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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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- Podlesnikar T, Pizarro G, Fernández-Jiménez R, Montero-Cabezas JM, Sánchez-González J, Bucciarelli-Ducci C, Ajmone Marsan N, Fras Z, Bax JJ, Fuster V, Ibáñez B, Delgado V. Five-year outcomes and prognostic value of feature-tracking cardiovascular magnetic resonance in patients receiving early reperfusion metoprolol in acute myocardial infarction. *Am J Cardiol* 2020. <https://doi.org/10.1016/j.amjcard.2020.07.037>.
- Lei J, Chen J, Dogra M, Gebaska MA, Shetty S, Ponnappureddy R, Roy SD, Wang JF, Liu K. Takotsubo effect" in patients with ST segment elevation myocardial infarction. *Eur Heart J Acute Cardiovasc Care* 2020. <https://doi.org/10.1177/2048872620926680>.
- Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masouli FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA focused update of the 2013 ACCF/AHA Guideline for the management of heart failure: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. *Circulation* 2017;136:e137–e161.
- De Lemos JA, Morrow DA, Bantley JH, Bentley JH, Omland T, Sabatine MS, McCabe CH, Hall C, Cannon CP, Braunwald E. The prognostic value of B-type natriuretic peptide in patients with acute coronary syndromes. *N Engl J Med* 2001;345:1014–1021.
- Haeck JD, Verouden NJ, Kuijt WJ, Koch KT, Van Straalen JP, Fischer J, Groenink M,

Bilodeau L, Tijssen JG, Krucoff MW, De Winter RJ. Comparison of usefulness of N-terminal pro-brain natriuretic peptide as an independent predictor of cardiac function among admission cardiac serum biomarkers in patients with anterior wall versus nonanterior wall ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Am J Cardiol* 2010;105:1065–1069. <https://doi.org/10.1016/j.amjcard>.

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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 Spiegler 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 Spiegeleer, 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 diseases¹⁸ 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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1. Kow CS, Hasan SS. Meta-analysis of effectiveness of statins in patients with severe COVID-19. *Am J Cardiol* <https://doi.org/10.1016/ajmcard.2020.08.004>.
2. Yan H, Valdes AM, Vijay A. Role of drugs affecting the renin-angiotensin-aldosterone system on susceptibility and severity of COVID-19: a large case-control study from

Zhejiang Province, China. *Preprint. medRxiv* 2020:20077875. 04.24.

3. Rodriguez-Nava G, Trelles-Garcia DP, Yanez-Bello MA, Chung CW, Trelles-Garcia VP, Friedman HJ. Atorvastatin associated with decreased hazard for death in COVID-19 patients admitted to an ICU: a retrospective cohort study. *Crit Care* 24:429.
4. Grasselli G, Greco M, Zanella A, Albano G, Antonelli M, Bellani G, Bonanomi E, Cabrini L, Carlesso E, Castelli G, Cattaneo S, Cereda D, Colombo S, Coluccello A, Crescini G, Forastieri Molinari A, Foti G, Fumagalli R, Iotti GA, Langer T, Latronico N, Lorini FL, Mojoli F, Natalini G, Pessina CM, Ranieri VM, Rech R, Scudeller L, Rosano A, Storti E, Thompson BT, Tirani M, Villani PG, Pesenti A, Cecconi M. COVID-19 Lombardy ICU Network. Risk factors associated with mortality among patients with COVID-19 in intensive care units in Lombardy, Italy. *JAMA Intern Med* :e203539.
5. Zhang XJ, Qin JJ, Cheng X, Shen L, Zhao YC, Yuan Y, Lei F, Chen MM, Yang H, Bai L, Song X, Lin L, Xia M, Zhou F, Zhou J, She ZG, Zhu L, Ma X, Xu Q, Ye P, Chen G, Liu L, Mao W, Yan Y, Xiao B, Lu Z, Peng G, Liu M, Yang J, Yang L, Zhang C, Lu H, Xia X, Wang D, Liao X, Wei X, Zhang BH, Zhang X, Yang J, Zhao GN, Zhang P, Liu PP, Loomba R, Ji YX, Xia J, Wang Y, Cai J, Guo J, Li H. In-hospital use of statins is associated with a reduced risk of mortality among individuals with COVID-19. *Cell Metab* 32:176-187.
6. Gupta A, Madhavan MV, Poterucha TJ, DeFilippis EM, Hennessey JA, Redfors B, Eckhardt C, Bikdeli B, Platt J, Nalbandian A, Elias P, Cummings MJ, Hourani SN, Lawlor M, Ranard LS, Li J, Boyle C, Givens R, Brodie D, Krumholz HM, Stone GW, Sethi SS, Burkhoff D, Uriel N, Schwartz A, Leon MB, Kirtane AJ, Wan EY, Parikh SA. Association between antecedent statin use and decreased mortality in hospitalized patients with COVID-19. *Res Sq*. doi.org/10.21203/rs.3.rs-56210/v1.1.
7. De Spiegeleer A, Bronselaer A, Teo JT, Byttebier G, De Tre G, Belmans L, Dobson R, Wynndaele E, Van De Wiele C, Vandaele F, Van Dijk D, Bean D, Fedson D, De Spiegeleer B. The effects of ARBs, ACEIs, and statins on clinical outcomes of COVID-19 infection among nursing home residents. *J Am Med Dir Assoc* 21:909-914.
8. Oesterle A, Laufs U, Liao JK. Pleiotropic effects of statins on the cardiovascular system. *Circ Res* 120:229-243.
9. Shyamsundar M, McKeown STW, O'Kane CM, Craig TR, Brown V, Thickett DR, Mathay MA, Taggart CC, Backman JT, Elborn JS, McAuley DF. Simvastatin decreases lipopolysaccharide-induced pulmonary inflammation in healthy volunteers. *Am J Respir Crit Care Med* 179:1107-1114.
10. Fonarow GC, Wright RS, Spencer FA, Fredrick FA, Dong W, Every N, French WJ. National Registry of Myocardial Infarction 4 Investigators. Effect of statin use within the first 24 hours of admission for acute myocardial infarction on early morbidity and mortality. *Am J Cardiol* 96:611-616.

11. Cubeddu LX, Seamon MJ. Statin withdrawal: clinical implications and molecular mechanisms. *Pharmacotherapy* 261288–1296.
12. Yang G, Tan Z, Zhou L, Yang M, Peng L, Liu J, Cai J, Yang R, Han J, Huang Y, He S. Effects of ARBs and ACEIs on virus infection, inflammatory status and clinical outcomes in COVID-19 patients with hypertension: a single center retrospective study. *Hypertension* 7651–58.
13. Li J, Wang X, Chen J, Zhang H, Deng A. Association of renin-angiotensin system inhibitors with severity or risk of death in patients with hypertension hospitalized for coronavirus disease 2019 (COVID-19) infection in Wuhan, China. *JAMA Cardiol* 5825–830.
14. Zhang P, Zhu L, Cai J, Lei F, Qin JJ, Xie J, Liu YM, Zhao YC, Huang X, Lin L, Xia M, Chen MM, Cheng X, Zhang X, Guo D, Peng Y, Ji YX, Chen J, She ZG, Wang Y, Xu Q, Tan R, Wang H, Lin J, Luo P, Fu S, Cai H, Ye P, Xiao B, Mao W, Liu L, Yan Y, Liu M, Chen M, Zhang XJ, Wang X, Touyz RM, Xia J, Zhang BH, Huaeg X, Yuan Y, Rohit L, Liu PP, Li H. Association of inpatient use of angiotensin converting enzyme inhibitors and angiotensin II receptor blockers with mortality among patients with hypertension hospitalized with COVID-19. *Circ Res* 1261671–1681.
15. Lam KW, Chow KW, Vo J, Hou W, Li H, Richman PS, Mallipattu SK, Skopicki HA, Singer AJ, Duong TQ. Continued in-hospital ACE inhibitor and ARB use in hypertensive COVID-19 patients is associated with positive clinical outcomes. *J Infect Dis* 2221256–1264.
16. Gustafson D, Raju S, Wu R, et al. Overcoming barriers: the endothelium as a linchpin of coronavirus disease 2019 pathogenesis? *Arterioscler Thromb Vasc Biol* 401818–1829.
17. Fedson DS. Treating the host response to emerging virus diseases: lesson learned from sepsis, pneumonia, influenza and Ebola. *Ann Transl Med* 4421.
18. Koh KK, Sakuma I, Shimada K, Hayashi T, Quon MJ. Combining potent statin therapy with other drugs to optimize simultaneous cardiovascular and metabolic benefits while minimizing adverse events. *Korean Circ J* 47432–439.
19. Fedson DS. A practical treatment for patients with Ebola virus disease. *J Infect Dis* 211661–662.
20. Fedson DS, Opal SM, Rordam OM. Hiding in plain sight; an approach to treating patients with severe COVID-19 infection. *mBio* 11. e00398-20.
21. Pirofski L-a, Casadevall A. Pathogenesis of COVID-19 from the perspective of the damage-response framework. *mBio* 11. e01175-20.
22. Parihar SP, Guler R, Brombacher F. Statins: a viable candidate for host-directed therapy against infectious diseases. *Nat Rev Immunol* 19104–117.
23. RECOVERY Collaborative Group, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, Linsell L, Staplin N, Brightling C, Ustianowski A, Elmahi E, Prudon B, Green C, Felton T, Chadwick D, Rege K, Fegan C, Chappell LC, Faust SN, Jaki T, Jeffery K, Montgomery A, Rowan K, Juszczak E, Baillie JK, Haynes R, Landray MJ. Dexamethasone in hospitalized patients with Covid-19 - preliminary report. *N Engl J Med* NEJMoa2021436.
24. Angus DC. Optimizing the trade-off between learning and doing in a pandemic. *JAMA* <https://doi.org/10.1001/jama.2020.4984>.
<https://doi.org/10.1016/j.amjcard.2020.09.050>

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



Accept

The use of amiodarone can result in a variety of long-term toxicities. Baseline and every 6 months to annual monitoring of liver function, thyroid, and pulmonary systems is recommended by the Heart Rhythm Society and major cardiovascular organizational guidelines. Specific recommendations can be found at: Goldschlager N, et al. *Heart Rhythm* 2007;4:1250–1259.

No results found for: TSH, AST, ALT, BILITOT, BILIDIR, ALKPHOS, ALB

- Hepatic function panel
Routine, Normal, ONE TIME LAB, First occurrence tomorrow at 0600, Blood, Venous P
- TSH Reflexive
Routine, Normal, ONE TIME LAB, First occurrence tomorrow at 0600, Blood, Venous P
- Pulmonary Function Tests, Adult
Routine, ONE TIME, First occurrence today at 0831
Please call the PFT Lab, 924-5219, to schedule. Tests to include: Complete PFTs - CPT will depend on what is actually performed
- AFib
 - amiodarone (PACERONE) tablet 400 mg
400 mg, Oral, 2 TIMES DAILY, 14 doses, with the First Dose today at 0900, Last dose on Sun 6/14 at 2100 Remove
 - Followed by
 - amiodarone (PACERONE) tablet 200 mg
200 mg, Oral, DAILY, First Dose on Mon 6/15 at 0900, Until Discontinued Remove
- VTach
 - amiodarone (PACERONE) tablet 400 mg
400 mg, Oral, 3 TIMES DAILY, 21 doses, with the First Dose today at 0900, Last dose on Sun 6/14 at 2100 Remove
 - Followed by
 - amiodarone (PACERONE) tablet 400 mg
400 mg, Oral, DAILY, 7 doses, with the First Dose on Mon 6/15 at 0900, Last dose on Sun 6/21 at 0900 Remove
- Maintenance Dose - specify start date at the end of loading period
 - amiodarone (PACERONE) tablet 200 mg
200 mg, Oral, DAILY, First Dose today at 0900, Until Discontinued

Next Required

Accept

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.