Managing Antithrombotic Therapy in Patients With Both Atrial Fibrillation and Coronary Heart Disease

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ABSTRACT

Purpose: Atrial fibrillation (AF) and coronary heart disease (CHD) commonly occur together. Previous consensus guidelines were published before the wide availability of novel oral anticoagulants (NOACs) and newer $P2Y_{12}$ antiplatelet agents. We examine recent evidence to guide management in 3 categories of patients with AF and CHD: patients with stable CHD, nonstented patients with recent acute coronary syndrome, and patients with a coronary stent requiring dual-antiplatelet therapy.

Methods: We conducted a literature search by evaluation of PubMed and other data sources including international meeting reports. We critically reviewed recent clinical trial and relevant registry evidence to update European and US consensus documents.

Findings: Oral anticoagulation with warfarin or NOACs is required to prevent embolic stroke in AF, and antiplatelet therapy is insufficient for this purpose. Antiplatelet therapy using monotherapy with aspirin is the standard of care in stable CHD. Dual-antiplatelet therapy with aspirin and clopidogrel or a new $P2Y_{12}$ inhibitor (dual-antiplatelet therapy) is needed to reduce coronary events after an acute coronary syndrome or after percutaneous coronary intervention. Combinations of these agents increase the risk of bleeding, and limited clinical trial evidence suggests that withdrawal of aspirin may reduce bleeding without increasing coronary events.

Implications: Available clinical trials and registries provide remarkably little evidence to guide difficult clinical decision making in patients with combined AF and CHD. In patients on triple antithrombotic therapy with vitamin K antagonists, aspirin, and clopidogrel, a single clinical trial indicates that withdrawal of aspirin may reduce bleeding risk without increasing the risk of coronary thrombosis. It is unclear whether this evidence applies to combinations of NOACs and newer $P2Y_{12}$ inhibitors. Clinical trials of combinations of the newer antithrombotic agents are urgently needed to guide clinical care. (*Clin Ther*. 2014;36:1176–1181)

Key Words: aspirin, atrial fibrillation, coronary heart disease, $P2Y_{12}$ antiplatelet agents novel oral anticoagulants, warfarin.

BACKGROUND

Previous European[1] and US[2] consensus statements for managing patients with combined coronary heart disease (CHD) and atrial fibrillation (AF) were published before the wide availability of novel oral anticoagulants (NOACs) and newer $P2Y_{12}$ antiplatelet inhibitors. In this commentary, we highlight the lack of sound evidence to guide clinical decision making and the need for the rapid development of clinical trials to close the large gaps in evidence.

THE NEED FOR COMBINED ANTICOAGULATION AND ANTIPLATELET THERAPY IN AF AND CHD

In patients with AF, the significant risk of stroke and the need for anticoagulation in patients is now widely recognized.[3] Randomized trials of antiplatelet agents have shown only marginal benefit over placebo,[4] whereas trials of oral anticoagulation with vitamin K antagonists (VKAs) have been convincing.[5] Oral anticoagulation is now recommended in all guidelines for AF patients with a risk of stroke, as estimated from their CHA_2DS_2VASc score.[6,7]

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CHD is also widely recognized as an atherothrombotic disease, but the mechanisms of coronary thrombosis in CHD differ so markedly from those that cause left atrial thrombus in AF that different antithrombotic agents are necessary. Antiplatelet therapy with aspirin has been shown to reduce the 2-year risk of cardiovascular events in stable CHD[8] and is now recommended in all guidelines for patients with stable CHD[9,10] and after an acute coronary syndrome (ACS).[11–14] In most medical systems, aspirin is now used in nearly 100% of patients recovering from an ACS.[15,16] Clopidogrel as monotherapy in stable CHD has only marginal benefits over aspirin,[17] but the addition of clopidogrel to aspirin has been shown to be superior to aspirin alone in patients after percutaneous coronary intervention (PCI)[18] and after an acute coronary syndrome,[19] whether they received conservative therapy[20] or PCI.[21] As a result of these convincing trials, the use of dual-antiplatelet therapy (DAPT) is now recommended in all patients who have experienced an ACS[11–17] and after PCI.[22] The ideal duration of DAPT is yet to be clarified but longer use is being examined in the ongoing DAPT (Dual-Antiplatelet Therapy) study[23] and shorter use in the ISAR-SAFE (Safety and Efficacy of Six Months Dual Antiplatelet Therapy After Drug-Eluting Stenting) study.[24]

The need to combine anticoagulation and antiplatelet therapy in patients with AF and CHD increases the risk of bleeding, which adversely influences prognosis.[25] Although bleeding risk scores such as HAS-BLED[26] (Hypertension, Abnormal renal/liver function, Stroke, Bleeding history or predisposition, Labile international normalized ratio, Elderly (>65 years), Drugs/alcohol concomitantly) can predict bleeding risk in AF,[27] their use has not been demonstrated in practice to reduce the risk of bleeding.

Clinical decision making in patients with concomitant CHD and AF has become more complex with the introduction to practice of NOACs including dabigatran,[28] rivaroxaban,[29] and apixaban,[30] which are more effective and easier to use than warfarin or other VKAs. Similar results were recently reported with edoxaban.[31] A recent meta-analysis showed the superiority of NOACs over warfarin with lower rates of stroke or systemic embolic events and half the rate of hemorrhagic stroke, significantly reduced all-cause mortality with a marginally significant increase in gastrointestinal bleeding.[32] The use of NOACs is recommended for nonvalvular AF in recent US and European guidelines.[6,7] The availability of new antiplatelet $P2Y_{12}$ inhibitors such as prasugel[33] and ticagrelor,[34] which have been shown to be more effective than clopidogrel but with higher bleeding risks, are also now recommended in recent guideline updates for ACSs[11–17] and add further complexity.

An overview of the evidence to guide the management of patients with stable CHD, nonstented patients with recent ACS, and patients with a coronary stent requiring dual-antiplatelet therapy shows significant deficits.

PATIENTS WITH STABLE CHD AND AF

All recent guidelines recommend that patients with AF and a risk of stroke with a CHA_2DS_2VASc score of ≥ 1 should be treated with oral anticoagulants (OACs),[6,7] and that patients with stable CHD should be treated with aspirin.[9,10] It is not possible to substitute aspirin and clopidogrel for warfarin in to prevent stroke.[31] Although patients with stable CHD and AF and a with low risk of stroke based on their CHA_2DS_2VASc score can be managed with aspirin alone, guidelines-directed therapy will result in almost all patients with CHD and AF being considered for triple antithrombotic therapy with 2 antiplatelet agents and an OAC. The anticipated increase in risk of bleeding when aspirin or clopidogrel are added to VKAs has been confirmed in large registry studies.[35]

Although there is evidence of a benefit of warfarin in CHD,[36] the finding of a marginally significant increase in myocardial infarction with the higher dose level of dabigatran (150 mg twice daily) in the RELY (Randomized Evaluation of Long-term Anticoagulation Therapy), the first NOAC trial, caused some initial concern.[32] It is reassuring that the most recent meta-analysis has shown no increase in myocardial infarction (relative risk = 0.97; 95% CI, 0.78–1.2) when all trials of NOACs versus warfarin are considered.[35] Current data to estimate the antithrombotic benefits and bleeding risks of the combinations of NOACs in combination with aspirin are limited to nonrandomized post hoc observations from within the randomized trials; they confirm a moderate increase in the risk of bleeding with the combination.[37,38] The lack of reliable randomized trial evidence to guide therapy in this group of patients is concerning.

NONSTENTED POST-ACS PATIENTS WITH AF

Although coronary intervention is regarded as the most effective treatment in ACSs, many patients experiencing an ACS will be managed conservatively