patients found that only 18% of patients with AF/flutter were discharged on triple therapy, while 27% of patients with AF/flutter who underwent percutaneous coronary intervention (PCI) were prescribed triple therapy (40). Risk factors for stroke or bleeding were associated with the choice of triple therapy in this patient population, yet it is unclear which patient characteristics ultimately led to a decision to prescribe triple therapy (40).

The wide variability in the choice of antithrombotic therapy in patients is likely due to a concern for bleeding. The risk of major bleeding in patients with AF and atherothrombosis is almost double compared with patients with atherothrombosis alone (3). Clinicians can utilize a risk stratification model for bleeding in AF patients on VKA (41). Unfortunately, the same clinical factors that increase the risk for bleeding also increase the risk for stroke (42, 43). Rates of major bleeding in clinical trials with AF or ACS patients underestimate the true rates of major bleeding in the community (44, 45). In AF patients, bleeding rates are typically established in younger patient populations and do not accurately reflect the true risk for bleeding in the elderly (44).

The uncertainty about selecting antithrombotic therapy coupled with a concern for bleeding has led to an under-utilization of antithrombotic therapy (3). A recent registry analysis found that approximately 17% of patients with both atherothrombosis and AF received a VKA and an antipatelet agent (3). Surprisingly, VKA were omitted in nearly 50% of patients with a history of AF, despite being at a high risk for stroke based on the CHADS2 score (3). Non-fatal stroke increased in AF patients with higher CHADS2 scores, yet the use of combined therapy did not increase. In another registry, only 39% of stroke patients with AF were admitted on warfarin, of which 25% (i.e. 10% of the total population) were therapeutic with an international normalised ratio (INR) ≥ 2 (44). On admission, 15% of the population was not on any antithrombotic therapy. The analysis concluded that a large proportion of strokes may have been prevented with appropriate antithrombotic selection (46).

The management of patients with AF is based on risk stratification for thromboembolism (47). The risk of stroke in patients with AF can be assessed using the well-known CHADS2 score (47). An increasing CHADS2 score portends a higher incremental risk for stroke (48). Aspirin is effective at preventing thromboembolism in patients with a low risk of stroke (CHADS2 score: 0), while patients with a CHADS2 score of 2 or higher have significantly higher rates of stroke on aspirin (49). The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-W) found that patients with a CHADS2 score > 1 had lower rates of vascular events with VKA compared with aspirin and clopidogrel (50). However, the benefit for VKA was lost over aspirin plus clopidogrel if the time in therapeutic range (i.e. INR 2–3) was < 65% (51). A CHADS2 score of 0 is considered low risk, ≥ 2 is high risk, and 1 is intermediate risk (52). The guidelines suggest VKA for patients at high risk for stroke, while low risk patients can be managed with aspirin (37). The choice of antithrombotic therapy should be irrespective of the burden of AF (i.e. permanent versus paroxysmal) (53). The CHADS2 score also does not include atherothrombosis and other notable risk factors thus its usefulness has been questioned (54).

Intermediate risk patients can be treated with VKA or aspirin (37). Many clinicians are confused as to which therapy to select for this patient population (55). A sub-study of the ACTIVE-W found that intermediate risk patients benefited from VKA compared with dual antiplatelet therapy (56). A recent observational study found that intermediate risk patients on warfarin had significantly lower rates of death and stroke compared with patients on antiplatelet therapy (57). The use of a variation of the CHADS2 score called the CHA2DS,VASc (►Table 1) allows clinicians to further stratify thromboembolic risk (57). The CHA2DS,VASc score added additional risk factors: vascular disease, age 65–74 years, and female sex, as well increasing the number of points assigned to patients with age ≥ 75 years old (52). Interestingly, the new schema incorporates prior non-stroke atherothrombosis as a risk factor. A recent analysis found that patients not on VKA classified as low risk with the CHADS2 score had a 1.4% yearly rate of thromboembolism, while with a CHA2DS,VASc of 0 did not have any thromboembolic events (52). Given the higher risk of stroke in patients with an intermediate risk CHADS2 score, clinicians can use the CHA2DS,VASc schema to assess the risk of stroke in low or intermediate risk CHADS2 patients.(55) Using the CHA2DS,VASc score, patients with a score ≥ 2 should definitely receive VKA, while patients with a score = 1 should most likely receive VKA (55). If the score is 0, then clinicians can consider aspirin or no antithrombotic therapy (55).

Despite the influence of age on the risk of stroke in AF, elderly patients are less likely to receive VKA due to concerns for bleeding
...and/or risk for falls (44, 58–60). In The Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA), patients age 75 years or older randomised to warfarin (INR 2 – 3) had a 52% risk reduction in stroke compared with patients on aspirin (61). No differences occurred in major bleeding between the two groups. A recent trial randomised patients to low intensity (Goal INR: 1.8, range 1.5–2) or standard (Goal INR: 2.5, range of 2–3) warfarin (62). No differences occurred in ischaemic or bleeding events, though a trend towards increased risk of bleeding was seen in the standard warfarin group (62). Despite these findings, the majority of data at present do not support the use of lower intensity warfarin for the treatment of AF (63, 64). The risk of falls and subsequent subdural haematoma is a concern for clinicians when prescribing VKA. An interesting study estimated that a patient would have to fall 295 times per year for the benefit of warfarin to become outweighed by the risk of subdural haematoma (65). Thus, elderly patients should not be precluded from receiving appropriate antithrombotic therapy based on misinterpretations of the risk/benefit ratio for VKA.

For AF patients who cannot tolerate VKA, antiplatelet therapy is indicated (37). Clinicians typically choose aspirin monotherapy over alternative regimens (3). Dual antiplatelet therapy is a mainstay in the treatment of acute coronary syndromes, yet the evidence for its use for stroke prevention in AF had been limited. The ACTIVE-A trial randomised patients with AF who were not candidates for VKA to aspirin plus clopidogrel or aspirin alone (66). Dual antiplatelet therapy reduced the risk of stroke, MI, vascular death, and systemic embolism by 11% compared with aspirin alone, but increased the risk of major bleeding by 57% (66). Thus, the number needed to treat with dual antiplatelet therapy to prevent one major vascular event is 125, while the number need to harm with dual antiplatelet therapy is 142. For patients who cannot tolerate VKA, clinicians can consider using dual antiplatelet therapy over aspirin monotherapy but must carefully weigh the risks of bleeding.

Clinicians face a unique challenge when patients with AF develop ACS and/or undergo PCI. The decision to use triple therapy in these patients has been widely debated (67, 68). The antithrombotic choices for patients with an indication for triple therapy vary widely (40). In patients with AF or flutter who underwent PCI in the setting of ACS, dual antiplatelet therapy was the most common antithrombotic regimen prescribed at discharge (64.5%) compared with triple therapy (27.2%), antiplatelet monotherapy plus VKA (3%), antiplatelet monotherapy (5%), or VKA alone (0.3%) (40). The current guidelines for ACS and/or PCI do not make specific recommendations about which patients should receive triple therapy, but do suggest that VKA should be titrated to an INR between 2.0 and 2.5 (69). The European Society of Cardiology (ESC) recently published a consensus document on recommendations for antithrombotic management in patients who require VKA for AF and present with ACS and/or are undergoing PCI (70). The recommendations call for triple therapy use for a period of time in all patients with a goal INR 2.0–2.5 (Table 2), yet the duration will depend upon the patients bleeding risk, type of stent, and PCI setting (70). The consensus document reiterates that the current evidence is very limited for this patient population and the recommendations are made largely on expert opinion of a limited number of small, single centre trials or observational data from cohort studies (70).

### Emerging therapies for the treatment of AF

Despite the effectiveness of VKA to prevent stroke in AF, the risks of bleeding and monitoring required to maintain a narrow therapeutic range has led to development of new therapies. Left atrial thrombus from stasis in AF is a well-known risk factor for thromboembolism (6). Given that roughly 90% of atrial thrombi develop in the left atrial appendage (LAA), interest in LAA occlusion has increased with the development of an occlusion device called WATCHMAN. The WATCHMAN Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation PROTECT-AF) trial randomised patients with a CHADS2 score of 1 or 2 (71). Patients receiving the device received warfarin for 45 days and were switched to aspirin and clopidogrel for six months followed by aspirin indefinitely (71). The WATCHMAN device was non-inferior to warfarin therapy at three years of follow-up for stroke, death, and systemic embolisation (71). However, there was a significant increase in pericardial effusions in the device group requiring percutaneous or surgical drainage. LAA occlusion may prevent thromboembolism from the LAA, yet may not completely protect AF patients from stroke as the device does not treat the underlying risks for atherothrombosis in AF patients (72).

The limitations of VKA have led to the development of new oral anticoagulants for treatment of AF (73, 74). Evidence on the use of two new oral direct thrombin inhibitors, dabigatran and AZD0837, for treatment of AF has recently been published. The Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial compared dabigatran with dose-adjusted warfarin in patients with AF (75). Stroke and systemic embolisation were sig-

### Table 1: The CHA2DS2-VASc score for thromboembolic risk in non-valvular atrial fibrillation. Reproduced from Lip (Thromb Haemost 2010; 103: 683–685).

<table>
<thead>
<tr>
<th>Stroke risk factors</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Aged ≥75 years</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/TE</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease [prior MI, PAD, or aortic plaque]</td>
<td>1</td>
</tr>
<tr>
<td>Aged 65–74 years</td>
<td>1</td>
</tr>
<tr>
<td>Sex category [i.e. female gender]</td>
<td>1</td>
</tr>
</tbody>
</table>

LV, left ventricular; PAD, peripheral artery disease; TE, thromboembolism outside the brain; TIA, transient ischaemic attack.
significantly lower with 150 mg of dabigatran twice daily compared with warfarin, while major bleeding was similar between the two groups. A lower dose of dabigatran (110 mg twice daily) was non-inferior to warfarin for rates of stroke and systemic embolisation. The risk of major bleeding decreased by 20% with 110 mg twice daily of dabigatran (2.7%) versus warfarin (3.4%), while rates of intracranial haemorrhage were significantly lower with both dosages of dabigatran compared with warfarin. MI rates were slightly higher in patients on both dosages of dabigatran compared with warfarin, which suggests that VKA have better protection against MI. Higher rates of discontinuation occurred with dabigatran, which was driven by gastrointestinal side effects, mainly dyspepsia. Dabigatran was also studied in a phase II Dose Finding Study for Dabigatran Etxelate in Patients with Acute Coronary Syndrome (RE-DEEM) study in ACS which added different dosages of dabigatran or placebo to aspirin and clopidogrel following ACS (76). Rates of major bleeding were similar between all groups, while minor bleeding increased in a dose-dependent manner for dabigatran. The ease of use and potential for improved efficacy with similar safety profiles makes dabigatran a potential alternative to warfarin for the treatment of AF in the future.

Two recent phase II studies were published on AZD0837 (77, 78). Both trials compared the safety profiles of several different dosages of AZD0837 with dose-adjusted warfarin. No differences occurred in stroke or major bleeding between the various dosages of AZD0837 and warfarin (77, 78). Dose-dependent increases in gastrointestinal side effects, mainly nausea and diarrhea, led to increases in drug discontinuation with AZD0837 (77, 78). The phase III AZD0837 Compared to Warfarin for the Prevention of Stroke and Systemic Embolic Events in Atrial Fibrillation (ASSURE) trial had been planned to study the efficacy of AZD0837 (74).

Several factor Xa inhibitors are currently under development for treatment of AF (74). Apixaban is currently being studied in two phase III clinical trials for stroke prevention. The Apixaban for the Prevention of Stroke in Subjects With Atrial Fibrillation (ARISTOTLE) trial is comparing apixaban with dose-adjusted warfarin in 15,000 AF patients, while the Apixaban Versus Acetylsalicylic Acid (ASA) to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial will compare apixaban with aspirin in VKA intolerant AF patients (79, 80). Recently, the AVERROES trial was stopped early for benefit, but the results have not been published.

In the phase II Apixaban for Prevention of Acute Ischemic Events (APRAISE) – 1 trial, a trend towards reduced ischaemic events in ACS patients was found in patients receiving apixaban compared with placebo, while a dose-dependent increase in major bleeding occurred with apixaban (81). The phase III APRAISE-2 trial is underway and will assess if apixaban reduces ischaemic events following ACS (82). Edoxaban is currently being studied in the phase III Global Study to Assess the Safety and Effectiveness of DU-176b versus Standard Practice of Dosing With Warfarin in Patients With Atrial Fibrillation (ENGAGE-TIMI-48) trial which will randomise

<table>
<thead>
<tr>
<th>Haemorrhagic risk</th>
<th>Clinical setting</th>
<th>Stent implanted</th>
<th>Recommendations</th>
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<tbody>
<tr>
<td>Low or intermediate</td>
<td>Elective</td>
<td>Bare metal</td>
<td>1 month: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day + gastric protection</td>
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<td></td>
<td></td>
<td></td>
<td>Lifelong: warfarin (2.0–3.0) alone.</td>
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<tr>
<td></td>
<td>Elective</td>
<td>Drug eluting</td>
<td>3 (olimus group) to 6 (paclitaxel) months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day* (or aspirin ≤100 mg/day)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Lifelong: warfarin (2.0–3.0) alone.</td>
</tr>
<tr>
<td>ACS</td>
<td>Bare metal/drug eluting</td>
<td>6 months: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day</td>
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<td>up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day* (or aspirin ≤100 mg/day)</td>
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<td></td>
<td></td>
<td></td>
<td>Lifelong: warfarin (2.0–3.0) alone.</td>
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<tr>
<td>High</td>
<td>Elective</td>
<td>Bare metal#</td>
<td>2 to 4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lifelong: warfarin (2.0–3.0) alone.</td>
</tr>
<tr>
<td>ACS</td>
<td>Bare metal#</td>
<td>4 weeks: triple therapy of warfarin (INR 2.0–2.5) + aspirin ≤100 mg/day + clopidogrel 75 mg/day</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>up to 12th month: combination of warfarin (INR 2.0–2.5) + clopidogrel 75 mg/day* (or aspirin ≤100 mg/day)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Lifelong: warfarin (2.0–3.0) alone.</td>
</tr>
</tbody>
</table>

*Combination of warfarin (INR 2.0–3.0) + aspirin ≤100 mg/day (with PPI, if indicated) may be considered as an alternative. #Drug-eluting stents should be avoided. INR, international normalized ratio; PPI, proton pump inhibitor; ACS, acute coronary syndrome.

Table 2: Recommendations for antithrombotic therapy in atrial fibrillation patients treated with vitamin K antagonists who undergo percutaneous coronary intervention. Reproduced from Lip et al. (Thromb Haemost 2010; 103: 13–28).
16,500 patients to edoxaban or warfarin (83). Rivaroxaban is being studied in the phase III clinical trial (ROCKET-AF) against warfarin for the prevention of thromboembolism in AF (84). In the phase II Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin With or Without Thienopyridine Therapy in Subjects With Acute Coronary Syndrome (ATLAS ACS-TIMI 46) trial, rates of death, MI, or stroke were lower in ACS patients receiving rivaroxaban added to aspirin or aspirin plus clopidogrel compared with placebo (85). The phase III ATLAS ACS 2-TIMI 51 trial is ongoing and will assess the efficacy of rivaroxaban versus placebo in 16,000 ACS patients (86). TAK-442 is being studied in a phase 2, Double-blind, Randomized, Placebo-controlled Study of the Safety and Efficacy of TAK-442 in Subjects With Acute Coronary Syndromes (AXIOM-ACS) (87). The emerging oral factor Xa inhibitors may offer clinicians additional options for treatment of AF and/or atherothrombosis (88).

Atherothrombosis and AF are prevalent diseases that co-exist in a large number of patients and share similar mechanisms of pathogenesis. The overlap of risk factors that lead to development of both diseases offers an opportunity for primary and secondary prevention. It is essential that clinicians accurately assess the risk of stroke and bleeding in patients with AF and not withhold VKA in patients who may benefit from its use. Dual antiplatelet therapy may be considered in high risk patients who cannot tolerate VKA. Intermediate and low risk patients may be assessed using the CHA2DS2VASc risk schema. Patients who require VKA for AF and develop ACS and/or undergo PCI should receive triple therapy for a period of time determined by their bleeding risk, stent type, and development of ACS and/or undergo PCI should receive triple therapy for a period of time determined by their bleeding risk, stent type, and PCI setting (Table 2). Newer anticoagulants for treatment of AF and atherothrombosis are on the horizon and hopefully will provide clinicians with an effective alternative to VKA for many patient types.

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