Registry Data Support NOACs for Single-Risk-Factor AF

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BIRMINGHAM, UK — A Danish nationwide cohort study of patients with atrial fibrillation (AF) and only a single non–sex-related risk factor for stroke shows no difference between novel oral anticoagulants (NOACs) and warfarin in preventing ischemic stroke[1].

In addition, bleeding events were significantly lower for apixaban (*Eliquis*, Bristol-Myers Squibb) and dabigatran (*Pradaxa*, Boehringer Ingelheim) but not rivaroxaban (*Xarelto*, Bayer/Janssen Pharmaceuticals), when compared with warfarin.

"The data provide added reassurance because the guidelines have often questioned what the evidence is for using NOACs in patients with a single stroke risk factor and the trials have had limited numbers of such patients," lead investigator Dr Gregory Lip (University of Birmingham, UK) told **theheart.org**|Medscape Cardiology.

European registries and the Loire Valley AF Project[2] already provide evidence of benefit for anticoagulation with warfarin in patients with one non–sex-related CHA_2DS_2-VASc risk factor, but the present 14,020-patient study is the largest to date, he said.

Nevertheless, Lip and colleagues report that falsification outcomes analyses did not falsify, indicating residual confounders may exist and "perhaps add bias toward NOACs."

The study was published June 14, 2017 in *JAMA Cardiology*.

The AF patients were drawn from Danish national registries, and all were new users of oral anticoagulation with either standard-dose NOACS (3272 dabigatran, 1604 rivaroxaban, and 1470 apixaban) or warfarin (7674). Roughly a third (36.7%) were women and an age of 65 to 74 years was the most common reason (59.3%) for receiving one point on the CHA_2DS_2-VASc score.

Inverse probability of treatment–weighted (IPTW) analyses were performed to address confounding by indication of treatment.

Within the first year, the primary effectiveness end point of ischemic stroke/systemic embolism occurred in 103 patients, with only three events of systemic embolism. Event rates ranged from 0.68 per 100 person-years with apixaban to 1.09 per 100 person-years with rivaroxaban; weighted event rates ranged between 0.65 (dabigatran) and 1.20 (rivaroxaban).

Any bleeding occurred in 157 patients during the first year, resulting in crude event rates ranging between 0.68 (apixaban) and 1.52 (warfarin) and weighted event rates between 0.57 (apixaban) and 1.53 (warfarin).

When compared with warfarin in propensity-weighted analyses, bleeding was significantly lower with apixaban and dabigatran (hazard ratios 0.35 and 0.48, respectively) but not with rivaroxaban (HR 0.84).

"The main argument for using NOACs in general is the higher safety and within the NOAC family, rivaroxaban is more and more on the outside," Prof Thomas Weiss (Sigmund Freud University, Vienna, Austria), who was not involved in the study, told **theheart.org**|Medscape Cardiology.

"We've seen in the real world that rivaroxaban tends to bleed more than the others; we don't know how or why, but it seems to be the case."

Weiss said apixaban and dabigatran are the two substances on the market with "the best real-world data at the moment, and edoxaban [*Savaysa*, Daiichi Sankyo] will establish itself as a third big player," but rivaroxaban will be slowly edged out "if these data continue to be consistent like they have been over the past 1 or 2 years."

Patients receiving any NOAC in the study had a lower risk of all-cause death compared with warfarin-treated patients, but this difference may be because of selective prescribing by physicians, Lip suggested.

Events at 1 Year for NOACs vs Warfarin*

End point	Hazard Ratio (95% CI)		
	Apixaban	**Dabigatran**	**Rivaroxaban**
Ischemic stroke/systolic embolism	1.01 (0.51–2.01)	0.81 (0.49–1.34)	1.46 (0.79–2.70)

Any bleeding	0.35 (0.17–0.72)	0.48 (0.30–0.77)	0.84 (0.49–1.44)
Death	0.47 (0.29–0.76)	0.59 (0.43–0.81)	0.52 (0.34–0.79)

*Propensity-weighted Cox hazard ratios at 1-year follow-up

Dr Jonathan Piccini (Duke Clinical Research Institute, Durham, NC) told **theheart.org**|Medscape Cardiology that the paper provides some reassurance in treating these lower-risk AF patients but that the failure to falsify is a key limitation.

"We know that there was residual confounding despite the fact they did adjusted analyses, which said plain and simple: comparing the apixaban, dabigatran, rivaroxaban, and warfarin groups is like comparing apples with oranges," he said.

Piccini added, "One thing that blew me away when I looked at the paper was the rates of antiplatelet use in the different groups were very different and ranged anywhere from 23% to 30% for aspirin, but if you look at the rates of vascular disease it was like 1% or 2% across the groups. We know that combining aspirin and an oral anticoagulant is something you don't want to do because it increases the risk of bleeding, so there's no reason the aspirin rate should be that high when the rate of vascular disease was in the single percentage points."

Weiss said it is difficult to know the true stroke risk in the patients because the CHA_2DS_2-VASc score overestimates risk and suggested the pendulum may be swinging too far from very few patients being anticoagulated 10 years ago to now patients with only a single stroke risk factor being anticoagulated, including women just for their gender and age.

"This study had only about 5000 women and it's a very, very big gray area to go from the trials that included patients with at least two risk factors and now all of a sudden we see how many patients with only one risk factor are being anticoagulated. I think it's quite aggressive, probably too aggressive."

Piccini said a real-world clinical trial that randomizes patients with a single risk factor to all available options is needed, particularly given the differences in the US and European guidelines.

The European Society of Cardiology recommends a stepwise approach to anticoagulation, where the first step is to identify low-risk AF patients (CHA_2DS_2-VASc score 0 in males and 1 in females) who do not need any antithrombotic therapy and then to offer stroke-prevention therapy to those with at least one non–sex-related risk factor.

The 2014 American College of Cardiology/American Heart Association/Heart Rhythm Society guidelines recommend anticoagulation for patients with a CHA_2DS_2-VASc score of $\geq$2, no treatment for patients with a risk score of 0, and nothing, aspirin, or anticoagulation for those with a score of 1.

Lip said it is "only common sense" that stroke rates would vary depending on the population and that not all CHA_2DS_2-VASc risk factors carry the same weight. For prescribing physicians, the take-home message is to evaluate each patient with AF individually and select the best agent based on their specific risk profile.

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*Follow Patrice Wendling on Twitter: @pwendl. For more from **theheart.org**|Medscape Cardiology, follow us on Twitter and Facebook.*

References

1. Lip GYH, Skjøth F, Brønnum Nielsen P, et al. Effectiveness and safety of standard-dose nonvitamin K antagonist oral anticoagulants and warfarin among patients with atrial fibrillation with a single stroke risk factor: A nationwide cohort study. *JAMA Cardiol* 2017; DOI:10.1001/jamacardio.2017.1883. Abstract

2. Fauchier L, Clementy N, Bisson A, et al. Should atrial fibrillation patients with only 1 nongender-related CHA_2DS_2-VASc factor be anticoagulated? *Stroke* 2016: 47:1831-1836. Article

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