**Breaking the rules for studies using real-world observational data: The case of direct-acting anticoagulants and antiepileptic drugs**

Joshua Brown, PharmD, PhD; Brian Cicali, MS; Phuong Pham, MS; Amir Sarayani, PharmD; Stephan Schmidt, PhD

**Correspondence**

Wang and colleagues’ recent articled explored the association between bleeding risk when direct-acting anticoagulants (DOACs) are used concomitantly with antiepileptic drugs (AED) in a real-world study using observational data from Taiwan.1 The research question is clinically important as AEDs pose high potential for drug-drug interactions (DDIs) and many are recommended to not be co-administered with DOACs.2,3 Further, stroke is a leading cause of epilepsy in adults4 and implies an underlying need for use of both AEDs and anticoagulation to provide control of these two conditions. However, just as the group’s article published in *JAMA* in 20175 on a broader list of medications gathered several scathing response letters including calls for withdrawal of the manuscript,6-10 this article suffers from the same study design flaws that bring into question any validity to the study findings.

To review, the article evaluated 11 AEDs and found that use of valproic acid, phenytoin, and levetiracetam increased the risk of bleeding events up to three-fold compared to those who did not use AEDs. “Did not use” is emphasized as this is the crux of the limitations to these two articles. Put simply, individuals with indications for AEDs, which range from primarily epilepsy but could include neuropathy, obesity, and other on or off-label uses, were compared to a mixture of individuals without these conditions. The other AEDs evaluated were found to have null associations with major bleeding.

Regardless of these findings, a review of the pharmacology of both AEDs and DOACs is needed. Many AEDs are inducers of *CYP3A4*, including phenytoin and possibly valproic acid, the main metabolic pathway for apixaban and rivaroxaban. Induction of *CYP3A4* would lower the bioavailability of these two DOACs with no implications for dabigatran. Several AEDs are also strong inducers of P-glycoprotein, an efflux pump that, when induced, would lower the influx and bioavailability of dabigatran, rivaroxaban, and apixaban. U.S. and European prescribing information generally agree that dabigatran should be avoided with strong inducers of P-gp as it would increase the stroke risk and apixaban and rivaroxaban should be avoided with strong inducers of both CYP3A4 and P-gp for the same reason.3,11 European Heart Rhythm Association guidelines refer to the combinations of AEDs that are inducers of P-gp and CYP3A4 to be contraindicated in all three DOACs citing reductions of 50% or more to drug levels and thus increasing the risk of stroke.3

Therefore, it is easy to conclude that many AEDs carry a risk of DDIs with DOACs which will result in an increased risk of stroke – NOT bleeding. Phenytoin fits this profile as it is a classic strong inducer as well as carbamazepine, oxcarbazepine, and phenobarbital. Thus, the findings for phenytoin are the complete opposite that one would expect. In fact, a “protective” effect against bleeding would have been predicted for the abovementioned AEDs and points to deep concerns for these results. Findings for levetiracetam, however, are more concerning as it often is less indicated in DDIs and may be a more safe option for patients requiring DOACs.

A simple response to our concerns would likely include that statistical methods, namely use of propensity score-based techniques, will have negated confounding in the study. While we are positively inclined to such techniques, clear indications of implausible results are reflective of the fact that such strong confounding by indication cannot be adjusted away. Put another way, the inherent differences between those using AEDs and those not using AEDs, the groups compared in the study, are just too different to adjust for. Rather, they must be controlled by design and are mostly easily addressed by use of active comparators or self-controlled study designs. In real-world observational studies of drug effects, the comparison of “user vs. non-user” should be avoided wherever possible to avoid such biases. Not only would this enhance the study design, it further enhances the clinical interpretation as “no use” is generally not an option for those requiring AED or DOAC therapy. Also, associations focused on baseline relationships alone are inadequate as bleeding risk is highly dynamic in patients with AF, and risks change over time [ref].

Given the severity of the study design shortcomings in the Wang et al. study, we urge clinicians to consider the plausibility of the findings versus the known pharmacologic effects of AEDs. Similar to other response letters,6-10 we believe that these results are too misleading to remain in the clinical literature and would recommend a redaction of this article. Real-world observational studies are important to inform clinical practice where clinical trials are not feasible or unlikely but must be carefully planned in order to avoid the common pitfalls of observational research. We urge authors and reviewers of such manuscripts to more closely consider design elements regardless of statistical approaches as they impact not only the validity of results but also the clinical usefulness of the findings.

**REFERENCES**

**1.** Wang CL, Wu VC, Chang KH, et al. Assessing Major Bleeding Risk in Atrial Fibrillation Patients Concurrently Taking Non-Vitamin K Antagonist Oral Anticoagulants and Antiepileptic Drugs. *Eur Heart J Cardiovasc Pharmacother.* Aug 6 2019.

**2.** Galgani A, Palleria C, Iannone LF, et al. Pharmacokinetic Interactions of Clinical Interest Between Direct Oral Anticoagulants and Antiepileptic Drugs. *Front Neurol.* 2018;9:1067.

**3.** Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association practical guide on the use of non-vitamin-K antagonist anticoagulants in patients with non-valvular atrial fibrillation: Executive summary. *Eur Heart J.* Jul 14 2017;38(27):2137-2149.

**4.** Wang JZ, Vyas MV, Saposnik G, Burneo JG. Incidence and management of seizures after ischemic stroke: Systematic review and meta-analysis. *Neurology.* Sep 19 2017;89(12):1220-1228.

**5.** Chang SH, Chou IJ, Yeh YH, et al. Association Between Use of Non-Vitamin K Oral Anticoagulants With and Without Concurrent Medications and Risk of Major Bleeding in Nonvalvular Atrial Fibrillation. *Jama.* Oct 3 2017;318(13):1250-1259.

**6.** Wang N, Giblin E, Rodgers JE. Drug Interactions With Non-Vitamin K Oral Anticoagulants. *Jama.* 2018;319(8):830.

**7.** Vazquez SR, Allen A. Drug Interactions With Non-Vitamin K Oral Anticoagulants. *Jama.* 2018;319(8):829-830.

**8.** Sennesael AL, Henrard S, Spinewine A. Drug Interactions With Non-Vitamin K Oral Anticoagulants. *Jama.* 2018;319(8):829.

**9.** Linnebur SA, Hanlon JT. Drug Interactions With Non-Vitamin K Oral Anticoagulants. *Jama.* 2018;319(8):828-829.

**10.** Li Y, Dong S, Soria-Saucedo R. Drug Interactions With Non-Vitamin K Oral Anticoagulants. *Jama.* 2018;319(8):827-828.

**11.** January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *J Am Coll Cardiol.* Jul 9 2019;74(1):104-132.