Misperceptions of aspirin efficacy and safety may perpetuate anticoagulant underutilization in atrial fibrillation

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The general public has been conditioned over many years to accept aspirin as an effective, safe, and inexpensive remedy for heart attacks and for primary and secondary prevention of cardiovascular events. In most countries aspirin was available as an over-the-counter remedy well before its widespread use in cardiovascular disease, which probably contributed to its widespread acceptability. Moreover, many physicians took part in the physicians health study,1 a pivotal study of primary prevention in cardiovascular disease, originally promoted as showing that aspirin reduced non-fatal myocardial infarction, but without emphasis of the increase in intracranial haemorrhage and unchanged mortality in this essentially neutral study.

In non-valvular atrial fibrillation (AF), aspirin has for a number of years been recommended as thrombo-prophylaxis for those not considered at high risk (see Table 1, e.g. CHADS2 score <2).6 Unfortunately, the implied benefit of guideline approbation probably led to widespread use of aspirin as the ‘easy’, or ‘soft’ option in those at higher stroke risk with either real or perceived contra-indications to Vitamin K antagonist (VKA, e.g. warfarin). This could be the result of differences in perception among physicians and patients of the risks of stroke vs. bleeding3,4 and also the misperception that aspirin is somewhat effective in stroke prevention in this setting and has lower bleeding risk. Another possible contributory factor may be an exaggerated estimate of VKA-associated bleeding, feared by physicians who do not see the strokes prevented, but do see the bleeds. Coupled with this is the issue that VKA therapy is hard to manage, and appears to be universally disliked by physicians, patients, the media, and industry. Perhaps the connotation with ‘rat poison’ has had a lingering impact. The limitations of VKA therapy are well known,5 but in randomized trials VKAs reduce rates of stroke and systemic embolism by 64% and death by 26%,6 with similar results noted in clinical practice settings.7,8 Commencing a VKA requires a detailed patient consultation, a comprehensive discussion of the risks and benefits, and overcoming perceptions and misperceptions of VKAs. While these issues may be less with Non-VKA OAC (NOACs), the fear of anticoagulant-related bleeding still remains a concern.

Convincing a patient to take an OAC is made even more difficult by a largely uninformed public, with a relative lack of awareness about AF and its association with stroke. Thus it is not surprising that over half of those with known AF are unaware or deny that they are at increased risk of stroke.9 In one study in which AF was detected during a screening programme in community pharmacies,10 44% of those with AF known to their physician were unaware of the diagnosis, even though most were taking warfarin.

For all the above reasons, the prescription of aspirin for AF may be a default position or even a ‘soft option’ for a physician faced with giving advice to the patient about thrombo-prophylaxis, and this may serve to perpetuate the seemingly intractable evidence-practice gap. In many surveys over the past 10–15 years, oral anticoagulants are prescribed to only 50–73% of those eligible on the basis of guideline recommendation, with a high proportion of the remainder on aspirin.11–13 The consequences of the underutilization of OAC are documented in the neurology literature reviewing incident strokes. The Adelaide Stroke Study reported in 201314 that AF-related strokes now constitute almost one-third of all strokes, and only 27% of those with AF known prior to stroke were taking warfarin, while a significant proportion of the remaining two-thirds were on aspirin (all with CHADS2 scores of ≥2). In previous studies of AF-related strokes in which AF was known prior to stroke, aspirin was being taken by half of those not on warfarin.15

Aspirin is now felt to be neither effective nor safe for thrombo-prophylaxis for stroke.16,17 When aspirin is compared with placebo/ control, there is a non-significant 19% effect of aspirin on stroke reduction, and mortality.6 The modest effect was driven by the one single positive trial, the Stroke Prevention in Atrial Fibrillation (SPAF-1),18 which reported a 42% reduction in stroke using aspirin 325 mg/day compared to control. This trial had major internal heterogeneity for the aspirin effect between the anticoagulation-eligible

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The opinions expressed in this article are not necessarily those of the Editors of the European Heart Journal or of the European Society of Cardiology.

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and ineligible subgroups, in which aspirin reduced stroke compared with placebo by 94 and 8%, respectively. Also, aspirin did not reduce strokes in those aged >75, nor did it prevent severe strokes and was used in a dose of 325 mg/day. These issues were highlighted in the most recent 2014 AHA/ACC/HRS guidelines.19

In the Birmingham Atrial Fibrillation Treatment of the Aged Study (BAFTA trial),26 aspirin had similar risk of major bleeding and intracranial haemorrhage to warfarin. Similarly, in the AVERROES study,21 patients with a mean age of 70 deemed unsuitable for VKA but at increased risk of stroke were randomized to either aspirin or apixaban, and the study was stopped early because of superior efficacy for apixaban, and no difference in major haemorrhage or intracranial bleeding. However, it is possible that aspirin may reduce less disabling non-cardioembolic strokes in AF.22 Thus, it has been practice to give aspirin for vascular prevention particularly in patients with increased risk, e.g. diabetes or peripheral artery disease, though even here, the results of recent trials have been disappointing.23

This lack of efficacy and safety in randomized, controlled studies has been confirmed recently by very large epidemiological studies from national registries,24,25 and the lack of a net clinical benefit of aspirin at any clinical risk stratum is important additional information. Similarly, an individual patient meta-analysis26 showed that aspirin efficacy in stroke prevention diminished as the age of patients increased, pari-passu with an increase in absolute risk of stroke, while the risk of bleeding did not diminish, so the net clinical benefit was not positive for aspirin in older subjects, in contradistinction to OAC. Taken in totality, this body of evidence has resulted in aspirin being no longer included in the new ESC,16 Asia-Pacific, and NICE guidelines21 (Table 1). While the recent 2014 US AHA/ACC/HRS major guideline update19 reduced the range of indications for aspirin, it still includes a recommendation for use in those with a low CHA2DS2-VASc score as a potential alternative to VKA (Table 1). Current 2012 ESC guidelines (Table 1) do state that the use of antiplatelet therapy should be considered where patients ‘refuse’ any form of oral anticoagulant, preferably with aspirin-clopidogrel, or less effectively, aspirin monotherapy.16

Of course these guideline recommendations do not preclude the use of aspirin or other antiplatelet agents alone or in addition to OAC for other reasons such as acute coronary syndromes or percutaneous coronary intervention with stents, where additional antiplatelet therapy will be required and is fully justified. However, in patients with stable coronary artery disease, a recent study showed that addition of aspirin to OAC increased bleeding risk without preventing cardiovascular events,27 raising questions about the role of adding aspirin when OACs are indicated in patients with coronary disease.28 And in a contemporary AF registry, just over a third on OAC were also

| Table 1 | AF guideline recommendations on aspirin |
| Guideline | CHADS2 = 0 | CHADS2 = 1 | CHADS2 ≥ 2 |
| AHA/ACC/ESC 2006 | No Rx if lone < 60 ASA or OAC if Fem or age 65–74 | OAC or ASA | OAC or ASA |
| Japan JCS JWG 2010 | No Rx | OAC | OAC |
| ACCP 2012 | No Rx unless pt choice, then ASA or ASA + C | ASA + C if unsuitable for OAC other than bleeding | ASA + C if unsuitable for OAC other than bleeding |
| CCS 2012 | No Rx, unless Fem or Vasc then ASA, OAC or ASA if Fem + Vasc age 65–74 | OAC (a reasonable alternative) | OAC |
| *ESC 2010 | No Rx preferred to ASA | OAC, preferred, or ASA | OAC |
| *ESC 2012 | No Rx (I B) | *OAC (I Ia) | *OAC (I A) |
| APHRS 2013 | No Rx | OAC | OAC |
| Japan JCS JWG 2014 | No Rx (Iib A) | No Rx or OAC or ASA (Iib C) | OAC |
| *NICE 2014 | No Rx | *OAC | *OAC |
| CCS 2014 | No Rx | OAC—take bleeding risk into account | OAC—modify bleeding risk factors |
| CHADS2 VASc = 0 | | | |
| CHADS2 VASc = 1 | | | |
| CHADS2 VASc ≥ 2 | | | |

AHA, American Heart Association; ACC, American College of Cardiology; ESC, European Society of Cardiology; Japan JCS JWG, Japanese Circulation Society Joint Working Groups for the Guidelines for Pharmacotherapy of Atrial Fibrillation; ACCP, American College of Chest Physicians; CCS, Canadian Cardiovascular Society; APHRS, Asia-Pacific Heart Rhythm Society; NICE, National Institute for Health and Care Excellence (UK); Rx, treatment; pt, patient; Fem, Female gender; Vasc, Vascular disease; ASA, aspirin generally 75–325 mg/day; ASA + C, Aspirin + Clopidogrel; OAC, oral anticoagulant (either Vitamin K antagonist or non-Vitamin K antagonist [NOAC]); C/I, contraindication.

*ESC recommended using CHA2DS2-VASc to stratify CHADS2 < 2.
Consider ASA + C or ASA if OAC not tolerated (unrelated to bleeding) or patient refuses OAC.
Reasonable to omit Rx for CHA2DS2 VASc = 0, caveat on ASA for AF based on heterogeneity of results in SPAF 1, ineffective in elderly, and unproven in low risk.
Antiplatelets not recommended as first line therapy. Only considered when anticoagulation cannot be used.
Do not offer ASA monotherapy solely for stroke prevention.
Modified/simplified the CHADS2/CHA2DS2-VASc scores so that everyone over 65 recommended for anticoagulation whether male or female. Coronary, aortic or peripheral vascular disease below age 65 does not contribute to recommending OAC as in CHA2DS2; VASc, but does get a recommendation for ASA 81 mg/day.
prescribed aspirin, and in over a third of these patients on combined therapy, there was no history of atherosclerotic disease.\(^2\) These patients were therefore exposed to the added risk of bleeding from the combination of aspirin and OAC without any reduction in thromboembolic risk.

 Particularly in the elderly, who do not derive a net clinical benefit from aspirin alone,\(^24\,26\) in the absence of other indications, no treatment may be preferable to aspirin alone for those who refuse OAC. Of course, in all patients, a full discussion about AF and its association with stroke and the risks and benefits of treatments is required, and a final decision on anti-thrombotic therapy should take into account patient values and preferences, as emphasized in guidelines.\(^17,\,19,\,30\)

The adoption in the guidelines of CHA\(_2\)DS\(_2\) VASc score for risk stratification in AF has been an advance, with the ability to initially define ‘truly low risk’ patients who need neither anticoagulant nor aspirin. Subsequent to that step, effective stroke prevention (whether as a NOAC or well-controlled VKA, with TTR \(\geq 70\%\)) can be offered for those with \(\geq 1\) additional stroke risk factors, but it would seem prudent to discourage the prescription of aspirin. Given that the large majority of patients with AF have a high enough CHA\(_2\)DS\(_2\) VASc score to justify OAC prescription, this would translate to large global cost burdens if NOACs were the most usual prescription. Nevertheless, a number of economic analyses have indicated that this drug class may be cost-effective,\(^31,\,32\) and it is likely that with additional NOAC drugs on the market and with the passage of time, drug costs will reduce. For all with AF, aggressive risk factor control should be instituted since in the majority, the disease may be the consequence of many of the same risk factors which determine atherosclerotic vascular disease as opposed to a primary arrhythmic aetiology.

To reduce the evidence-practice gap and to remove the ‘soft option’ of prescribing a drug that is neither effective nor safe, it may be necessary to completely exclude aspirin for stroke prevention in AF (without comorbid conditions requiring aspirin) from all AF guidelines, as has been done by the UK National Institute for Health and Care Excellence (NICE).\(^17\) Strong statements of inefficacy would be even more helpful to reduce the temptation to prescribe aspirin. The FDA seems to have bitten the bullet in this space recently, making a strong statement that aspirin not be used for primary prevention of cardiovascular disease. Perhaps it is opportune to adopt the same approach for stroke prevention in AF: the June 2014 NICE guidelines\(^17\) now state ‘Do not offer aspirin monotherapy solely for stroke prevention to people with atrial fibrillation’.

**Summary**

- Evidence of benefit of aspirin for stroke prevention in AF is insubstantial.
- There is little or no reduction in major bleeding using aspirin compared with oral anticoagulant (OAC).
- Underutilization of OAC for AF may be perpetuated by aspirin remaining a soft option for physicians, based on misperceptions of both safety and efficacy of aspirin.
- Effective stroke prevention for AF essentially means oral anticoagulant, either NOAC or well-controlled VKA OAC (time in therapeutic range \(\geq 70\%\)).

**Authors’ contributions**

All authors contributed to the concept and revised the manuscript for important intellectual content. S.B.F. drafted the manuscript.

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