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'New' Oral Anticoagulant Stroke-Protection Benefits in AF Cut Across Subgroups in Meta-Analysis

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LONDON, UK — Collectively, four new oral anticoagulants (NOACs) protect against stroke or systemic embolism better than **warfarin** and compare favorably on safety in patients with atrial fibrillation (AF), concludes a meta-analysis[1] of four big randomized trials, all major showcases for the agents' potential value in AF.

"NOAC" in the current analysis meant four warfarin alternatives that are already available or seem headed for approval in AF: the direct thrombin inhibitor **dabigatran** (Pradaxa, Boehringer Ingelheim) and factor Xa inhibitors **rivaroxaban** (Xarelto, Bayer Pharma/Janssen Pharmaceuticals), **apixaban** (Eliquis, Pfizer/Bristol-Myers Squibb), and **edoxaban** (Lixiana, Daiichi-Sankyo).

"Although the percent reductions and statistical significance of benefit of new oral anticoagulants vary somewhat from trial to trial, the results of the meta-analysis indicate that the benefit of these new agents in reducing stroke, intracranial hemorrhage, and mortality are quite similar," according to lead author **Dr Christian T Ruff** (http://www.medscape.com/viewarticle/815251) (Brigham and Women's Hospital, Boston, MA).

In their matches with warfarin, the new agents conferred significant reductions in risk of stroke or systemic embolism, intracranial hemorrhage (ICH), and all-cause mortality; their major bleed risk trended lower. In contrast, the risk of gastrointestinal bleeding was greater on the NOACs.

"Our data demonstrate that the relative benefit and safety is consistent across a wide range of subjects, including vulnerable populations such as the elderly, patients with a prior stroke, and those with renal dysfunction," Ruff said to **heart*wire*** (http://www.medscape.com/cardiology/news) in an email. Also, "we showed that the reduction in

stroke and systemic embolism seen with the NOACs was not dependent on how well warfarin was managed. These agents are more effective than warfarin even in patients who have well-controlled INRs."

Anticoagulation effectiveness on warfarin did have an effect on NOAC safety outcomes, he noted. "There was even greater reduction in bleeding with the new oral anticoagulants compared with warfarin in patients who have difficulty maintaining a therapeutic INR."

Ruff et al's meta-analysis of the new agents' pivotal clinical trials, **RE-LY** (http://www.medscape.com/viewarticle/708133) , **ROCKET AF** (http://www.medscape.com/viewarticle/732524) , **ARISTOTLE** (http://www.medscape.com/viewarticle/748682) , and **ENGAGE AF–TIMI 48** (http://www.medscape.com/viewarticle/814639)**,** was published December 4, 2013 in the *Lancet*.

"Effective stroke prevention in patients with atrial fibrillation with more than one stroke risk factor means oral anticoagulation, whether delivered by use of a novel oral anticoagulant or well-controlled vitamin-K antagonists [such as warfarin] with high time in therapeutic range," write **Dr Torben Bjerregaard Larsen** (Aalborg University, Denmark) and **Dr Gregory YH Lip** (University of Birmingham, UK) in an accompanying editorial[2] ◊.

"Previously," they continue, "the only available anticoagulant was a vitamin-K antagonist, but clinicians now have a choice and can fit the drug to the patient and vice versa. With the availability of four novel oral anticoagulants, perhaps we are now spoiled for choice."

To **heart*wire*** , Ruff said he agrees "that warfarin will remain a legitimate option for stroke prevention in patients with atrial fibrillation. There are many patients in whom warfarin remains the only option, such as those with a mechanical heart valve or end-stage renal disease. Warfarin performed very well in all of these trials and remains an effective and affordable anticoagulant."

Still, added meta-analysis coauthor **Dr Robert P Giugliano** (Brigham and Women's Hospital) by email, "for atrial fibrillation, the NOACs should be preferred over warfarin, as they are clearly superior at reducing a variety of bleeding complications (including fatal bleeding and intracranial bleeding), lower mortality by 10%, and are much easier to use: no need for routine monitoring, no food-drug interactions, far fewer drug-drug interactions, no 'off-target' side effects. In patients with atrial fibrillation, it is really just cost that is the major issue for the NOACs."

Gruff and Giugliano are lead authors on the ENGAGE AF–TIMI 48 primary publication[3].

For the meta-analysis, they and their colleagues looked only at phase 3 NOAC-warfarin comparisons that reported both efficacy and safety outcomes; the four trials that turned up encompassed 42 411 patients who received a NOAC and 29 272 warfarin recipients. The trials' median follow-ups ranged from 1.8 years to 2.8 years.

The risk of stroke or systemic embolic events, the primary outcome of the analysis, fell by 19% on NOACs compared with warfarin ($p<0.0001$). Hemorrhagic strokes accounted for much of the reduction ($p<0.0001$), while the risk of ischemic stroke wasn't affected by NOAC use vs warfarin.

Relative Risk (95% CI) for Efficacy and Safety Outcomes, New Oral Anticoagulants* vs Warfarin, in Meta-analysis

End points	RR (95% CI)	p
Stroke or systemic embolic events	0.81 (0.73–0.91)	<0.0001
Hemorrhagic stroke	0.49, 0.38–0.64	<0.0001
Intracranial hemorrhage	0.48 (0.39–0.59)	<0.0001
Ischemic stroke	0.92 (0.83–1.02)	0.10
All-cause mortality	0.90 (0.85–0.95)	0.0003
MI	0.97 (0.78–1.20)	0.77
Major Bleeding	0.86 (0.73–1.00)	0.06
Gastrointestinal bleeding	1.25 (1.01–1.55)	0.04

*Dabigatran 150 mg twice daily; rivaroxaban 20 mg once daily; apixaban 5 mg twice daily; edoxaban 60 mg once daily

No significant differences in NOAC effects were seen for stroke or systemic embolism or for major bleeding, by age, sex, history of stroke or transient ischemic attack, history of diabetes, renal function, $CHADS_2$ score, or history of vitamin-K–antagonist therapy.

The stroke or systemic embolism risk didn't vary by each center's mean warfarin time in the therapeutic range. But when INR management on warfarin was subpar, NOACs were the most protective against major bleeding. That risk fell by 31% vs warfarin at centers where the mean warfarin time in the therapeutic range was <66%, but it dropped only 7% at centers where it was ≥66% (p=0.022 for interaction).

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