Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHEST

Dihydropyridine Calcium Channel Blockers and the Risk of Severe COVID-19

To the Editor:

$\dot{V}/\dot{Q}$ mismatch and the loss of hypoxic pulmonary vasoconstriction play a pivotal role in the pathophysiology of COVID-19 respiratory distress.[1,2] Dihydropyridine calcium channel blockers (CCBs), frequently prescribed first-line antihypertensive agents, have the potential to disrupt hypoxic pulmonary vasoconstriction[3] and worsen $\dot{V}/\dot{Q}$ mismatch that leads to profound hypoxemia in patients with pulmonary disease.[4] We hypothesized that CCBs would be associated with worse respiratory failure in patients with COVID-19.

Methods

Among 444 consecutively hospitalized patients with confirmed COVID-19 (admitted between March 13 and April 7, 2020, at a quaternary referral center and an affiliated community hospital in Massachusetts), 245 patients had hypertension and were included in the analysis. Data elements were abstracted retrospectively from the electronic health record by trained study personnel who followed standardized protocol. The study was approved by the Partners Healthcare Institutional Review Board with a waiver of informed consent.

Dihydropyridine CCB exposure status was based on confirmed home medication list at the time of hospital admission. The primary end point was a composite of intubation or death modeled as a time-to-event analysis.[5] For patients who died after intubation, the time of intubation was considered time of primary end point as with previous studies.[5] Cox models were used to evaluate the association between CCBs and the primary end point. Models were adjusted for age, sex, race/ethnicity, BMI, diabetes mellitus, coronary artery disease, heart failure, pulmonary hypertension, chronic kidney disease, asthma/COPD, peripheral arterial disease, Charlson Comorbidity Index, and the following medications: angiotensin-converting enzyme inhibitor/angiotensin receptor blocker, thiazide diuretic, loop diuretic, beta blocker, aspirin, and statin. To further account for potential confounding, an additional analysis was performed with propensity score matching. The propensity score for CCB use was estimated with a logistic regression model that incorporated the same covariates used in the multivariable Cox model.

Results

Of the 245 individuals with hypertension included in our analysis, 70 (29%) were taking CCBs, and 175 (71%) were not. Baseline characteristics according to CCB use are shown in Table 1 for both the unmatched and matched samples. The propensity score matched cohort consisted of 116 individuals; 58 exposed to CCBs and 58 who were not. In both the matched and unmatched samples, slightly less than one-half the cohort was female, and nearly 50% of the cohort was non-white. Average time from symptom onset to hospital presentation was 7 $\pm$ 5 days. At the time of hospital presentation, patients who had been taking CCBs were more likely to have an oxygen saturation <90% (Table 1).

Over a median follow up of 10 days (interquartile range, 6-21), 111 patients (45%) had a primary end point (90 were intubated, 21 died before intubation). Patients who were taking CCBs had an increased risk of the primary end point: 40 patients (57%) vs 71 (41%); hazard ratio (HR), 1.8 (95% CI, 1.2-2.6); $P = .004$) (Fig 1). After multivariable adjustment, the association persisted: HR, 1.8 (95% CI, 1.2-2.8); $P = .006$. An additional multivariable-adjusted competing-risk analysis evaluating risk of intubation alone revealed similar findings: HR, 1.9 (95% CI, 1.2-3.0); $P = .006$). Among the 90 patients who were intubated, those taking CCBs had a lower Pao_2:Fio_2 ratio on the postintubation arterial blood gas than patients not taking CCBs (Table 1). At time of censoring, 53 patients (22%) had died (CCB, 27%; no CCB, 19%), 2 (1%) remained hospitalized (CCB, 0%; no CCB, 1%), and 190 (77%) survived to hospital discharge (CCB, 73%; no CCB, 79%; $P = .29$).

Given that 37 patients (53%) in the CCB group had their CCBs discontinued on hospital admission, we performed a sensitivity analysis to evaluate the association between CCB use and the primary end point within 24 hours of admission, before the potential

TABLE 1] Baseline Characteristics Stratified by Dihydropyridine Calcium Channel Blocker Exposure

Variable	Unmatched Patients			Matched Patients		
	No Calcium Channel Blocker (n = 175)	Calcium Channel Blocker (n = 70)	Standardized Difference	No Calcium Channel Blocker (n = 58)	Calcium Channel Blocker (n = 58)	Standardized Difference
Baseline demographics						
Age, mean ± SD, y	70 ± 14	70 ± 15	0.01	73 ± 12	70 ± 16	0.20
Female, No. (%)	85 (49)	28 (40)	0.17	28 (48)	25 (43)	0.10
BMI, mean ± SD, kg/m^2	30 ± 7	30 ± 6	0.08	30 ± 7	30 ± 7	0.05
Race/ethnicity, No. (%)						
White	88 (50)	30 (43)		30 (52)	27 (47)	
Black	27 (15)	9 (13)		10 (17)	8 (14)	
Hispanic	43 (25)	24 (34)		15 (26)	17 (29)	
Asian	7 (4)	2 (3)		1 (2)	2 (3)	
Other	1 (1)	0		0	0	
Unknown	9 (5)	5 (7)		2 (3)	4 (7)	
Baseline comorbidities						
Diabetes mellitus, No. (%)	78 (45)	41 (59)	0.28	30 (52)	31 (53)	0.03
Coronary artery disease, No. (%)	45 (26)	13 (19)	0.17	11 (19)	13 (22)	0.09
Heart failure, No. (%)	35 (20)	10 (14)	0.15	5 (9)	9 (16)	0.21
Asthma/COPD, No. (%)	37 (21)	13 (19)	0.06	10 (17)	11 (19)	0.04
Chronic kidney disease (creatinine >3 mg/dL), No. (%)	10 (6)	3 (4)	0.07	1 (2)	3 (5)	0.19
Pulmonary hypertension, No. (%)	7 (4)	1 (1)	0.16	1 (1)	1 (1)	0
Peripheral arterial disease, No. (%)	18 (10)	9 (13)	0.08	7 (12)	9 (16)	0.10
Charlson Comorbidity Index, mean±SD	2.1 ± 2.0	2.0 ± 1.7	0.07	1.8 ± 1.7	2.1 ± 1.6	0.18
Baseline medications, No. (%)						
Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker	88 (50)	37 (53)	0.05	29 (50)	30 (52)	0.03
Thiazide diuretic	34 (19)	16 (23)	0.08	14 (24)	14 (24)	0
Loop diuretic	29 (17)	11 (16)	0.02	8 (14)	8 (14)	0
Beta blocker	66 (38)	31 (44)	0.13	23 (40)	24 (41)	0.04
Statins	96 (55)	46 (66)	0.22	34 (59)	36 (62)	0.07
Aspirin	76 (43)	29 (41)	0.04	22 (38)	26 (45)	0.14

(Continued)

TABLE 1 (Continued)

Variable	Unmatched Patients			Matched Patients		
	No Calcium Channel Blocker (n = 175)	Calcium Channel Blocker (n = 70)	Standardized Difference	No Calcium Channel Blocker (n = 58)	Calcium Channel Blocker (n = 58)	Standardized Difference
Clinical presentation						
SpO_2 % in ED, median (interquartile range)	96 (94-97)	94 (92-97)	0.42	96 (94-97)	94.5 (91 -97)	0.40
SpO_2 in ED <90%, No. (%)	8 (5)	11 (16)	0.38	2 (3)	9 (16)	0.42
P:F ratio after intubation, mean±SD (No.)	210 ± 91 (55)	164 ± 81 (35)	0.53	225 ± 90 (17)	164 ± 83 (28)	0.71

expected effect of drug discontinuation. CCB use was associated with a two-fold increased risk of intubation and death (95% CI, 1.1-3.9; $P = .03$) within 24 hours of admission.

In the propensity score matched sample, 55 patients (47%) had a primary end point (45 were intubated, 10 died before intubation). Similar to the unmatched cohort, patients who had been taking CCBs had an increased risk of the primary end point: HR, 1.9 (95% CI, 1.1-3.2); $P = .02$ (Fig 1). Adjustment for the five covariates with standardized difference of >0.1 (Table 1) revealed an HR of 1.9 (95% CI, 1.1-3.3; $P = .02$). As a robustness check, an inverse probability treatment weighted Cox model yielded similar results: HR, 1.6 (95% CI, 1.1-2.3; $P = .02$). At time of censoring, 27 patients (23%) had died (CCB, 29%; no CCB, 17%), and 89 patients survived to hospital discharge (CCB, 71%; no CCB, 83%; $P = .12$).

Discussion

In our cohort of consecutive patients who were hospitalized with confirmed COVID-19, patients with a history of hypertension who had been taking dihydropyridine CCBs had a significantly increased risk of intubation or death compared with those not taking dihydropyridine CCBs. These findings support the pathophysiologic-based hypothesis that, in patients with COVID-19, dihydropyridine CCBs (medications that can disrupt hypoxic pulmonary vasoconstriction) are associated with an increased risk for respiratory failure. Our results are consistent with previously published data that showed a modestly increased likelihood of severe COVID-19 in patients with hypertension who were taking CCBs.[6] Additionally, previous research has demonstrated that, in patients with ARDS, systemically administered pulmonary vasodilators can decrease regional hypoxic pulmonary vasoconstriction leading to worse hypoxemia, whereas selective pulmonary vasodilation with the use of inhaled pulmonary vasodilators can attenuate hypoxemia through improving $\dot{V}/\dot{Q}$ mismatch by acting in only well-ventilated lung regions.[7]

Limitations include small sample size, retrospective observational study design; although we adjusted for likely confounders, we were unable to adjust for chronicity of hypertension and cannot rule out unmeasured confounding.

Although we would not advocate currently for a change in practice based on these results, we would urge caution

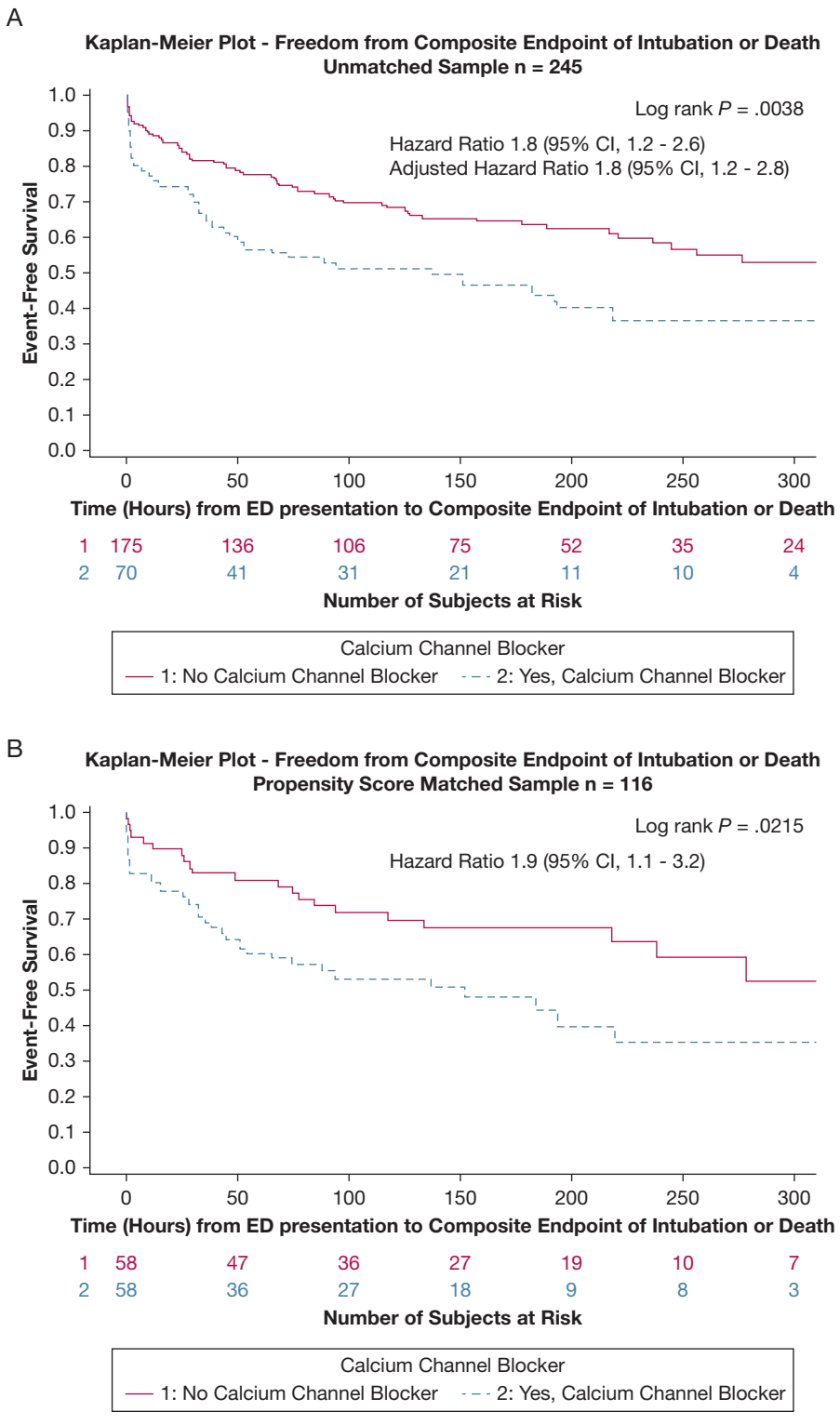

Figure 1 – *A-B, Risk of intubation or death in patients with COVID-19 according to calcium channel blocker exposure. A, Unmatched cohort. B, Propensity score matched cohort.*

against the suggestion to transition patients empirically from angiotensin-converting enzyme inhibitor/angiotensin receptor blocker to CCBs.[8] If our findings are confirmed, it may be reasonable to transition patients from dihydropyridine CCBs to alternative agents. Given the high prevalence of hypertension and its associated risk for COVID-19 coupled with the frequency of dihydropyridine CCB use, these findings may have significant public health implications and warrant further study.

Sean R. Mendez, MD
Rachel C. Frank, MD
Boston, MA
Elizabeth K. Stevenson, MD
Salem, MA
Mabel Chung, MD, MPH
Michael G. Silverman, MD, MPH
Boston, MA

AFFILIATIONS: From the Department of Medicine (S. Mendez), the Cardiology Division, Department of Medicine (R. Frank and M. Silverman), the Department of Anesthesia, Critical Care and Pain Medicine (M. Chung), and the Heart Center Intensive Care Unit (M. Chung and M. Silverman), Massachusetts General Hospital; the Division of Pulmonary, Critical Care, and Sleep Medicine (E. Stevenson), North Shore Medical Center; and the Smith Center for Outcomes Research in Cardiology, Division of Cardiovascular Medicine, Department of Medicine (M. Chung), Beth Israel Deaconess Medical Center.

FINANCIAL/NONFINANCIAL DISCLOSURES: The authors have reported to *CHEST* the following: M. S. receives support from Harvard Catalyst/The Harvard Clinical and Translational Science Center (National Center for Advancing Translational Sciences, National Institutes of Health Award UL 1TR002541) and financial contributions from Harvard University and its affiliated academic healthcare centers. M. Chung receives support from the National Institutes of Health [Grant 5T32GM007592-40] and from Medtronic outside the submitted work. None declared (S. M., R. F., E. S.).

CORRESPONDENCE TO: Michael G. Silverman, MD, MPH; email: mgsilverman@mgh.harvard.edu

DOI: https://doi.org/10.1016/j.chest.2021.01.073

Acknowledgments

Other contributions: The content is solely the responsibility of the authors and does not necessarily represent the official views of Harvard Catalyst, Harvard University and its affiliated academic healthcare centers, or the National Institutes of Health.

References

1. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA*. 2020;323(22):2329-2330.
2. Sweeney RM, Mcauley DF. Acute respiratory distress syndrome. *Lancet*. 2016;388(10058):2416-2430.
3. Simonneau G, Escourrou P, Duroux P, Lockhart A. Inhibition of hypoxic pulmonary vasoconstriction by nifedipine. *N Engl J Med*. 1981;304(26):1582-1585.
4. Mishra A, Reed RM, Eberlein M. Severe, rapidly reversible hypoxemia in the early period after bilateral lung transplantation. *Ann Am Thorac Soc*. 2016;13(6):979-985.
5. Geleris J, Sun Y, Platt J, et al. Observational study of hydroxychloroquine in hospitalized patients with Covid-19. *N Engl J Med*. 2020;382(25):2411-2418.
6. Reynolds HR, Adhikari S, Pulgarin C, et al. Renin-angiotensin-aldosterone system inhibitors and risk of Covid-19. *N Engl J Med*. 2020;382(25):2441-2448.
7. Radermacher P, Maggiore SM, Mercat A. Fifty years of research in ARDS: gas exchange in acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;196(8):964-984.
8. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21.