Impact of Chronic Kidney Disease and Anemia on Outcomes After Percutaneous Coronary Revascularization

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Few studies have evaluated outcomes after percutaneous coronary intervention (PCI) in patients with both anemia (hemoglobin < 12 g/dl in women; <13 in men) and chronic kidney disease (CKD, estimated glomerular filtration rate < 60 ml/min/1.73 m^2). Patients with coronary artery disease who underwent PCI in our health system from 2010 to 2018 were included (n = 10,756), excluding those with ST-elevation myocardial infarction or shock. We evaluated the individual and combined effects of anemia and CKD on outcomes. Five-year mortality was highest in the cohort with both anemia and CKD and lowest in those with neither. After multivariate analysis, with the group with neither anemia nor CKD as a reference, the adjusted hazard ratio for mortality was 1.68 (95% confidence interval [CI] 1.45 to 1.95, p <0.001) for those with anemia alone, 1.33 (95% CI 1.15 to 1.53, p <0.001) for those with CKD alone, and 2.83 (95% CI 2.49 to 3.22, p <0.001) for those with both anemia and CKD. With respect to readmission and reintervention, similar tends were observed, with patients with both CKD and anemia having the highest risk for these outcomes. In conclusion, the combined effects of anemia and CKD on outcomes post-PCI appear to be worse than either of their effects individually. **(Am J Cardiol 2019;124:851−856)**

Coronary artery disease is the leading cause of death in the United States (US) in both men and women.[1] Anemia and CKD are 2 common co-morbid conditions in patients with coronary artery disease, and each individually has been shown to negatively affect outcomes after PCI through a variety of mechanisms.[2−5] Several studies have shown that patients with CKD have higher risk for ischemic and bleeding events, as well as the highest rate of all-cause and cardiovascular mortality after PCI compared to patients with normal kidney function.[6−9] One study examined major adverse cardiac events in patients with CKD who underwent a first PCI within the Coronary REvascularization Demonstrating outcome study in Kyoto (CREDO-Kyoto) cohort-2, and illustrated that the combined presence of anemia and CKD in patients is associated with worse outcomes.[2] Other than this one study, however, there is a paucity of data evaluating outcomes post-PCI in patients with both CKD and anemia in contemporary practice from the United States. Therefore, this analysis aims to evaluate how anemia and CKD affect mortality, readmission, and reintervention in patients after PCI individually and when they coexist.

METHODS

The study is a retrospective cohort study evaluating patients who underwent PCI within our health system between the years of 2010 to 2018. The University of Pittsburgh Medical Center (UPMC) is a large multihospital system that consists of both academic and private-practice hospitals. This analysis included patients who were treated across 6 cardiac catheterization laboratories. Patients were identified using hospital administrative claims data, and all clinical data were collected from electronic healthcare records (EHR). Patients were excluded if they underwent coronary artery bypass grafting during the index admission, or if they had a ST-elevation myocardial infarction, cardiogenic shock, or cardiac arrest. Anemia was defined as hemoglobin less than 12 g/dl in women and less than 13 g/dl in men.[10] CKD was defined as an estimated glomerular filtration rate less than 60 ml/min/1.73 m^2.[11]

The primary outcome was overall mortality which was assessed using the EHR and the US Social Security Death Index. Secondary outcomes included freedom from inpatient readmission and freedom from repeat revascularization. Inpatient readmission and repeat revascularization rates were measured based upon those events occurring within the UPMC Health System and based upon the EHR. Repeat revascularization was defined as any unplanned PCI or coronary artery bypass grafting.

Descriptive characteristics are presented as mean for continuous variables and n (%) for categorical variables. Continuous variables are compared using the unpaired *t* test. Discrete categorical variables are expressed as counts with percentages and analyzed by Pearson's chi-squared test or Fisher's exact test. Differences between groups for the time-to-event outcomes (survival; readmission; and repeat revascularization) are presented using Kaplan-Meier curves and Cox proportional-hazards regression to compare anemia only, CKD only and anemia and CKD groups versus no disease. Cox's proportional hazards regression modeling, with

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adjustment for covariates, were used and all adjusted models are adjusted for the following: age, gender, body mass index, race, tobacco use, alcohol use, congestive heart failure, hypertension, chronic obstructive pulmonary disease, diabetes, coronary artery disease, atrial fibrillation, liver disease, and cancer. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

There was a total of 10,756 patients in our analytical dataset who met the inclusion criteria: 3,957 patients without anemia or CKD; 1,441 with anemia only; 3,054 with CKD only; 2,304 with both anemia and CKD. Table 1 shows the baseline data for the 4 cohorts. There were differences in numerous baseline characteristics, many of them statistically significant given the large population sizes. The mean age of the population was 67.8 years with 32.7% female. Those without anemia or CKD tended to be younger whereas those with both anemia and CKD tended to be older. Those with CKD and anemia had more co-morbidities.

Figure 1 shows the Kaplan-Meier curve for 5-year freedom from mortality. The mean follow-up duration was 4.01, 3.78, 3.13, and 2.87 years in the no anemia or CKD, anemia only, CKD only, and both anemia and CKD groups, respectively. There was a total of 1,889 deaths in the overall cohort. The estimated 1-year mortality was 1.9%, 7.3%, 3.6%, and 12.2% in the no anemia or CKD, anemia only, CKD only, and both anemia and CKD groups, respectively. The estimated 3-year mortality was 6.3%, 16.7%, 10.0%, and 28.7% in the no anemia or CKD, anemia only, CKD only, and both anemia and CKD groups, respectively. The estimated 5-year mortality was 12.2%, 23.9%, 20.2%, and 43.1% in the no anemia or CKD, anemia only, CKD only, and both anemia and CKD groups, respectively. Using the group without CKD or anemia as the reference, the overall adjusted hazard ratio for mortality of both anemia and CKD was 2.83 (95% confidence interval [CI] 2.49 to 3.22, p <0.001), and 1.68 (95% CI 1.45 to 1.95, p <0.001) and 1.33 (95% CI 1.15

Table 1
Baseline characteristics

	Total n = 10,756	No anemia or CKD n = 3,957	Anemia only n = 1,441	CKD only n = 3,054	Both anemia and CKD n = 2,304	p Value
Age (years)	67.8 (19.3- 105)	64.4 (19.3-96.1)	70.5 (25.3-96.2)	67.7 (22.8- 105)	73.0 (31.2-98.8)	<0.001
Men	7241 (67.3%)	2903 (73.4%)	916 (63.6%)	2044 (66.9%)	1378 (59.8%)	
Women	3515 (32.7%)	1054 (26.6%)	525 (36.4%)	1010 (33.1%)	926 (40.2%)	
White	9856 (91.6%)	3694 (93.4%)	1278 (88.7%)	2854 (93.5%)	2030 (88.1%)	
Black	691 (6.4%)	197 (5.0%)	120 (8.3%)	142 (4.6%)	232 (10.1%)	
Other/not identified	209 (1.9%)	66 (1.7%)	43 (3.0%)	58 (1.9%)	42 (1.8%)	
BMI (kg/m^2)	29.5 (12.9-92.3)	29.8 (15.4-63.5)	28.4 (12.9-71.9)	29.9 (15.0-67.0)	28.9 (14.8-92.3)	<0.001
Tobacco use						<0.001
No	4,825 (44.9%)	1,785 (45.1%)	646 (44.8%)	1,306 (42.8%)	1,088 (47.2%)	
Yes	1,434 (13.3%)	612 (15.5%)	174 (12.1%)	467 (15.3%)	181 (7.9%)	
Former	4,497 (41.8%)	1,560 (39.4%)	621 (43.1%)	1,281 (41.9%)	1,035 (44.9%)	
Alcohol use	3,636 (33.8%)	1,579 (39.9%)	443 (30.7%)	1,048 (34.3%)	566 (24.6%)	<0.001
Insurance type						<0.001
Commercial	3,270 (30.4%)	1,694 (42.8%)	329 (22.8%)	927 (30.4%)	320 (13.9%)	
Medicaid	664 (6.2%)	256 (6.5%)	87 (6.0%)	198 (6.5%)	123 (5.3%)	
Medicare	6,643 (61.8%)	1,931 (48.8%)	1,000 (69.4%)	1,879 (61.5%)	1,833 (79.6%)	
Self-pay/other	179 (1.7%)	76 (1.9%)	25 (1.7%)	50 (1.6%)	28 (1.2%)	
Heart failure	951 (8.8%)	172 (4.3%)	123 (8.5%)	273 (8.9%)	383 (16.6%)	<0.001
Valvular disease	1,156 (10.7%)	294 (7.4%)	164 (11.4%)	319 (10.4%)	379 (16.4%)	<0.001
Peripheral vascular disease	1,329 (12.4%)	348 (8.8%)	187 (13.0%)	370 (12.1%)	424 (18.4%)	<0.001
Hypertension	6,735 (62.6%)	2,307 (58.3%)	849 (58.9%)	1,974 (64.6%)	1,605 (69.7%)	<0.001
Neurological disorders	423 (3.9%)	119 (3.0%)	67 (4.6%)	118 (3.9%)	119 (5.2%)	<0.001
Diabetes mellitus	3,446 (32.0%)	970 (24.5%)	450 (31.2%)	962 (31.5%)	1,064 (46.2%)	<0.001
Coronary artery disease	6,819 (63.4%)	2,454 (62.0%)	896 (62.2%)	1,989 (65.1%)	1,480 (64.2%)	0.032
Pulmonary hypertension	180 (1.7%)	32 (0.8%)	30 (2.1%)	49 (1.6%)	69 (3.0%)	<0.001
Atrial fibrillation	1,081 (10.1%)	296 (7.5%)	155 (10.8%)	275 (9.0%)	355 (15.4%)	<0.001
Hypothyroidism	1,066 (9.9%)	337 (8.5%)	134 (9.3%)	315 (10.3%)	280 (12.2%)	<0.001
Liver disease	300 (2.8%)	106 (2.7%)	56 (3.9%)	73 (2.4%)	65 (2.8%)	0.039
Cancer	850 (7.9%)	263 (6.6%)	137 (9.5%)	206 (6.7%)	244 (10.6%)	<0.001
Hemoglobin (g/dl)	13.1 ± 1.8	14.3 ± 2.3	11.4 ± 1.2	14.1 ± 1.2	10.9 ± 1.3	<0.001
Glomerular filtration rate*	55.9 ± 8.5	62.3 ± 8.4	61.4 ± 6.3	54.1 ± 8.9	44.0 ± 16.3	<0.001
Obesity[†]	1,239 (11.5%)	462 (11.7%)	135 (9.4%)	359 (11.8%)	283 (12.3%)	0.044
Drug abuse	77 (0.7%)	29 (0.7%)	12 (0.8%)	17 (0.6%)	19 (0.8%)	0.622
Psychoses	167 (1.6%)	60 (1.5%)	25 (1.7%)	46 (1.5%)	36 (1.6%)	0.942
Depression	1126 (10.5%)	359 (9.1%)	148 (10.3%)	345 (11.3%)	274 (11.9%)	0.001

Continuous variables are presented as Median (Range).

* Glomerular filtration rate units expressed in ml/min/1.73 m^2.

† Obesity defined as body mass index of greater than 25 kg/m^2.

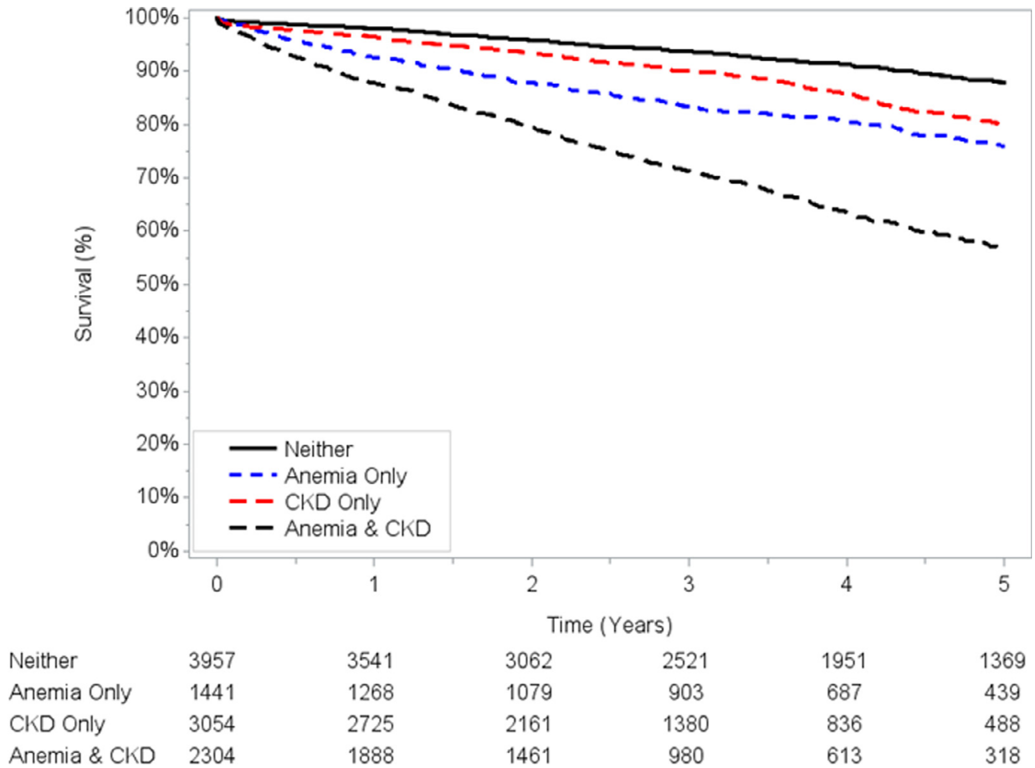


Figure 1. Kaplan-Meier curve for 5-year freedom from mortality. The estimated 5-year mortality was 12.2%, 23.9%, 20.2%, and 43.1% in the no anemia or CKD, anemia only, CKD only, and both anemia and CKD groups, respectively.

Table 2
Adjusted hazard ratios

Anemia/CKD status	Mortality		Readmission		Reintervention	
	HR (95% CI)	p Value	HR (95% CI)	p Value	HR (95% CI)	p Value
No anemia or CKD	Ref	—	Ref	—	Ref	—
Anemia only	1.68 (1.45-1.95)	<0.001	1.30 (1.19-1.41)	<0.001	1.09 (0.90-1.31)	0.381
CKD only	1.33 (1.15-1.53)	<0.001	1.18 (1.10-1.26)	<0.001	1.13 (0.98-1.31)	0.097
Both anemia and CKD	2.83 (2.49-3.22)	<0.001	1.59 (1.47-1.71)	<0.001	1.42 (1.21-1.66)	<0.001

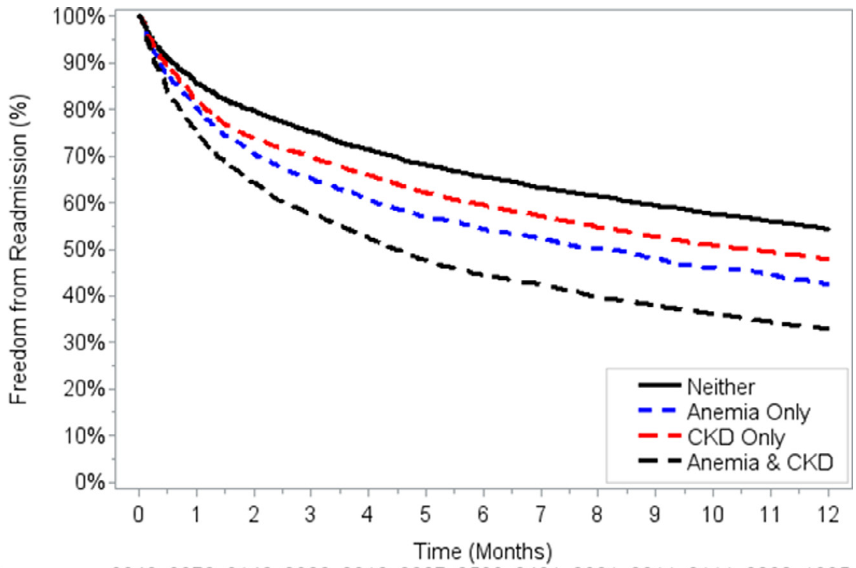
to 1.53, p <0.001) in the anemia only and CKD only groups, respectively (Table 2).

Figure 2 shows the Kaplan-Meier curve for 1-year freedom from any readmission. The estimated 1-year readmission rate was 45.7%, 57.5%, 52.1%, and 67.1% in the no anemia or CKD, anemia only, CKD only, and both anemia and CKD groups, respectively. Using the group without CKD or anemia as the reference, the overall adjusted hazard ratio for readmission of both anemia and CKD was 1.59 (95% CI 1.47 to 1.71, p <0.001) and 1.30 (95% CI 1.19 to 1.41, p <0.001) and 1.18 (95% CI 1.10 to 1.26, p <0.001) in the anemia only and CKD only groups, respectively (Table 2).

Figure 3 shows the Kaplan-Meier curve for 1-year freedom from repeat revascularization. The estimated 1-year repeat revascularization rate was 10.3%, 11.1%, 11.6%, and 14.6% in the no anemia or CKD, anemia only, CKD only, and both anemia and CKD groups, respectively. Using the group without CKD or anemia as the reference, the overall adjusted hazard ratio for repeat revascularization for both anemia and CKD was 1.42 (95% CI 1.21 to 1.66, p <0.001), 1.09 (95% CI 0.90 to 1.31, p = 0.38) and 1.13 (95% CI 1.21 to 1.66, p = 0.10) for the anemia only and CKD only groups, respectively (Table 2). One-hundred percent of the patients received at least 1 drug eluting stent.

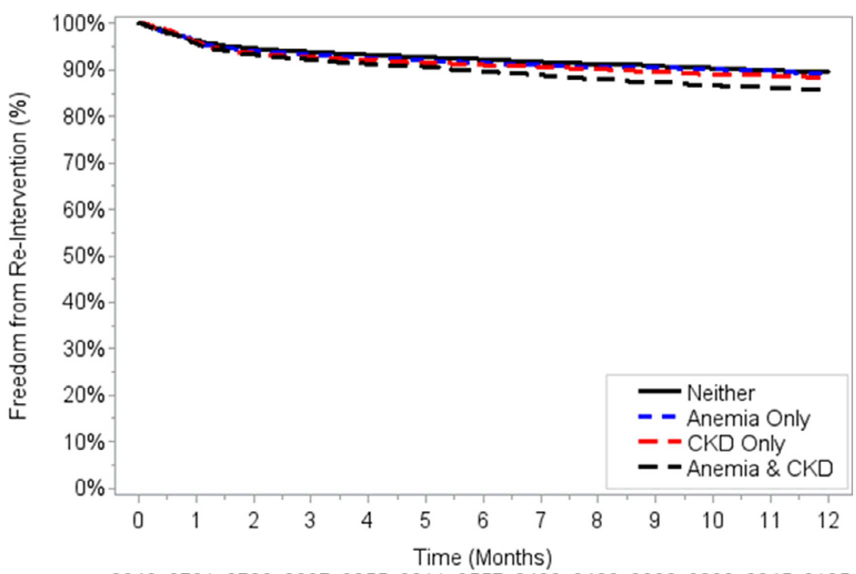
DISCUSSION

This contemporary analysis of patients after PCI demonstrates that those with both anemia and CKD have worse outcomes in regards to survival, readmission, and repeat revascularization, compared to those patients with neither CKD nor anemia or only one of those conditions. Although the results may not be surprising, they are informative and highlight the importance of recognizing the high-risk nature of these patients, which can help in proper informed consent, and it can help lay the foundation for mechanistic studies and for potential interventions to decrease the risk where possible. These results are consistent with a previous study that investigated outcomes in patients with both CKD and anemia after PCI where the authors found that even mild anemia was associated with significantly worse 3-year



	0	1	2	3	4	5	6	7	8	9	10	11	12
Neither	3948	3376	3146	2966	2816	2667	2539	2421	2321	2211	2111	2030	1935
Anemia Only	1436	1150	1009	932	859	809	766	732	690	655	624	602	569
CKD Only	3033	2478	2222	2106	1986	1866	1768	1674	1583	1501	1439	1381	1324
Anemia & CKD	2279	1703	1451	1296	1179	1068	985	924	859	814	763	714	671

Figure 2. Kaplan-Meier curve for 1-year freedom from any readmission. The estimated 1-year readmission rate was 45.7%, 57.5%, 52.1%, and 67.1% in the no anemia or CKD, anemia only, CKD only, and both anemia and CKD groups, respectively.



	0	1	2	3	4	5	6	7	8	9	10	11	12
Neither	3948	3791	3723	3687	3655	3611	3557	3483	3426	3366	3298	3245	3185
Anemia Only	1436	1371	1336	1315	1295	1274	1251	1228	1201	1186	1172	1154	1131
CKD Only	3033	2893	2811	2780	2761	2731	2688	2636	2591	2540	2493	2452	2403
Anemia & CKD	2279	2155	2088	2039	1994	1961	1895	1842	1793	1758	1708	1669	1623

Figure 3. Kaplan-Meier curve for 1-year freedom from repeat revascularization. The estimated 1-year repeat revascularization rate was 10.3%, 11.1%, 11.6%, and 14.6% in the no anemia or CKD, anemia only, CKD only, and both anemia and CKD groups, respectively.

clinical outcomes in patients who underwent elective PCI, and coexisting CKD additively increased the risk for major adverse cardiac events in these patients.[2] Our results extend this knowledge by showing insights into the implications that CKD and anemia have upon readmission and revascularization. In our analysis, readmission and repeat revascularization were most frequent in those patients with combined CKD and anemia. One additional study that evaluated mortality only showed that decreased kidney function and anemia are risk factors for all-cause mortality in patients with LV dysfunction, especially when both are present.[12] Their focus was not on the post-PCI patient population, however, and noted the need for additional studies to evaluate outcomes in patients with both anemia and CKD.

Several other studies have focused on outcomes in patients with either anemia or CKD, individually and these observations demonstrate that low hemoglobin is independently associated with the increased risk of mortality in acutely decompensated and chronic heart failure patients with both impaired and preserved LV function.[12–24] Anemia increased the risk of death in these studies by 20% to 50%. There may be several mechanisms for the higher adverse event rate in patients with anemia including poor nutritional status and worse neurohormonal or proinflammatory status.[15,18,25–27] In the population that undergoes coronary revascularization, high residual platelet reactivity on clopidogrel is a predictor of recurrent ischemic events in patients who underwent PCI, and anemia is an important contributor to apparent high residual platelet reactivity on clopidogrel, potentially explaining the worse outcomes after PCI in patients who are anemic.[5] Similarly, studies in patients with CKD show a similar pattern. Several studies have implicated CKD with worse outcomes after coronary revascularization, and, again, there are multiple proposed mechanisms, most notable is that patients with CKD tend to have a higher percentage of co-morbidities,[6,8,12] all contributing to worse outcomes after PCI.

As previously stated, CKD and anemia are common comorbid conditions and there are a few potential mechanisms that explain why patients with both anemia and CKD tend to do worse compared to those with neither or just one disease individually. The mechanisms for worse long-term outcomes in anemic patients who underwent elective PCI are multifactorial. For example, anemia leads to impaired oxygen delivery to the coronary arteries and therefore myocardial cell ischemia. Anemia also increases myocardial oxygen demand through increases in heart rate, cardiac index, and stroke volume. These hemodynamic responses induce additional stress to left ventricular function, which may lead to progressive left ventricular hypertrophy and further myocardial cell death.[2] CKD deteriorates anemia and may complicate the association between anemia and clinical outcomes through various causal mechanisms such as impaired erythropoietin production[28] and bone suppression from increased levels of proinflammatory cytokines.[29] These data may help us decide the appropriate timing of PCI in patients with anemia and CKD, particularly in elective cases. Future studies are needed to formally assess whether we should be treating these patients with both disease states differently from patients with neither or just one disease state.

Our analysis has limitations. It is an observational study, and, as such, although we performed multivariate analysis adjusting for several variables, there remains the potential for unmeasured confounders to have influenced the findings. However, the large cohort of this study helps to support validity of the findings. All readmission and procedure outcome data were based on UPMC events only; accordingly, if readmissions or repeat procedures did occur outside of this health system, they will not have been accounted for in this analysis; nonetheless, given the nature of the healthcare in this region, we do not believe that this should have affected the results substantively. Next, the determination of anemia and CKD was made at the time of their index percutaneous revascularization, and we did not assess serial measurements. We also could not reliably attain data regarding specific therapies that may have been used to treat anemia such as iron supplementation or erythropoietin.

Disclosures

The authors have no conflicts of interest to report pertaining to this manuscript.

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