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# Current Evidence for the Use of Aspirin in Patients with Atrial Fibrillation and a $CHA_2DS_2$-Vasc=1

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## Abstract

Aspirin was once the mainstay of stroke prevention in patients with atrial fibrillation. Its popularity was based on the results of the SPAF and PATAF trials, which showed the low risks of this therapy and the many benefits it had to offer in terms of embolic complications prevention. Nevertheless, aspirin has lost popularity in atrial fibrillation since the CHADS, $CHA_2DS_2$-VASc and HASBLED scoring systems were first introduced. These scoring systems showed a different perspective, which highlighted that thromboembolic risk varied among individuals and that a generalization on antiplatelet therapy for atrial fibrillation was not effective. These caveats gave support to additional treatments based on anticoagulation, including warfarin and direct oral anticoagulants. These treatments gained popularity based on the superiority over warfarin, first described on the BAFTA trial, which nominated the warfarin as the standard of care for atrial fibrillation thromboembolic prevention. Since then, direct anticoagulation therapies have gained popularity based on the results of the ARISTOTLE (apixaban), RE-LY (dabigatran), ROCKET-AF (rivaroxaban), ENGAGE TIMI 48 AF (edoxaban) trials. However, the $CHA_2DS_2$-VASc score was generous with aspirin, since it opened a possible recommendation for low $CHA_2DS_2$-VASc scores (0-1). This comprehensive literature review is intended to discuss the arguments behind this last statement and to show the available evidence in favor of and against aspirin for non-valvular atrial fibrillation in low thromboembolic risk patients.

**Keywords:** Atrial fibrillation, Anticoagulation therapies, Cardiovascular health.

**Abbreviations:** VKAs-Vitamin K Antagonists, DOACs-Direct Oral Anticoagulants, SPAF-Stroke Prevention in Atrial Fibrillation, PATAF-Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation. RE-LY- Randomized Evaluation of Long Term Anticoagulant Therapy.

## Background

Aspirin was once the mainstay of stroke prevention in atrial fibrillation. However, the development of Vitamin K Antagonists (VKAs) and the evolution and availability of Direct Oral Anticoagulants (DOACs), has left aspirin (ASA) therapy by the wayside, based on the results of the BAFTA, ARISTOTLE, RE-LY and ROCKET-AF trials. Both ASA as monotherapy and ASA as dual-antiplatelet therapy are no longer recommended as first line stroke prevention in patients with $CHA_2DS_2$-VASc $\geq$ 2 [1,2]. Exceptions in the guidelines exist only in certain clinical settings, particularly in those with $CHA_2DS_2$-VASc score=1 [3]. Besides primary outcomes, including endpoints such as cardiovascular death and mortality, VKAs have additionally shown no increased risk of bleeding compared to ASA, especially among the moderate to high-risk sub-group of atrial fibrillation patients [4,5,6-9].

Regarding ASA use for cardiovascular benefit, ASA is ineffective at increasing disability-free survival or at decreasing mortality among healthy elderly adults without clear risk factors [10,11]. This calls into question the popular assumption that the benefits of ASA therapy for cardiovascular health of the general population outweigh negative side effects. Therefore, ASA use overall should be carefully assessed, particularly in patients with atrial fibrillation.

Interestingly, even more than a decade after the first generation of studies showing superiority of VKAs for stroke prevention in atrial fibrillation, ASA continues to be prescribed to patients with $CHADS_2$ scores of greater than or equal to 2 despite overwhelming evidence against, based on the results of the PINNACLE trial, which involved 210,380 patients with high $CHADS_2$ scores [12]. In fact, in 2012 the European Society of Cardiology recommended ASA for patients who refused anticoagulation, consistent with evidence at the time that ASA did have benefit over no therapy for this patient population [13]. Regarding specifically lower risk patients, the 2014 American College of Cardiology/American Heart Association guidelines recommend "no antithrombotic therapy or treatment with an oral anticoagulant or aspirin" for non-valvular atrial fibrillation with $CHA_2DS_2$-VASc=1 [2]. With a spotlight on ASA this year in the literature, it is appropriate to re-evaluate ASA as alternative therapy to VKA or DOAC for patients

| Clinical Studies/Author | Type of study | Year of publication | Population | Comparison | Primary end-points | $CHA_2DS_2$-VASc |
|---|---|---|---|---|---|---|
| SPAF trial (2) | Randomized Controlled Trial | 1991 | 1330 | Aspirin vs. placebo | Ischemic stroke or systemic embolism | - |
| Hsu JC et al. (3) | Nationwide registry | 2016 | 210,380 | Aspirin vs. oral anticoagulant | - | ≥ 2 |
| PATAF trial (4) | Randomized Controlled Trial | 1999 | 729 | Aspirin vs. Warfarin (low intensity and high intensity, defined by INR range) | Stroke, systemic embolism, major hemorrhage, or vascular death | - |
| Lip et al. (5) | Cohort Study | 2015 | 39,400 | Aspirin vs. Warfarin vs. no treatment | Stroke and bleeding | 0-1 |
| Forslund, et al (6) | Cohort Study | 2014 | 41,810 | Aspirin vs. Warfarin vs. no treatment | Ischemic stroke, bleeding, or death | 0-1 |
| Olesen JB et al. (7) | Cohort Study | 2011 | 132,372 | ASA, VKA+ASA, and no treatment, respectively, compared to VKA | Stroke and thromboembolism | ≥ 0 and ≥ 1 |
| BAFTA trial (8) | Randomized Controlled Trial | 2007 | 973 | Aspirin vs. Warfarin | Fatal or disabling stroke | - |

**Table 1:** Most remarkable clinical studies studying aspirin use for thromboembolic prevention in atrial fibrillation.

with atrial fibrillation. Specifically, evidence should be evaluated behind the benefit of ASA vs VKA or DOAC vs no therapy for patients with non-valvular atrial fibrillation and $CHA_2DS_2$-VASc=0 or 1 (**Table 1**).

## The Evidence

The evidence for ASA for stroke prevention in patients with atrial fibrillation with low risk of stroke (CHADSVASC<2) stems from the Stroke Prevention in Atrial Fibrillation (SPAF) trial, published in 1991, which followed patients for a mean of 1.3 years and found a 42% reduction in ischemic stroke and embolism, as well as decreased mortality, with ASA compared to placebo. Nevertheless, the SPAF trial also looked at warfarin outcomes and found that warfarin had a superior reduction of primary events or death compared to aspirin, 58% (p=0.01) vs. 32% (p=0.02). The risk of significant bleeding was 1.5% vs. 1.4%, respectively [2]. Based on this early study, ASA appeared to be a safe and effective (albeit less so) alternative to VKAs.

Nevertheless, this study was performed in an era where CHADSVASC had not been described before, and generalization among different thrombotic risks and lack of standardized criteria was evident. Even though the SPAF trial gave a hope for aspirin, evidence has been slowly proving it differently. In 2000, the Primary Prevention of Arterial Thromboembolism in Nonrheumatic Atrial Fibrillation (PATAF) trial supported the popular opinion that ASA was an accessible and inexpensive therapy for those at low risk of stroke or embolism, with a decreased risk of bleeding compared to anticoagulation and a low drug-interaction profile. It should be noted, however, that the PATAF trial was a relatively small study of a uniform, elderly population in the Netherlands [14].

More recently, a meta-analysis published in 2007 supported these early findings. Hart et al. concluded that ASA did reduce risk of stroke and embolism in patients with atrial fibrillation by 20% compared to placebo, in addition to a similar decrease in mortality. Nonetheless, warfarin was found to reduce stroke by 60%. Of note, this meta-analysis included patients with both low and high $CHA_2DS_2$-VASc values. Sub-group analysis was not performed, so conclusions for low vs high $CHA_2DS_2$-VASc values were not assessed. Most studies included in this meta-analysis specifically targeted primary prevention [15]. In 2011, a large study in Denmark performed sub-group analyses of VKA vs ASA vs placebo by $CHADS_2$ and $CHA_2DS_2$-VASc scores. The results showed no net clinical benefit of ASA in patients with a low risk of stroke or embolism (CHADS ≥ 0 or $CHA_2DS_2$-VASc ≥ 1).

This study also found that ASA did not decrease risk of bleeding compared to warfarin. Specifically, this study supported "a neutral or positive net clinical effect" of warfarin over ASA in low risk patients with atrial fibrillation, which contradicts the prior assumption that as risk decreased, the efficacy of ASA increased enough to become clinically indicated [16]. This study was the cornerstone for developing the most recent studies that advocate for anticoagulation over antiplatelet in $CHA_2DS_2$-VASc ≥ 1. Numerous other studies throughout the last several decades also support either similar bleeding risk or insignificant difference in bleeding risk between ASA and VKA or between ASA and DOACs [4,5,6-8].

A Swedish study in 2014 also evaluated the risk of stroke or embolism in atrial fibrillation. Their findings were consistent with a low support of ASA in low risk patients, finding that patients with $CHA_2DS_2$-VASc scores of 0-1 had a 1.0-1.2% one-year risk of ischemic stroke with ASA therapy compared to a 0.1-0.2% risk without any treatment, which suggests that ASA likely has no clinical benefit compared to no therapy for patients with low risk of stroke or embolism [17]. It should be noted that both the aforementioned Danish and this Swedish study were regional studies with presumably homogenous populations, thus lacking external validity in other populations and ethnicities.

A recent study published in 2015 by Lip, et al. compared ASA to warfarin therapy for primary prevention of stroke or embolism in those with $CHA_2DS_2$-VASc scores of 0 or 1 [18]. They included a total of 39,400 patients, of which 10,475 were treated with VKAs; 5,353 were treated with ASA; and 23,572 were left untreated. Primary endpoints, including stroke, bleeding and death, were evaluated by both an intention-to-treat and Continuous Treatment analyses. The authors found that for those with a low risk of stroke or embolism, defined as $CHA_2DS_2$-VASc=0 for males and $CHA_2DS_2$-VASc=1 for females, the risk of stroke, bleeding, and death was truly low, and there was therefore no net clinical benefit of treatment with either VKA or ASA.

In those with one additional risk factor ($CHA_2DS_2$-VASc=1 for male and $CHA_2DS_2$-VASc=2 for female), ASA did not significantly reduce risk of stroke and was significantly associated with increased risk for bleeding, i.e., regardless of sex, ASA therapy does not prevent stroke in those with $CHA_2DS_2$-VASc=1, and furthermore does not prevent stroke in women with $CHA_2DS_2$-VASc=2. However, in untreated patients with one additional risk factor ($CHA_2DS_2$-VASc=1 for male and $CHA_2DS_2$-VASc=2 for female), 1-year stroke risk increased by 3.01-fold, bleeding by 2.35-fold and death by 3.12-fold. The authors also found that for those with one additional risk factor ($CHA_2DS_2$-VASc=1 for male and $CHA_2DS_2$-VASc=2 for female), there were reductions in stroke and death with VKAs compared to no treatment and with VKAs compared to ASA, without a significant increase in bleeding with VKA vs ASA [18] .

## Conclusion

In the last three decades, ASA therapy has repeatedly been found to be inferior to anticoagulation for preventing stroke in patients with non-valvular atrial fibrillation, even for those with low risk of embolism or stroke ($CHA_2DS_2$-VASc ≤ 1). Furthermore, ASA is not associated with decreased risk of bleeding compared to VKA. The net benefit of ASA therapy for these patients, therefore, does not have supporting evidence, and we conclude that patients with low $CHA_2DS_2$-VASc should not be offered ASA as a "safer" alternative to anticoagulation. Reasons to prescribe ASA in this patient population include availability, financial accessibility, and convenience, but these values are counterbalanced by similar bleeding risk to VKA and significantly decreased efficacy at preventing the primary outcome.

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