JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
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PUBLISHED BY ELSEVIER

VOL. 71, NO. 1, 2018
ISSN 0735-1097/$36.00
https://doi.org/10.1016/j.jacc.2017.10.069

EDITORIAL COMMENT

Silent Myocardial Infarction

Listen to the Evidence*

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It has been 30 years since the first report from the Framingham study demonstrated that silent or unrecognized myocardial infarction (MI), defined as evidence of MI on electrocardiography (ECG) in the absence of a history of MI, is associated with a greater risk of all-cause death, heart failure, and fatal MI (1). Despite this finding, silent MIs are rarely included as a component of clinical endpoints in randomized controlled trials.

Clinical endpoints should be clinically meaningful (2). MI presents in a wide variety of ways across a broad spectrum of clinical settings. The severity of MI can range from silent to life threatening, and can occur in a wide variety of clinical settings such as stent thrombosis-related or procedural-related MI (3). As a result, there are different classification schemes, and thresholds to define MI (3). Silent MI is no exception to the rule. The definition depends on the methods used to identify the MI: ECG characteristics based on the Minnesota Classification (appearance of a Q-wave, abnormalities of the ST-segment or T-wave), stress echocardiography, dipyridamole scintigraphy, or cardiac magnetic resonance (4). Silent MI has variably been included as a component of composite endpoints in clinical trials to this point. (5).

SEE PAGE 1

In this issue of the *Journal*, Qureshi et al. (6) highlight the clinical importance of ECG-defined silent MI among >9,000 participants enrolled in the ARIC (Atherosclerosis Risk In Communities) study. A prior analysis of ARIC study has already confirmed the association between ECG-defined silent MI and all-cause death (7). For the second time in 10 years, the present analysis again demonstrates that silent or unrecognized myocardial infarction, defined as a new appearance of a Q- or QS-wave abnormality or minor Q- or QS-wave plus major ST-T-wave abnormality, is associated with an increased risk of heart failure (8). The present study provides new and consistent evidence regarding the consequences of silent MI. Interestingly, contrary to previous studies, there was no effect modification of sex on the association between silent MIs and heart failure in this analysis (9). The growing body of evidence on ECG-defined silent MI over the past 10 years, summarized in **Figure 1**, supports its use as a meaningful clinical endpoint.

Moreover, ECG-defined silent MI accounts for 5% to 30% of the total number of all nonfatal MI (4). The addition of ECG-defined silent MI to a composite endpoint may increase the number of events among a population enrolled in a clinical trial. This would increase the statistical power, reduce the required sample size, and thus reduce the duration and cost of a randomized clinical trial. The LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial clearly illustrates this point (10). Silent MI was assessed among all subjects in the LEADER (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results) trial, which randomly assigned subjects with type 2 diabetes and high cardiovascular risk to liraglutide or placebo. Silent MI accounted for 138 additional MI events, increasing the power of the study, which may not have otherwise achieved statistical significance for its primary endpoint.

The ARIC study also raises an important clinical issue. Over the past 30 years, the incidence and

*Editorials published in the *Journal of the American College of Cardiology* reflect the views of the authors and do not necessarily represent the views of *JACC* or the American College of Cardiology.

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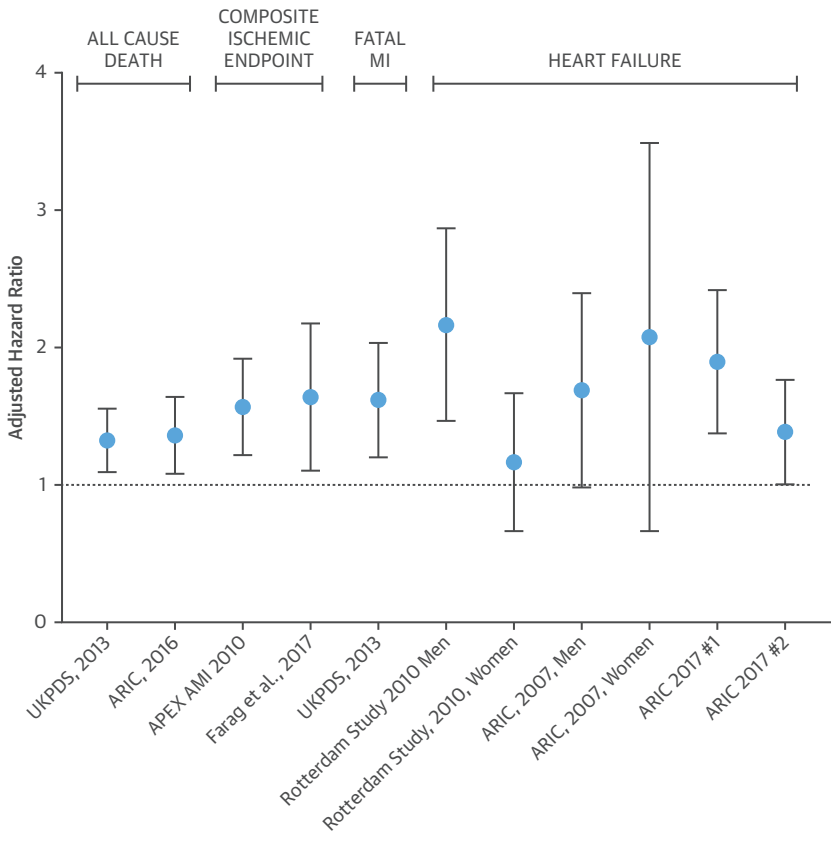
FIGURE 1 Association Between Silent or Unrecognized MI and Clinical Events



Adjusted hazard ratios and 95% confidence intervals for the association between silent myocardial infarction (MI) and all-cause death or composite ischemic endpoints (including all-cause death, MI, and revascularization and all-cause death, cardiogenic shock, and heart failure) or fatal MI or heart failure in all studies published between 2007 and 2017: the ARIC (Atherosclerosis Risk in Communities) (6–8), Rotterdam (9), UKPDS (United Kingdom Prospective Diabetes Study) (15), and Farag et al. (16) studies. APEX AMI = Assessment of Pexelizumab in Acute Myocardial Infarction.

prevalence of heart failure has continued to increase in line with an expanding aging population and therapeutic advances in the treatment of ischemic heart disease and hypertension (11). The median survival time does not exceed 4 years from diagnosis, and nearly 1 in 2 patients hospitalized for heart failure will die or be readmitted within 1 year (12). Whereas the causal mechanism is not directly demonstrated by Qureshi et al. (6), the association between myocardial damage leading to electrically inert tissue (a Q-wave) and subsequent heart failure would be apparent to any cardiologist. Early identification of patients with an increased risk of heart failure is crucial because early initiation of treatment may improve the patient's prognosis and may reduce the related health care costs. Although Qureshi et al. (6) provide new evidence supporting this mechanism, further studies are required to provide data demonstrating improved outcomes based upon acting on this information.

There are some limitations to consider in the analysis of Qureshi et al. (6). First, a significant number of patients (40%) were excluded from the analysis due to missing an ECG. This raises a concern about whether patients with missing ECGs were fundamentally different from those that had an ECG obtained with respect to their risk of heart failure. Second, the diagnosis of heart failure was retrospectively collected on the basis of International Classification of Diseases-9th Revision codes of hospital discharge or death certificate. Third, the rate of silent MI, which was lower than in other registries, may be underestimated, as silent MI was only diagnosed on the ECG findings that may not persist over time (regression of the Q waves) (13). The infarction size also influences its detectability

on ECG, suggesting that a large proportion of small silent MIs are not associated with characteristic ECG-defined silent MI, and thus their association with heart failure remains unknown (14). Fourth, alternate definitions of silent MI, defined as an imaging evidence of a region of loss of viable myocardium in the absence of a nonischemic cause, were not captured.

Nonetheless, in an era when complex microRNA samples and biomarkers are being developed to identify patients with an increased risk of heart failure, Qureshi et al. (6) remind us that, sometimes, preventive cardiology could be as simple as a Q-wave.

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KEY WORDS electrocardiogram, heart failure, silent myocardial infarction