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Editorial

Apples will never be oranges, but when you go fishing you may get a bite

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Dronedarone is the newest available oral antiarrhythmic drug (AAD). In a paper by Ehrlich et al. [1] accompanying this editorial the authors report on risks for myocardial infarction (MI) and stroke in AF patients given a first prescription for dronedarone, amiodarone, flecainide, propafenone, or sotalol in 1258 general and 62 cardiology practices between January 2010 and March 2017. They attempt to compare MI and stroke risks in dronedarone patients (n = 3498) versus those treated with all the other stated antiarrhythmic drugs (AAD) analyzed in combination (n = 17,724). They report less MI in dronedarone patients (3.9%) than on other AADs (5.2%) [HzR 0.76, p = 0.002] and less stroke (7.4% vs 8.3%; HzR 0.84, p = 0.003) over 6 follow up years. Unfortunately, their report compares "apples to oranges" rather than "apples to apples."

Ehrlich et al. [1] did not study each therapy in identical patient populations in this non-randomized, retrospective, observational report where selection bias is an enormous confounder. Their dronedarone patients were younger; had less heart failure, peripheral arterial disease, chronic renal insufficiency, and more care by a cardiologist than a generalist; a different profile of anticoagulants; and more. This concern is important since each AAD used has different pharmacologies, contraindications, serious risks, drug interactions, and ideal demographics and likely were given to different patient types. Flecainide/propafenone should not be used (and I presume were not used) in patients with structural heart disease. Sotalol, via beta blockade, could affect acute coronary syndrome presentations and carries greater proarrhythmic risk in women than in men. Amiodarone is the most likely to be used in heart failure patients and/or after another AAD has failed, and has an almost endless list of drug interactions, including with all oral anticoagulants such that it could affect their dosing and the risk for embolic and hemorrhagic strokes. Even the authors clearly recognized their confounding selection bias in their Limitations section. Given these differences, can we truly compare, interpret, and utilize the differences in MI and stroke rates reported in this paper? Probably not reliably. At best, we might consider them hypothesis-generating.

To their credit, the authors attempted to "avoid confounding" in two ways: (1) by using a multivariate Cox proportional regression model to estimate relationships between the drugs studied and the risk of MI and stroke in the full patient cohort; (2) by subgroup matching each patient treated with dronedarone to a matched patient treated with another AAD, based on propensity scores. While these approaches are commonly employed, propensity matching corrections can never give results that are more than hypothesis-generating. Consider that even the CHA_2DS_2-VASc score can be a misleading comparator for stroke in AF since both older age and prior stroke have a greater risk for ensuing stroke than the other CHA_2DS_2-VASc score components. Thus, a 67-year old female diabetic hypertensive (score = 4) likely has a lower risk than a 78-year old man with a prior stroke (score also = 4).

Propensity-matching (PM) has become popular when comparing different populations or to assess subpopulations within a trial – especially retrospectively and/or post-hoc. PM attempts to adjust cohorts such that major clinical/demographic variables that could cause alterations in outcomes appear to be equalized. However, very few such clinical/demographic variables are considered in terms of severity (quantitatively), drug doses or interactions, or past patient history when in fact such may significantly affect study results. For example, in the sustained-release propafenone vs placebo AF trials, RAFT [2] (R) and ERAFT [3] (ER), lower efficacy was seen in ER vs R despite using identical study drug, dose, and placebo. Importantly, ER had greater AF burden, longer AF history, more advanced underlying disease, and more prior AAD failure. Simply comparing these two populations based on the presence of prior AF and on specific underlying disease would have missed these important result-altering details. Moreover, in most PM patient's drug types are simply listed for each study arm though specific drugs and doses (virtually never listed) are not the same. Yet more specific to Ehrlich et al. [1] are the dronedarone vs placebo results in ADONIS/EURIDIS [4] in contrast to other placebo-controlled AAD trials for AF. Typical PM would miss that ~75% of enrollees in ADONIS/EURIDIS [4] had AADs stopped to allow enrollment and that patients could start study drug immediately after stopping the prior AAD (including amiodarone). Stopping an AAD for inefficacy would bias against dronedarone efficacy in this study since efficacy rates are lower for an AAD if it is tried after prior AAD failure. Enrolling patients immediately upon

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cessation of amiodarone could bias towards efficacy since for several months amiodarone's effects are still present.

Another concern regarding Ehrlich et al. [1] is the lack of any clear hypothesis. Did the authors hypothesize dronedarone would be less likely to cause an MI and/or stroke than another AAD? If so, based on what? If not, why was the comparison being examined? If we examine the large, prospective AF trials performed in the dronedarone development program – ADONIS/EURIDIS [4], ATHENA [5], and PALLAS [6] – we see no signal of a lower MI or stroke risk with dronedarone vs placebo. Nor was there any in DIONYSIS that directly compared dronedarone to amiodarone [7]. In ADONIS/EURIDIS [4] no MI was reported and stroke was not significantly different at 0.5% vs 0.7% respectively. In contrast, in ATHENA [5], while there were fewer acute coronary events on dronedarone vs placebo (2.7% vs 3.8%) and less stroke (0.9% vs 1.7%), this was only noted in a post-hoc sub-analysis. In fact, to test the validity of these observations, these endpoints were included in preplanned analyses of the subsequent PALLAS trial, where they were soundly refuted [6]. In PALLAS, dronedarone had a greater stroke risk (HzR 2.32, $p = 0.02$) and trend towards more MIs (HzR 1.54, $p = 0.63$).

Troublesome then, is the fact that Ehrlich's report misleadingly states “Furthermore, a recent meta-analysis demonstrated a reduced stroke rate with dronedarone that was not present with any other antiarrhythmic agent” and went on to say “this effect was largely corroborated by the results of the ATHENA trial” [1]. If one actually examines the meta-analysis [8] the report states there were no differences in stroke in the dronedarone pivotal trials other than in the one subgroup report [which was later refuted by PALLAS] [6]. Moreover, in DIONYSIS [7], no differences for MI or cerebrovascular events were reported between dronedarone and amiodarone. Finally, the ATHENA post-hoc sub-analysis demonstrates the risk of erroneous data by chance, especially if multiple analyses are performed. When you fish, you might get a bite, but not land a “keeper.”

Consequently, did the report by Ehrlich et al. [1] really demonstrate an impact of dronedarone on the risk of myocardial infarction and stroke in AF patients followed in general practices in Germany as the title implies? Probably not. However, given the large number of patients included in their study and the length of follow up I agree with the authors that it might be worthwhile to conduct additional dronedarone studies. To do so, however, clear hypotheses would need to be formed; demographically enriched populations would be best to study prospectively; comparative drugs should be studied in similar populations; and any PM should consider as many relevant factors in those populations and their concomitant treatments as feasible.

Disclosures

In the past 3 years, Dr. Reiffel has been a consultant for Sanofi; an investigator and consultant for Gilead; a consultant for Acesion, InCardia Therapeutics, Medtronic; an investigator and consultant for Janssen; and a consultant for Portola and Roivant. He was also an investigator in ADONIS.

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