

Did we really need another comparison of warfarin with aspirin? An assessment of the BAFTA trial

Czy naprawdę było potrzebne kolejne porównanie warfaryny z kwasem acetylosalicylowym w prewencji udaru mózgu? Analiza badania BAFTA

Robert G. Hart

Department of Neurology, University of Texas Health Science Center, San Antonio, TX, USA

Even prior to the recent publication of the Birmingham Atrial Fibrillation Treatment in the Aged (BAFTA) study [1], the superiority of adjusted-dose warfarin over aspirin therapy for prevention of stroke in patients with atrial fibrillation was firmly established by relatively consistent results of eight randomized clinical trials [2]. By meta-analysis of 3647 participants in those 8 trials, all stroke was reduced by 38% (95% CI: 18–52) [2]. Did we really need another randomized trial comparing these two treatments?

Participants in these earlier trials generally have been younger (averaging about 70 years old) than atrial fibrillation patients commonly encountered in clinical practice (averaging in the late 70s and with a substantial fraction of octogenarians), and the efficacy and safety of adjusted-dose warfarin in the very elderly is less clear. Primary care physician investigators in the English Midlands undertook to address this issue, randomizing 973 atrial fibrillation patients aged 75 years or over (mean age = 81.5) to adjusted-dose warfarin (target international normalized ratio [INR] 2–3) vs. aspirin 75 mg/d given open-label [1]. Anticoagulation management was by the standard of UK general practices; 67% of INRs were within the therapeutic rate with median INR = 2.3 and mean INR = 2.4 during follow-up. Despite patient selection for trial participation, one-third of those assigned warfarin were not taking it after the mean follow-up of 2.7 years.

The total stroke rate was 5.0% per year on aspirin and reduced 46% by adjusted-dose warfarin (Tab.). Most surprisingly, major extracranial hemorrhages was low in those assigned to warfarin (1.4% per year) and even slightly lower than those assigned aspirin (1.6% per year). Of note, 40% had previously received warfarin prior to study entry, likely biasing toward lower bleeding rates than expected in warfarin-naïve patients. The investigators conclude “these data lend support

to the use of anticoagulation for all people over age 75 years who have atrial fibrillation, unless there are contraindications or the patient decides that the size of the benefit is not worth the inconvenience of treatment” [1]. While this is a sensible interpretation of the BAFTA study results, I have two caveats based on results of other studies.

Two other studies have reported that men over age 75 (but not women) without prior stroke/transient ischemic attack (TIA) have stroke rates averaging about 3% per year, making the number-needed-to-treat with warfarin for one year to prevent one stroke about 70 [3,4]. In contrast, the primary event rate among those assigned aspirin in the BAFTA study was not higher in women [1]. Men ≥ 75 years old but without hypertension, diabetes or prior stroke/TIA had a stroke rate of 1.6% per year (95% CI: 0.7–3.9) in the SPAF study [4], although the mean age of this cohort was likely lower than similar participants in the BAFTA study. In short, there may be atrial fibrillation patients age 75 year or older who have relatively low stroke rates if given aspirin, but these predictors must be independently confirmed before they can be applied clinically with confidence.

Based on the BAFTA study results, it appears that fears of anticoagulation in elderly atrial fibrillation are exaggerated. However a recently-reported by Hylek et al. [5] inception cohort (i.e. all warfarin-naïve) of 472 atrial fibrillation patients given warfarin (58% of INRs within the target INR range of 2–3) and followed for one year found a major hemorrhage rate of 13% per year of those ≥ 80 years old and 4.7% per year for younger patients! The rate of intracranial hemorrhage in the entire cohort was 2.5% per year (mean age = 77 years); the rate of major hemorrhage in the first 90 days was three times higher than in the subsequent 9 months. The most likely explanation for the difference in major hemorrhage rates seen in the BAFTA study (2% per year) vs. Hylek et al. (7.2% per year) was that first-year exposure in warfarin-naïve patients (the greatest risk for bleeding) made up only 22% of the BAFTA study data vs. 100% of Hylek et al. Another recent study reported a 10% annual rate of serious hemorrhage in atrial fibrillation patients over age 75 given warfarin [6].

So did we really need the BAFTA study? Yes! The important BAFTA study provides welcome reassurance about the

Correspondence to:

Professor Robert G. Hart, MD, Department of Neurology, University of Texas Health Science Center, 7703 Floyd Curl Drive MC 7883, San Antonio, TX, USA 78229-2900, phone: 210-592-0404, fax: 210-592-0552, e-mail: hartr@uthscsa.edu

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Table. Key results of the BAFTA study

| Outcome | Aspirin n = 485 (annualized rate) | Warfarin n = 488 (annualized rate) | RRR (p value) | NNT ^a |
|---|---|--|------------------|------------------|
| Primary outcome: fatal or disabling stroke, intracerebral hemorrhage or non-CNS arterial emboli | 48 (3.8%) | 24 (1.8%) | 52%; p = 0.003 | 50 |
| All strokes ^b | 62 (5.0%) | 35 (2.7%) | 46%; p = 0.002 | 43 |
| Ischemic strokes + unknowns | 56 (4.5%) | 27 (2.0%) | 56%; p <0.001 | 40 |
| Intracranial hemorrhages ^c | 6 (0.5%) | 8 (0.6) | – | – |
| Major extracranial hemorrhages | 20 (1.6%) | 18 (1.4%) | – | – |
| Myocardial infarctions | 15 | 15 | – | – |
| All-cause mortality | 108 (8.4%) | 107 (8.0%) | 5%; NS | |

^a Annualized rate

^b Includes ischemic, intracerebral hemorrhages, subdural hematomas, and unknown type

^c Includes subdural hematomas: two with warfarin, one with aspirin

CNS – central nervous system, NNT – number-needed-to-treat for one year with warfarin instead of aspirin to prevent one event, NS – not significant, RRR – relative risk reduction

efficacy and safety of adjusted-dose warfarin in very elderly patients with atrial fibrillation managed in a primary care setting (with the caveat of probably underestimating the early bleeding risk in warfarin-naïve patients). Meta-analysis of the BAFTA study with the previous eight trials shifts only slightly the overall relative risk reduction in all strokes by adjusted-dose warfarin over aspirin (39%; 95% CI: 27–49), but confidently extends this best estimate of efficacy to very elderly patients with atrial fibrillation.

Based on all available randomized trial evidence, adjusted-dose warfarin reduces stroke (ischemic and hemorrhagic together) by about 60% for patients with atrial fibrillation, while antiplatelet agents reduce stroke by about 20% (preventing mainly smaller, non-cardioembolic strokes) [2]. Compared with antiplatelet therapy, warfarin reduces stroke by about 40% [2]. For now, in my view, despite the risk of hemorrhage which is especially high during introduction of anticoagulation, it is safest to assume that all atrial fibrillation patients

aged 75 years or older (and especially women) have sufficient stroke risk to substantially benefit from anticoagulation. In general, high-risk atrial fibrillation patients, including all age 75 years or older, are best treated with adjusted-dose warfarin if it can be safely administered and is consistent with the patient's preference. The unmet need remains for antithrombotic agents that are more efficacious than aspirin and that are safer, more easily administered, and sustainable than adjusted-dose warfarin.

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From the Editor

Synopsis: Mant J, Hobbs FD, Fletcher K, et al. Murray E on behalf of the BAFTA investigators and the Midland Research Practices Network. Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial. *Lancet*. 2007; 370: 493-503.

In this randomized controlled trial of almost 1000 patients with persistent atrial fibrillation recruited from primary care it has been shown that during 2.7 year follow-up warfarin (with a target INR of 2.5, with an acceptable range 2–3) compared with aspirin (75 mg daily) reduced the risk of fatal or disabling stroke (RRR ~50%, NNT ~20) and did not increase significantly the risk of major bleeding.

Prepared by: *Wiktoria Leśniak, MD, PhD*

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