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Editorial

Is Lighter Intensity of Warfarin Therapy Enough for Korean Patients with Non-Valvular Atrial Fibrillation?

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▸ See the article "Impact of Anticoagulation Intensity in Korean Patients with Atrial Fibrillation: Is It Different from Western Population?" in volume 50 on page 163.

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Oral anticoagulation (OAC) therapy is the most fundamental treatment for patients with atrial fibrillation (AF).[1] Warfarin played a main role in OAC therapy for decades in patients with AF with a 51% reduction in thromboembolic events.[2] However, an increase of intracranial hemorrhage was a critical limitation of warfarin therapy, especially in Asians.[2][3] Since non-vitamin K antagonist oral anticoagulants (NOACs) have been introduced, NOACs were preferred to warfarin in patients with non-valvular AF for stroke prevention.[1] However, warfarin is still considered for patients with AF; 11.4% of total patients with non-valvular AF in Korea received warfarin in 2017 (unpublished data). Maintenance of good treatment quality is essential to get enough benefit from warfarin therapy. Although the optimal therapeutic range of international normalized ratio (INR) in the use of warfarin has not been extensively evaluated in Asians, an INR 2.0-3.0 is recommended as the optimal therapeutic range, with attention on the average time in therapeutic range (TTR) at least 65% in Korean and Taiwanese AF guidelines.[1][4] On the other hands, Japanese and Chinese AF guidelines suggest a lower INR of 1.6 to 2.5 for patients older than 70 years or those with high bleeding risk.

In this issue of the *Korean Circulation Journal*, Lee et al.[5] report the impact of anticoagulation intensity of warfarin in Korean population. Patients were categorized into 5 groups by mean INR value (<1.6, 1.6–1.99, 2.0–2.59, 2.6–2.99, and ≥3.0). Obviously, mean INR under 1.6 group showed the highest thromboembolic events as expected. Also, mean INR ≥3.0 groups showed higher major bleeding events. Major bleeding, primary net clinical outcome, and secondary net-clinical outcome were the lowest in patients with mean INR 1.6–1.99 and 2.0–2.59. The dichotomous analysis showed that mean INR 1.6 and 2.6 could be appropriate cut-off to avoid both excessive thromboembolic and major bleeding events. Patients with mean INR 1.6–2.6 was significantly associated with the reduced risk of thromboembolic events, major bleeding, primary and secondary net clinical outcome, and mortality compared with patients with mean INR <1.6 or >2.6. Mean INR ranged from 2.0 to 3.0 did not show significant benefit compared with mean INR <2.0 or >3.0. In the aspect of TTR, TTR ≥70% was associated with less major bleeding risk than TTR <70% in all of TTR calculating criteria suggested in this study. Combined ideal mean INR (1.6–2.6) and satisfied TTR (≥70%), major bleeding, primary, and secondary net clinical outcome was significant lower in patients with ideal mean INR range and satisfied TTR compared to those with unsatisfied INR or TTR. Statistically insignificant, but numerically, the risk of thromboembolic events was lower in

patients with ideal mean INR range and satisfied TTR. These data provide evidence to use warfarin more safely in a lower target INR range in Korean population.

There are several limitations to be mentioned. Firstly, this study was a single center study, thus, identification of clinical outcomes was limited. Second, this study was a retrospective analysis. The hypothesis about the optimal ranges of INR for Korean population could be suggested from this kind of retrospective observational studies, however, what optimal target INR is in a certain population can be warranted by prospective randomized clinical trials. In patients with mean INR <1.6, major bleeding incidence was numerically higher than INR 1.6–1.99 and 2.0–2.59 (7.0%/year vs. 3.7%/year vs. 4.3%/year, respectively). This finding suggested that physician might intentionally target lower INR in patients with high bleeding risk. Physicians' intention to achiever lower or higher INR target in a certain subset of patients cannot be adjusted in a retrospective study. Third, Japan suggested lower INR in elderly patients aged ≥70 years. Although median age of this study population was about 70 years, almost 30% of patients were younger than 70 years. Further studies are needed to determine whether age or body size-specified INR target can achieve better net clinical outcome in Asian patients. Lastly, the use of warfarin dramatically decreased in patients with non-valvular AF and rapidly replaced with NOACs, therefore, the clinical impact of this study might be attenuated in contemporary era. However, warfarin still had a certain role for special subgroups such as patients with moderate chronic kidney disease or end-stage renal disease, thus, optimal INR target for these patients with special considerations should be evaluated in future studies. In addition, in the use of NOACs, what optimal dose for Asian or Korean is controversial. There were pre-defined dose reduction criteria for all NOACs from pivotal randomized clinical trials, but these were not tested in a large-size Asian population. Many observational data from Asian population told us that lower doses of NOACs could be safely used without increase of thromboembolic event.[6-8] Considering low TTR in Asian population even in randomized clinical trial,[9] these previous observational data should be cautiously interpreted, because common comparator of these studies was warfarin who might have low TTR in real-world setting. Off-label underdosed NOAC was associated with increased risk of thromboembolic events and at least attenuated the net clinical benefit of NOACs compared with warfarin in previous studies.[8][10]

In conclusion, warfarin plays an important role in OAC therapy for AF patients, and the current study provides for applying of a lower target INR (1.6–2.6) in Korean population treated with warfarin, with better clinical effectiveness and safety compared to a standard target INR (2.0–3.0). However, there is still limited evidence to support a lower INR range for warfarin or lower dose for NOAC in East Asian patients; therefore, further studies are needed to find both optimal target INR in warfarin therapy and optimal dose in NOAC therapy for Korean AF patients in various clinical scenario.

REFERENCES

1. Joung B, Lee JM, Lee KH, et al. 2018 Korean guideline of atrial fibrillation management. *Korean Circ J* 2018;48:1033-80.
PUBMED | CROSSREF
2. Go AS, Hylek EM, Chang Y, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? *JAMA* 2003;290:2685-92.
PUBMED | CROSSREF

3. Shen AY, Yao JF, Brar SS, Jorgensen MB, Chen W. Racial/ethnic differences in the risk of intracranial hemorrhage among patients with atrial fibrillation. *J Am Coll Cardiol* 2007;50:309-15.
PUBMED | CROSSREF
4. Chiang CE, Wu TJ, Ueng KC, et al. 2016 guidelines of the Taiwan Heart Rhythm Society and the Taiwan Society of Cardiology for the management of atrial fibrillation. *J Formos Med Assoc* 2016;115:893-952.
PUBMED | CROSSREF
5. Lee KH, Cho JG, Lee N, et al. Impact of anticoagulation intensity in Korean patients with atrial fibrillation: is it different from western population? *Korean Circ J* 2020;50:163-75.
PUBMED | CROSSREF
6. Lin YC, Chien SC, Hsieh YC, et al. Effectiveness and safety of standard- and low-dose rivaroxaban in Asians with atrial fibrillation. *J Am Coll Cardiol* 2018;72:477-85.
PUBMED | CROSSREF
7. Chan YH, Lee HF, See LC, et al. Effectiveness and safety of four direct oral anticoagulants in Asian patients with nonvalvular atrial fibrillation. *Chest* 2019;156:529-43.
PUBMED | CROSSREF
8. Cho MS, Yun JE, Park JJ, et al. Outcomes after use of standard- and low-dose non-vitamin K oral anticoagulants in Asian patients with atrial fibrillation. *Stroke* 2019;50:110-8.
PUBMED | CROSSREF
9. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet* 2010;376:975-83.
PUBMED | CROSSREF
10. Yao X, Shah ND, Sangaralingham LR, Gersh BJ, Noseworthy PA. Non-vitamin K antagonist oral anticoagulant dosing in patients with atrial fibrillation and renal dysfunction. *J Am Coll Cardiol* 2017;69:2779-90.
PUBMED | CROSSREF