Contemporary drug-eluting stents are associated with low thrombotic event rates. Hence, recent RCTs had lower than anticipated event rates,[6,8] which may partly explain the overall neutral findings in these individual trials. In our pooled analysis of multiple RCTs, significant reduction in the rates of MACE, MI, and stent thrombosis was noted with the GGS. Patients with ACS are at higher risk of thrombotic events. Therefore, in our study, we did a subgroup analysis of patients with ACS after excluding the Assessment of Prospective *CYP2C19* Genotype Guided Dosing of Anti-Platelet Therapy in Percutaneous Coronary Intervention (ADAPT) trial.[9] This trial included heterogeneous population (50% stable coronary artery disease and 50% ACS). Our findings showed similar reductions in MACE, MI, and stent thrombosis with GGS. The lower odds of MACE with GGS are possibly driven by higher use of clopidogrel in the CS group of the PHARMCLO (Pharmacogenomic Approach to Selecting Antiplatelet Therapy in Acute Coronary Syndrome) and TAILOR-PCI trials.[6,10] It is quite plausible that some of these patients were poor metabolizers of clopidogrel, and hence at higher thrombotic risk. In fact, 36% of randomized subjects in the CS group of TAILOR-PCI trial had *CYP2C19* loss of function variants. The higher use of clopidogrel in these trials may also explain the similar risk of major bleeding noted in our meta-analysis. In the study by Claassens et al included in our analysis, significantly less bleeding was noted with GGS compared to CS, likely driven by higher use of Ticagrelor (90.5%) in the CS group.[8]

In conclusion, this meta-analysis demonstrates that in patients who underwent PCI and those with ACS, a genotype-guided initiation of oral $P2Y_{12}$ inhibitors is associated with lower rates of MACE, MI, and stent thrombosis. Implementation of point-of-care genotype testing, and P2Y12 inhibitor selection algorithms into practice is needed. In addition, further research is needed to evaluate the cost-effectiveness of such treatment strategies.

Disclosures

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Beta Blockade in Patients After Acute Myocardial Infarction

We read with great interest the article published (on-line July 28, 2020) by Podlesnikar et al,[1] on the long-term effect of early intravenous metoprolol in ST-segment elevation myocardial infarction patients. Previously,

Cardioprotection during an Acute Myocardial Infarction (METOCARD-CNIC) trial demonstrated the beneficial impact of early β-blockade in ST-segment elevation myocardial infarction patients. Using myocardial strain assessment in feature-tracking cardiac magnetic resonance imaging, the present study further suggested that the beneficial prognostic effect from early β-blockade particularly occurred in patients with severely impaired left ventricular (LV) systolic function. Their finding begs 2 pertinent questions in our daily practice: what is the factual barricade for early β-blockade during acute coronary syndrome (ACS)? and is there any practical strategy helping maximize the benefit from β-blockade?

In the present study, the authors excluded patients with Killip class III to IV acute heart failure (or systolic blood pressure persistently <120 mm Hg). Was severely impaired LV systolic function attributed to these clinical phenotypes? If so, those patients might benefit the most from early β-blockade. ACS can induce significant LV dysfunction and chamber dilation (sometimes beyond the culprit coronary artery territories).[2] Even after successful coronary revascularization, the ventricular dilation can last for days whereas the patients stay in coronary intensive care units, which can result in an assumption of reciprocal causation of persistent pump failure and ventricular pressure overload. Strict volume restriction and over-diuresis sometimes results in intolerance of vasodilators, circulatory aggravation, even hemodynamic instability.[3] Therefore, in many patients to be expected to benefit from early β-blockade, the application of beta blockers becomes "intolerable."

Pain and other stressors during ACS stimulate central and autonomic nervous systems, which increases body fluid loss. Evidence is mounting that brain natriuretic peptide release during ACS is likely proportional to the ischemic burden.[4,5] Other than as an important prognostic marker, brain natriuretic peptide causes diuresis, vasodilatation, and inhibition of the renin—aldosterone system, which decrease the mean arterial pressure and pulmonary capillary wedge pressure.[4,5] The patients with coronary artery disease risk factors often already received vasodilators (as outpatients), and experience less severe vasoconstriction when ACS develops. Low peripheral resistance and low preload can occur simultaneously. Therefore, post-ACS volume management cannot be solely based on LV morphological abnormalities. The guidance from real-time parametric imaging (such as quantitative doppler echocardiography) helps timely titrate ventricular preload, avoid hemodynamic compromise, and support early and adequate β-blockade treatment, helping achieve long term beneficial effect.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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Statin Treatment of COVID-19

In a recent meta-analysis of 4 observational studies, Kow and Hasan reported that statins were 30% effective in reducing the severity or mortality of COVID-19.[1–5] Since their report was published, 2 additional observational studies have appeared.[6,7] Most of these 6 studies reported on statin treatment in reducing 30-day mortality (Table 1). However, Kow and Hasan considered studies in which patients received statins either as outpatients or inpatients (Table 1). For this reason, their estimate of statin effectiveness was probably imprecise.

Statins are known to downregulate inflammatory cytokines and other biomarkers of inflammation.[8] Studies in human volunteers showed that these effects occur in a matter of a few hours or a day or 2.[9] Moreover, in patients who have been taking statins, withdrawing treatment is followed by a rebound that increases both cytokine levels and mortality.[10,11] Yan et al and Grasselli et al did not report on whether outpatient statin treatment was continued after hospital admission.[2,4] A recent report of statins treatment by Gupta et al was also based on outpatient records (Table 1).[6] In this study, only 77% of outpatient statin users continued treatment as inpatients, which means that 23% of the group of statin outpatient users were at risk of a rebound effect and increased mortality after hospital admission. This could have led to an underestimate of survival in patients who received statins as inpatients.

Two of the 4 studies reported by Kow and Hasan were correctly based on inpatient statin treatment and both showed statistically significant improvement in survival (Table 1).[3,5] The smaller study by De Spiegleer et al also reported benefits in statin users among nursing home