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

Table 1
Statin treatment and 28-30-day COVID-19 mortality

Study, type (ref)	Statin treatment Outpatient/Inpatient	Controls/ treated (no.)	Adjusted hazard ratio	95% CI	p value
Yan, cohort (2)*	Outpatient	482/128	0.98	0.32-2.99	0.97
Rodriguez-Nava, cohort, ICU (3)	Inpatient	39/48	0.38	0.18-0.77	0.008
Grasselli, cohort (4)	Outpatient	2,062/1,926	0.98	0.81-1.20	0.87
Zhang, PSM, 4:1 (5)	Inpatient	3,444/861	0.58	0.43-0.80	0.001
Gupta, PSM (6)	Outpatient	648/648	0.49	0.38-0.63	<0.001
de Spiegleer, cohort, NH (7)†	Inpatient	133/31	0.51	0.14-1.35	0.209

CI = confidence interval; ICU = intensive care unit; PSM = propensity score matched.

* The study by Yan et al evaluated the effect of statin treatment in reducing the severity of COVID-19, not its mortality.

† The study by de Spiegeleer et al evaluated residents of nursing homes who either died in hospital or experienced hospital stays ≥7 days.

residents, but the result did not reach statistical significance.[7]

The largest and most detailed study of inpatient statin treatment by Zhang et al also reported that inpatient treatment with angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) did not provide a survival benefit greater than that provided by statin treatment alone.[5] Nonetheless, several reports have shown that in hypertensive COVID-19 patients, outpatient or inpatient treatment with ACEIs or ARBs is not harmful,[12–14] and in some instances, these drugs actually improve survival.[14] In addition, inpatient ACEI/ARB treatment can reduce levels of inflammatory biomarkers.[12] Importantly, survival was significantly better in COVID-19 patients whose ACEI/ARB outpatient treatment was continued in the hospital compared with those whose treatment was discontinued.[15] This echoes the experience with statin withdrawal.

Patients with COVID-19 experience severe endothelial dysfunction.[16] Statins and ARBs (and presumably ACEIs) have broad effects in maintaining or restoring normal endothelial cell function.[17] Combination treatment with both drugs has been suggested for cardiovascular diseases[18] and for emerging infectious diseases,[17] including Ebola and COVID-19.[19,20] These drugs primarily target the host response to infection,[21] not the viruses themselves.[17–20,22] Like dexamethasone, which has been shown in a randomized controlled trial to modestly improve survival in COVID-19 patients who require oxygen treatment or mechanical ventilation,[23] they are available worldwide as inexpensive generic drugs and could be used on the first pandemic day in any country that has a basic healthcare system.

Several randomized controlled trials of statins, ACEIs and ARBs are planned or are underway for COVID-19 patients, but most of them will not report results until 2021. In the meantime, many physicians will feel an immediate need to offer effective treatments for their COVID-19 patients.[24] The studies of inpatient statin treatment are supported by solid experimental and clinical findings,[17] but it is unclear whether they provide a sufficient basis on which physicians can decide how to treat their patients. Nonetheless, the studies summarized in Table 1, together with future observational reports on the effectiveness of inpatient treatment of COVID-19 patients with statins (and perhaps ACEIs/ARBs), will undoubtedly contribute to their treatment decisions.

Disclosure

The author has no conflicts of interest to disclose. 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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Implementation of a Novel Order Set to Improve Baseline Pulmonary, Hepatic, and Thyroid Function Testing at Time of Inpatient Amiodarone Initiation

Amiodarone is a chemically-unique class III antiarrhythmic drug and is commonly-prescribed by internists and cardiologists alike.[1] In addition to its

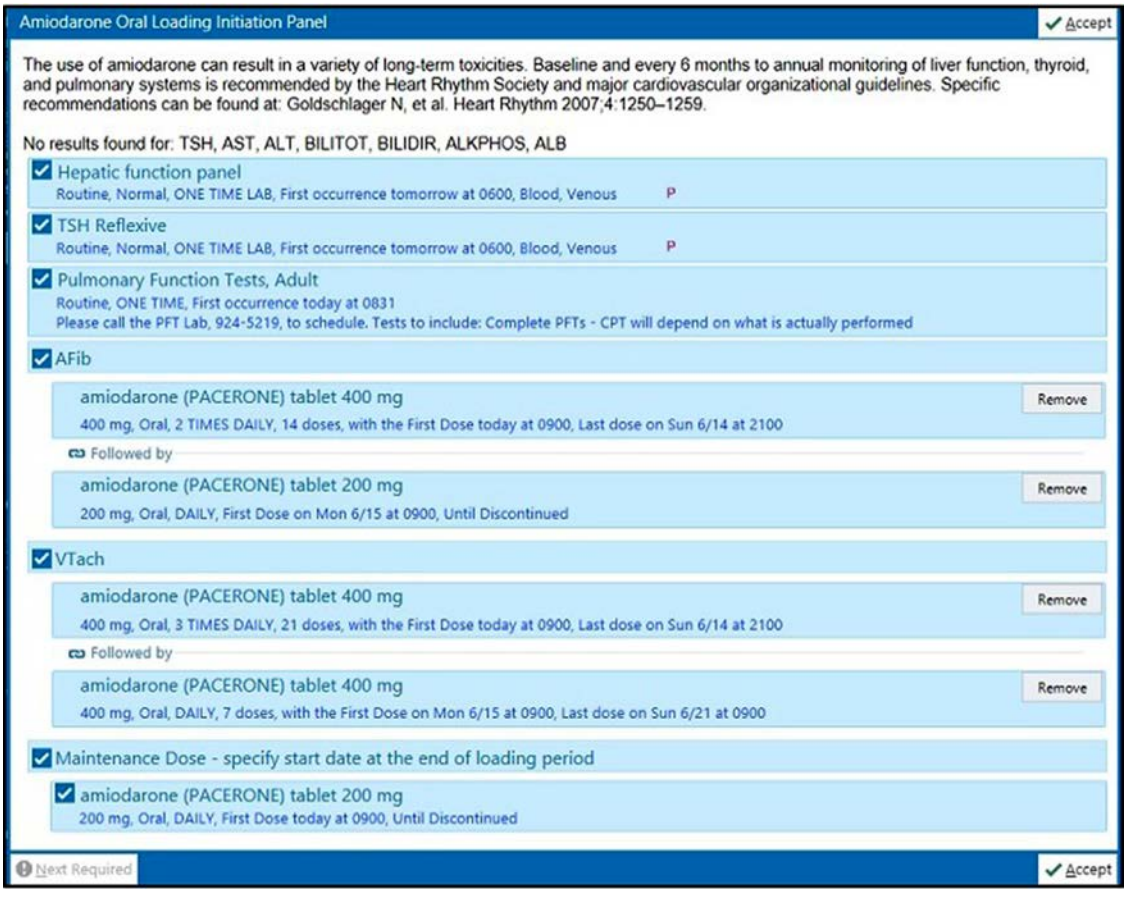

Figure 1. Oral amiodarone initiation order set. Searches for available thyroid, hepatic, and pulmonary function testing over the past six months, and provides orders for each. Also provides dosing and duration for common amiodarone indications.