To the Editor:

We read with great interest, “Intravenous Flecainide for Emergency Department Management of Acute Atrial Fibrillation”, by Markey et al.[1] We commend the authors for performing a comprehensive literature search and multiple, informative meta-analyses of emergency department (ED)-relevant outcomes in order to clarify the evidence-based management of a common acute dysrhythmia. However, we feel compelled to call attention to some inconsistencies in the study’s[1] methods and data analysis that may limit the strength of its findings.

In their methods, Markey et al[1] state that the population of interest is patients with AF onset within 48 hours, an appropriate time limit that considers thromboembolism risk and recommendation by current guidelines.[2,3] However, in their meta-analysis of flecainide versus other anti-dysrhythmics (Figure 3), six of nine pooled trials recruited patients with AF duration *more than 48 hours*: two trials with AF up to 72 hours, one trial with AF up to 2 weeks, and three trials with AF up to six months. When one compares the data in Figure 3 with the data presented in those six papers, it appears that Markey et al[1] included *all* patients from those six studies; they did not limit their analysis to individual patient-level data from participants with AF onset within 48 hours. Therefore, some of their pooled data is from patients in whom AF was present for more than 48 hours. The meta-analysis of data from a number of patients with AF duration more than 48 hours creates two predicaments. First, such analysis constitutes protocol violation of their inclusion criteria and subsequently risks significant selection bias. Atrial

fibrillation for more than 48 hours may respond relatively more[4] or less frequently[5] to flecainide than other anti-dysrhythmic agents. This potential bias may result in an imprecise estimate of flecainide's comparative efficacy for conversion of acute AF by Markey et al,[1] when "acute AF" is strictly defined as AF onset within 48 hours. Second, since current guidelines[2,3] recommend a 48-hour AF duration limit for cardioversion without prior anticoagulation, Markey et al's[1] analysis of data from patients with AF duration more than 48 hours will therefore limit external validity.

Through meta-analysis of nine trials, including six that examined patients of varying AF duration for more than 48 hours, Markey et al[1] report a risk ratio (RR) of 1.5 (95% CI 1.24-1.80) for flecainide over other anti-dysrhythmic agents for cardioversion of acute AF. We redid the meta-analysis with the three trials that included only participants with AF onset within 48 hours and calculated a RR of 1.19 (95% CI 0.93-1.52). The 95% confidence interval crosses 1.0; therefore, with the caveat that applicable patient-level data from the other six trials are not factored in, flecainide cannot be considered superior to other anti-dysrhythmic drugs for cardioversion of AF less than 48 hours. Markey et al[1] introduce a well-reasoned, meta-analytic approach to the study of anti-dysrhythmic therapy for acute AF, but flecainide may need further investigation in ED patients with a stringent 48-hour AF duration limit in order to influence anti-dysrhythmic selection in current, established ED protocols.[6]

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