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EDITORIAL

If it were only that simple

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This editorial refers to 'The impact of atrial fibrillation type on the risk of thromboembolism, mortality, and bleeding: a systematic review and meta-analysis'[†], by A.N. Ganesan *et al.*, on page 1591.

As a group, we physicians are highly organized. Organization allows us to categorize diseases, better understand their mechanisms, formulate therapeutic algorithms, etc. With particular respect to atrial fibrillation, organization has led us to categorize it as paroxysmal vs. non-paroxysmal, or paroxysmal vs. persistent vs. long-standing persistent vs. permanent. Such categorization promotes specific considerations regarding presentations, prognosis, and therapy. However, to date, such categorization has not been a determinant regarding anticoagulation. Current guidelines lump all atrial fibrillation types together in terms of anticoagulation, with the major determinants being associated co-morbidities translated into risk marker scores (e.g., CHA_2DS_2-VASc, representing congestive heart failure, hypertension, age, diabetes, prior stroke or systemic embolism, vascular disease, and gender in a point system risk marker score). Important, then, is the article by Ganesan *et al.*[1] in this issue of the journal where morbidity and mortality outcomes are reported to be worse for non-paroxysmal vs. paroxysmal atrial fibrillation (though demographic differences may also have been at play). Notably, there were no group differences in bleeding rates. The authors suggest that the latter indicates that more advanced co-morbid conditions in the non-paroxysmal patients did not explain their thrombo-embolism/mortality results because if these were the main factors, then increased bleeding with non-paroxysmal atrial fibrillation should also have been present. Accordingly, they recommended that we consider atrial fibrillation type when determining risk and anticoagulation.

Certainly, we have long known that all atrial fibrillation patients are not alike in terms of consequences. However, these differences have largely been attributed to the presence/absence of co-morbid risk markers (such as those used in risk marker scores) rather than to atrial fibrillation type. Importantly, therefore, factors such as age, heart failure, hypertension, diabetes, vascular disease, etc. have adverse effects on morbidity and mortality independent of atrial fibrillation. Even our great-grandparents probably knew that old sicker patients exceed young healthy patients in risk for stroke or death (regardless of their pulse rhythm). Now, however, Ganesan and colleagues implore us to consider the co-morbid risk markers in concert with each patient's specific atrial fibrillation type.

Are these observations new? Not entirely. Vanassche *et al.*[2] reported that in unanticoagulated patients, the yearly ischaemic stroke rates progressed going from paroxysmal to persistent and permanent atrial fibrillation, with the atrial fibrillation pattern being the second strongest predictor after prior thrombo-embolism. Similarly, Steinberg *et al.*[3] reported a higher risk of death and stroke with persistent vs. paroxysmal atrial fibrillation in anticoagulated patients with moderately high risk for stroke based upon their clinical factors; as did Al-Khatib *et al.*[4] in a similar population for non-paroxysmal vs. paroxysmal atrial fibrillation.

But, oh, if it were only that simple: let us just add atrial fibrillation type to our current clinical risk factor scoring systems. Unfortunately, such observations have not been uniformly consistent.[5,6] More importantly, the story must go beyond just atrial fibrillation type and presence/absence of specific co-morbidities (*Figure 1*). We have all encountered patients with both paroxysmal and intermittent persistent atrial fibrillation. How should they be categorized? Moreover, a patient with atrial fibrillation for 5 min twice a year has paroxysmal atrial fibrillation (but of what clinical significance?) but so would a patient with atrial fibrillation 18 h/day. Yet few would disagree that the latter patient probably has more associated adverse atrial remodelling and a different underlying substrate than the former—with a more adverse risk profile for untoward outcomes. Thus, the observations of Ganesan *et al.*[1] notwithstanding, while categorizing atrial fibrillation by type is useful, it seems to me to be still too simple to be optimal. Rather, if we add atrial fibrillation characteristics to our clinical risk scoring systems, a better approach would be to use atrial fibrillation burden. (Atrial fibrillation burden is generally defined as the percentage of time a patient is in atrial fibrillation vs. the total recording time and is most accurately assessed with implantable devices, such as the percutaneously insertable Medtronic Linq recorder, although prolonged external recording with 30-day monitors can be a reasonable surrogate in many patients.) Importantly, by definition, atrial

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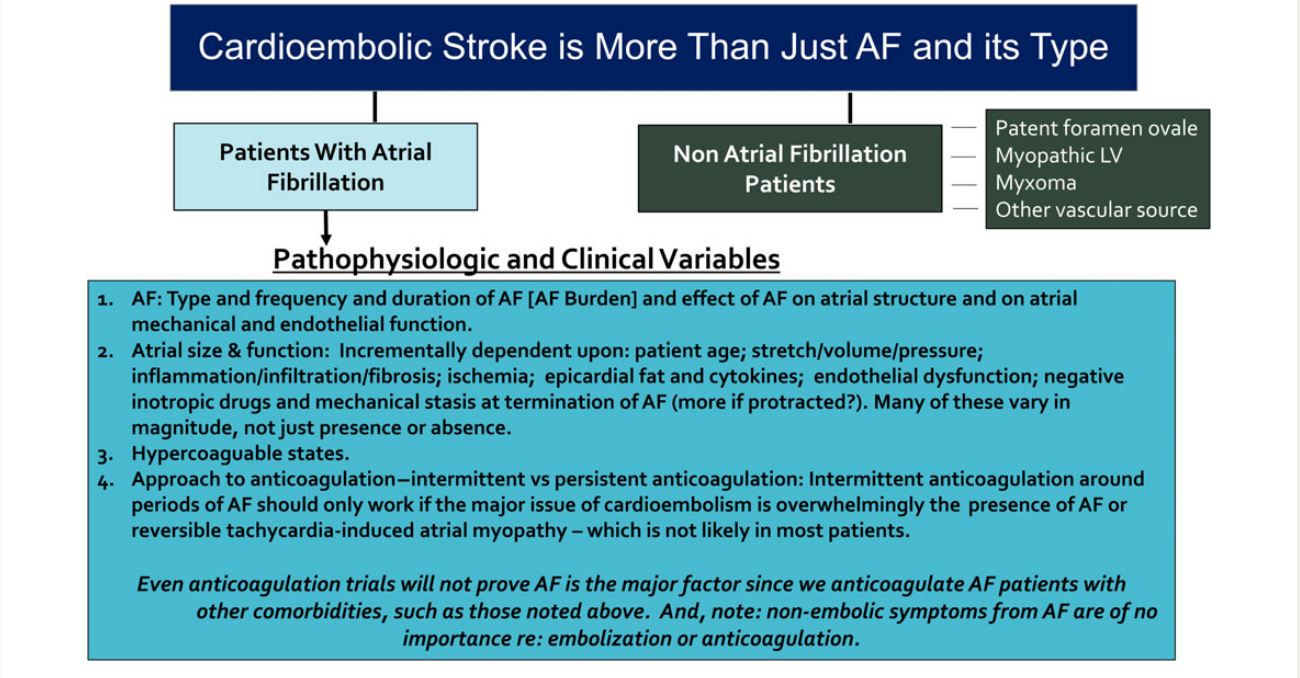

Figure 1 A schematic indicating that cardio-embolism in atrial fibrillation (AF) is a complex issue that is dependent upon more than just AF type and an incremental list of co-morbid disorders. LV, left vemtricle.

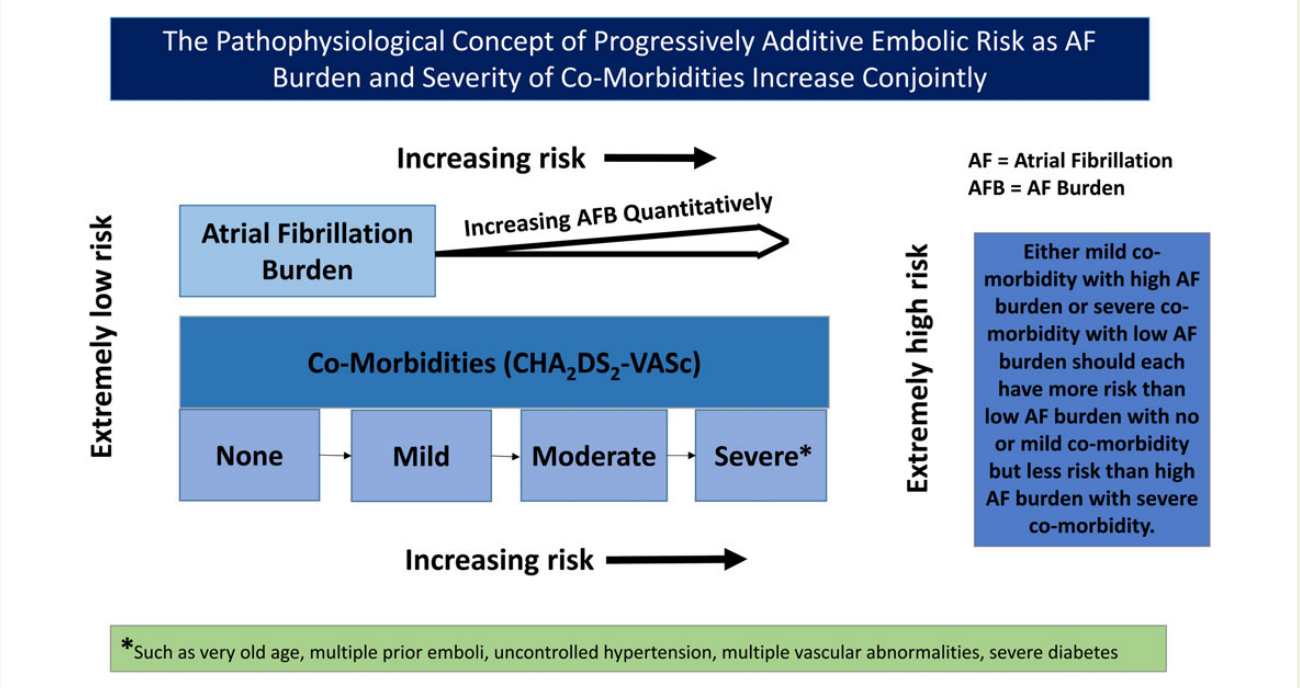

Figure 2 The concept of quantitatively additive embolic risk with increasing atrial fibrillation burden and increasing co-morbidity severity.

fibrillation burden would usually (but not always—consider the above 18 h per day example) be increased with non-paroxysmal vs. paroxysmal atrial fibrillation and would explain the observations of Ganesan.

There are already enticing data to suggest that atrial fibrillation burden provides more valuable prognostic information than atrial fibrillation type alone—especially if combined with co-morbid disorders—which, in my opinion, should also be considered in a

qualitative–quantitative manner rather than just as binomial present/absent factors. Each co-morbidity's magnitude as well as specifics of its therapy probably interplays with the causes, severity, treatment, and/or consequences of any atrial fibrillation present. Hence, simplicity is not the story.

Multiple retrospective studies using implanted pacemakers or defibrillators (thus a subset of atrial fibrillation patients with additional rhythm abnormalities) strongly suggest that atrial fibrillation burden relates to outcomes, including those of Glotzer *et al.*,[7] Shanmugam *et al.*,[8] Healey *et al.*,[9] and others. One strength of the report by Ganesan *et al.*[1] is that all patients were assessed prospectively. That atrial fibrillation burden should be an important consideration added to clinical risk scoring factors is underscored by the report of Botto *et al.*[10] in which no atrial fibrillation, atrial fibrillation >5 min, and atrial fibrillation >24 h contributed a progressively and interactively higher risk for thrombo-embolism when added to a standard risk marker score. In concert, Lim *et al.*[11] reported that atrial fibrillation with co-morbidities has a greater propensity for atrial thrombo-embolism formation, as determined by platelet and endothelial biomarkers, than does lone or no atrial fibrillation.

Expectedly, atrial fibrillation burden and clinical factors should act in concert. Formation of atrial thrombi relates to several factors, including endothelial dysfunction, stasis, and abnormal coagulation factors (including platelet function). Disease-mediated dysfunction (through such contributors as fibrosis, inflammation, chemical mediators, and atrial anatomic alterations) enhances this process. When such factors are magnified by atrial fibrillation (via additional adverse anatomic and functional remodelling), the effects should be additive and thrombotic risk should increase (*Figure 2*). Accordingly, Ganesan and colleagues have awakened us anew to consider the effects of atrial fibrillation characteristics beyond those of clinically present co-morbidities. Hopefully they will trigger further investigation into the pathological interplay between atrial fibrillation burden and underlying disorders, allowing us to better determine optimal risk assessment and therapy. Also, perhaps, they will nudge us slightly away from our categorical habits and more towards thinking pathophysiologically where atrial fibrillation and risk markers appear additive but where quantitative risk from atrial fibrillation burden probably interacts with the degree of co-morbid contributors.

Conflict of interest: J.A.R. has no conflict of interest with respect to this manuscript other than serving as principal investigator on the Medtronic-sponsored REVEAL AF trial.

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