

Rhythm Control and Increased Risk of Noncardiovascular Death in the Atrial Fibrillation Follow-up Investigation of Rhythm Management Trial

In their recent analysis of the causes of death that occurred in the course of the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial,¹ the AFFIRM investigators speculate that a favorable effect of oral anticoagulants and/or an unfavorable effect of amiodarone could explain the higher noncardiovascular death rate—especially pulmonary and cancer-related deaths—recorded among patients originally randomized to rhythm control (versus rate control). Cause-specific mortality was analyzed on an intention-to-treat basis.¹ However, in view of the high crossover rates (21% of the population during the course of the study),² we think that exposure times to each of the strategies and therapies need to be taken into account. To do this, a time-dependent, on-treatment analysis would be necessary, whereby patients are analyzed according to the actual therapy received, and adverse events or outcomes are attributed to the treatments actually applied.³ The necessity for this is stressed by the survival curves for noncardiovascular mortality, where excess mortality in the rhythm control arm began to emerge after 1 year of treatment.¹ By that time, the crossover from rhythm to rate control was already substantial (rates of 16.7%, 27.3%, and 37.5% were recorded at 1, 3, and 5 years, respectively).² In addition to evaluation of time-dependent covariates, a series of known potential determinants of pulmonary and cancer-related mortality (including environmental, lifestyle, and occupational factors) also require consideration. Such an analysis would allow a more reliable exploration of the possible relations between rhythm control and occurrence of pulmonary and cancer-related deaths.

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Response

We thank Boriani et al for their interest in our paper describing modes of death in Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) patients, a study indicating a higher noncardiovascular death rate in the rhythm-control arm.¹ They suggest that the analysis should be redone using a time-dependent, on-treatment methodology, rather than the intention-to-treat protocol that we followed.

There are multiple problems inherent to an on-treatment analysis, including the potential introduction of bias by investigators' actions regarding changes of drug therapy and the loss of

balance of clinical factors inherent to randomized groups. Compounding the problems with this type of analysis are our lack of specific start/stop dates for medications and an absence of knowledge of patients' compliance with drug administration. Furthermore, it is difficult to assess when a drug effect ends, even if the stop date of the drug is known, especially for amiodarone. It is also difficult to assess patients who repeatedly change drugs, dropping in and out of the assigned randomized arms (common in the management of atrial fibrillation). Additionally, we imposed protocol restrictions on antiarrhythmic drugs, dictating which drugs could be prescribed to certain clinical subgroups, making bias certain in drug administration.

Data were not collected on "environmental, lifestyle and occupational factors," except for smoking history.

With these limitations in mind, it is noteworthy that another recent AFFIRM paper² performed a retrospective on-treatment analysis and found a negative association between rhythm-control drug use and all-cause mortality, in keeping with our findings. Thus, we continue to have a fundamental paucity of knowledge on how rhythm-control strategy or drugs may have adversely contributed to fatal outcomes.

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2. The AFFIRM Investigators. Relationships between sinus rhythm, treatment, and survival in the Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Study. *Circulation*. 2004;109:1509–1513.