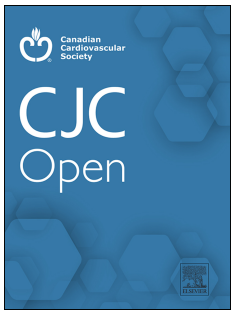

Numbers Don't Lie – Or Can They?

James A. Reiffel, M.D

PII: S2589-790X(23)00060-4

DOI: https://doi.org/10.1016/j.cjco.2023.03.006

Reference: CJCO 649

To appear in: *CJC Open*

Received Date: 5 March 2023

Accepted Date: 8 March 2023

Please cite this article as: J.A. Reiffel, Numbers Don't Lie – Or Can They?, *CJC Open* (2023), doi: https://doi.org/10.1016/j.cjco.2023.03.006.

Numbers Don't Lie – Or Can They?

James A. Reiffel, M.D.

Address correspondence to:

James A. Reiffel, M.D.

c/o 202 Birkdale Lane, Jupiter, FL 33458

Phone and Fax: 561-203-2161

email: jar2@columbia.edu

Word count of text: 400

Key Words: atrial fibrillation; amiodarone; dronedarone, cardiovascular hospitalization

Conflict of Interest Disclosure: Investigator and/or consultant for J&J, Sanofi, Acesion, Amarin, InCarda Therapeutics; speakers bureau for Sanofi.

I read with interest the Brophy/Nadeau paper “seeking to determine the comparative drug effectiveness of” amiodarone vs dronedarone [1] -- although their primary outcome was only repeat cardiovascular hospitalization (CVH) or within-hospital death subsequent to an initial hospital discharge for which ICD codes indicated atrial fibrillation (AF) as primary diagnosis. Using analyses with several statistical adjustments and propensity-score matching, the authors reported more CVH in the dronedarone group (12.7% vs 8.4%). The majority of recurrent CVH listed AF as primary diagnosis; there were no differences for other CVH or total mortality. Unfortunately, the data has several apparently unrecognized flaws: The known accuracy limitations of ICD codes (very commonly used in retrospective studies and often arbitrary when multi-morbidities are present) without verifying review of the hospital chart was not addressed. [2] The important limitations of propensity-score matching (PSM), particularly when considering cardiovascular outcomes was also not addressed. [3] PSM typically adjusts for underlying comorbidities (though herein, hypertension, the most common, was not listed), but often not for specific medications used in these diseases which can themselves alter cardiovascular outcomes, including arrhythmic, such as statins, beta blockers (BB), RAAS inhibitors, SGLT2 inhibitors. And in the few that do, PSM usually does not adjust for specific agents within a drug class or doses thereof – all of which can alter mortality, arrhythmias, CVH. While the Brophy/Nadeau report [1] listed several drugs for the 2 comparison groups, BBs and SGLT2 inhibitors (among others) were absent. BBs can enhance antiarrhythmic drug (AAD) efficacy; thus, group imbalances

in BBs can alter outcomes. However, my most serious concern is a major bias re: recurrent CVH. The authors referenced the one direct amiodarone-dronedarone comparison trial [4] in which amiodarone had fewer AF recurrences but more adverse effects. Indirect comparisons from the literature are supportive. Importantly, many AF recurrences require elective hospitalization for subsequent therapy, e.g., dofetilide, sotalol, or ablation. Since dronedarone provides less recurrent AF prevention than amiodarone, an increase in elective AF hospitalization for subsequent therapy in dronedarone vs amiodarone patients would be expected apriori. Thus, only unplanned AF hospitalizations should have been included. Given no differences in non-AF CVH in this study [1] and no mortality difference, if such were done the result would have been a negative (no differences) trial. Accordingly, numbers can lie. Finally, many other AF outcomes beyond CVH determine AAD efficacy: AF burden, event numbers, symptoms, etc., not just the ones studied here.

References:

1. Brophy JM, Nadeau L. Amiodarone vs dronedarone for atrial fibrillation: a retrospective cohort study. CJC Open 5 (2023) 8-14.
2. Burns EM, Rigby E, Mamidanna R, et al. Systematic review of discharge coding accuracy. J Public Health 2012; 34:138-148.

3. Freemantle N, Marston L, Walters K, et al. Making inferences on treatment effects from real world data: propensity scores, confounding by indication, and other perils for the unwary in observational research. BMJ 2013; 347-350.
4. Le Heuzey JY, Ferrari GM, Radzik D, et al. A short-term, randomized, double-blind, parallel-group study to evaluate the efficacy and safety of dronedarone versus amiodarone in patients with persistent atrial fibrillation: the Dionysos study. J Cardiovasc Electrophysiol 2010; 21:597-605.