Despite significant progress in the prevention and treatment of cardiovascular diseases over the past 2 decades, the incidence, prevalence, morbidity, mortality, and economic impact associated with heart failure (HF) represent a major and growing public health concern (1,2). Thrombotic occlusions and thromboembolism are critical, but relatively uncommon life-threatening complications of HF. The existence of HF per se increases the risk of thromboembolic events, regardless of whether concomitant atrial fibrillation is present (3,4). Clopidogrel is a second-generation thienopyridine, an adenosine diphosphate receptor antagonist acting via platelet P2Y12 receptor blockade, and an established antiplatelet agent. Clopidogrel either as an alternative (5), or more commonly as an adjunct (6), to aspirin represents a cornerstone of modern chronic oral antiplatelet therapy for treatment and secondary prevention of acute vascular events. However, the role of antithrombotic therapy in general, and clopidogrel in particular, in patients with HF has long been debated. Several markers of platelet activity subsequently have been found to be increased in HF patients, including thromboglobulin, platelet factor 4, and cellular adhesion molecules such as P-selectin, platelet and endothelial cell adhesion molecule, and osteonectin (7–9). The pathogenesis of platelet activation in HF remains to be established; it is probably multifactorial and related to calcium imbalance, sympathoadrenal activation, catecholamine release, and reduced kidney and liver blood flow, resulting in decreased clearance of platelet-activating substances. Nevertheless, therapy with clopidogrel inhibited platelet indexes independently of HF cause, New York Heart Association functional class, or ejection fraction (10,11).

More importantly, there is a discrepancy between favorable changes in platelet indexes after clopidogrel in patients with HF: positive results of randomized trials with clopidogrel in a peripheral vascular disease cohort (6), stroke (12), and coronary artery disease (6,7,13,14), but negative data from the long-awaited—although underpowered because of low enrollment—WATCH (Warfarin and Antiplatelet Therapy in Chronic Heart Failure) trial (15). It is still unclear whether clopidogrel use is justified for all HF patients, whether it should be limited only to patients with HF of ischemic origin, or whether bleeding risks outweigh vascular benefits, challenging any use of clopidogrel in the HF population. Because the data on these critical issues are very limited, the elegant and convincing report published in this issue of the Journal (16) is of unquestionable practical importance. Using the National Patient Register of 56,994 first documented myocardial infarctions (MIs) in Denmark, Bonde et al. (16) demonstrated highly significant positive impact of clopidogrel use on mortality reduction in patients with antecedent HF (hazard ratio: 0.86; 95% confidence interval: 0.78 to 0.95; with a highly significant p = 0.002) compared with patients with HF, but not treated with clopidogrel. Importantly, such an impressive outcome benefit occurs over a relatively short follow-up, suggesting potentially even better long-term survival. Impact on mortality in the Danish MI cohort is impressive, the hardest to achieve, and unquestionably the most important outcome measure yielded from the National Prescription Registry, especially considering that the data were pooled from the entire population of Denmark. Notably, the diagnosis codes of MI previously were validated with a sensitivity of 91% and a positive predictive value of 93% (17), improving the quality of the current analyses even further. Importantly, oral antiplatelet agents belong to the elite class of pharmaceuticals known to reduce mortality significantly in outcome-driven clinical studies. Historically, only 2 clinical trials, one with aspirin (18) and the other with clopidogrel (14), were associated with rare absolute mortality reduction benefit in patients after acute vascular thrombotic events. Recently, a remarkable and somewhat surprising achievement has been reported with ticagrelor in the PLATO (PLAtelet Inhibition and Clinical Outcomes) trial (19), when 107 more lives were saved with ticagrelor than after conventional clopidogrel, representing a highly significant

*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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absolute mortality reduction (hazard ratio: 0.78; 95% confidence interval: 0.69 to 0.89; \( p < 0.001 \)). However, being a first-in-class cyclopyrenyl-triazolo-pyrimidine, ticagrelor is not a pure antiplatelet agent and exhibits numerous properties beyond platelet inhibition via modulation of plasma adenosine levels and up-regulation of adenosine receptors (20). Recognizing the mortality advantage of aspirin in ISIS-2 (Second International Study of Infarct Survival) (18), clopidogrel in COMMIT (Clopidogrel and Metoprolol in Myocardial Infarction Trial) (14), and ticagrelor in PLATO (19), the positive impact of clopidogrel on HF survival may be anticipated and is not that surprising. A few issues, however, remain unsettled. The registry does not collect many clinical characteristics such as blood pressure, left ventricular ejection fraction, B-type natriuretic peptide levels, and other risk factors that could define how the HF origin, severity, comorbidities, or concomitant medications influenced the patients’ prognosis. Also, the study was not controlled for clopidogrel compliance, duration of antiplatelet therapy, drug intolerance, or, finally, side effects, including bleeding complications.

Aside from the failure of the WATCH trial to show superiority of clopidogrel over aspirin, and especially over warfarin (15), we have no randomized evidence linking clopidogrel, HF, and improved survival. The highly anticipated results of the WARCEF (Warfarin versus Aspirin in Patients with Reduced Cardiac Ejection Fraction) trial (21) are pending, although the clopidogrel arm is lacking in that study. A head-to-head randomized study of conventional HF therapy with and without clopidogrel is needed urgently, although the chances for such a study are slim considering generic clopidogrel competition, the need for a large sample size, and the long 3 to 5 years of follow-up needed to adequately test the mortality end point hypothesis.

Despite some well-recognized limitations, Bonde et al. (16) advanced our current understanding of the potential benefit of clopidogrel in reducing all-cause mortality in patients after first MI and associated HF. Future attempts to improve survival in HF by reducing platelet activation and thrombotic burden are warranted. Reduced-dose, once-daily ticagrelor looks especially promising considering the remarkable absolute mortality benefit achieved in the recent PLATO trial.

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REFERENCES


Key Words: clopidogrel • mortality • heart failure • acute myocardial infarction.