Atrial fibrillation: mortality, morbidity, and money; is that all? Importance and variability of burden measurement

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Primary endpoint selection in atrial fibrillation (AF) therapy trials is currently under critical debate. Health economists promote the evaluation of therapy efficacy only in terms of the 'three big Ms': Mortality, Morbidity, and Money. From our perspective, this can only be correct when a therapeutic approach has found its optimum or cannot further increase its efficacy. In addition, even in this case, the 'three big Ms' should, at least in the field of AF, be complemented by quality of life evaluation.

For new and developing interventions in AF therapy, such as ablation and device therapy, it is not reasonable to conduct huge mortality-driven trials since these therapies have not found their optimal or close to optimal, technical and conceptional stage. Thus, to reach this stage, investigators are in need of endpoints which react adequately and represent a positive or negative therapy effect. For interventions with a curative intention, the endpoint 'complete freeness of AF' is the key point and desired form of success. However, even in those strategies primarily targeting cure of AF, such as left atrial ablation procedures, physicians and patients had to learn that there are also variants of incomplete success including ongoing AF disease with a reduced AF burden compared with the pre-ablation status.1 Furthermore, we also have to guide therapies which a priori do not completely suppress, but reduce, AF. These therapies, for example the pharmacological and ablative hybrid therapy or preventive pacing manoeuvres with a highly diverse arsenal of different methodological approaches, need measurements of their specific variant of success to guide changes or modifications of concept. For this purpose AF burden, continuously documented by an implanted device, has become the most important measurement parameter, especially in the field of preventive pacing.2 However, there are significant limitations using AF burden as a study endpoint; aside from the majority of patients with a low AF burden, few patients with a high burden do significantly change the mean AF burden. This problem can in part be solved by the use of the median, however changes in the median are much more difficult to interpret and to translate into clinical practice than mean values. Another difficulty is that a reduction in AF burden from 60 to 30%, indicating a relative change of 50% and measured over a reasonable time, seems to be a significant improvement to us. Whereas a burden reduction of 2.4 to 1.2% within 6 or 9 months of therapy application looks more or less like a variation of the underlying problem. This is not convincingly an effect of therapy, even when the burden reduction is again 50%. Current studies are equipped to overcome these problems at least in part, for example by using a multi-factorial definition of therapy responders including a composite of relative, but also absolute, changes in AF burden. Furthermore it is unclear whether the composition of a certain AF burden is of relevance: is there a difference in risk for stroke, or 'tachycardiomyopathy', when the same amount of burden is in one case the result of many but short episodes, compared with a few but long episodes?

The article by Padeletti et al.3 raises a very important issue; knowing that the ability to demonstrate changes in AF burden and then further to detect whether these changes are of clinical relevance will be essential for the development of AF preventive pacing therapies. The article’s main message, that a longer trial duration may increase the variability of the studied phenomenon
of AF, leading to the need for many more patients as calculated in the past to demonstrate significant differences, is like an alarm signal for all investigators in the field. Moreover, aside from the length of follow-up, the study design is another major impact factor influencing the needed patient number: cross-over studies require more patients for a 12 month follow-up than with 6 months!

The calculations of Padeletti and co-workers will start an important discussion about the majority of ongoing, or already published, trials which, to our perspective, in part fail Padeletti’s requirements. In addition, the presented parameters should be discussed intensively while designing future trials in the field of preventive pacing.

References

