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Association between smoking, outcomes, and early clopidogrel use in patients with acute coronary syndrome: Insights from the Global Registry of Acute Coronary Events

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Background Smoking induces CYP1A2, thereby enhancing clopidogrel conversion to its active metabolite. We sought to determine the association between clopidogrel use and clinical outcomes in smokers versus nonsmokers with a broad spectrum of acute coronary syndrome (ACS).

Methods We examined the association between early clopidogrel use in-hospital and 6-month outcomes among 44,426 patients with ACS in relation to smoking status in the Global Registry of Acute Coronary Events. We tested for heterogeneity of clopidogrel effect among smokers versus nonsmokers in separate multivariable models that adjusted for (1) established prognosticators in the Global Registry of Acute Coronary Events risk score and (2) independent predictors of major bleeding.

Results Rates of in-hospital mortality, death/myocardial infarction, and major bleeding were 4.3%, 5.9%, and 2.5%, respectively. Current smokers (n = 12,149) were more likely to be younger men without documented vascular disease; had lower rates of hypertension, hyperlipidemia, and diabetes; and more frequently presented with ST elevation (all $P < .0001$). Early clopidogrel use (55%) was associated with a reduction in the composite endpoint of mortality and myocardial infarction both in-hospital and at 6 months among current smokers and nonsmokers. There was no interaction between current smoking and clopidogrel use for ischemic endpoints. Major bleeding associated with early clopidogrel use was actually lower among current smokers compared with nonsmokers.

Conclusions Despite prior observations of smoking-enhanced clopidogrel effects, early clopidogrel use among smokers presenting with ACS compared with nonsmokers was not independently associated with a greater reduction in cardiovascular events. In contrast with nonsmokers, clopidogrel use among smokers was not associated with excess bleeding, perhaps because of unmeasured confounders. (Am Heart J 2010;160:855-61.)

Background

Clopidogrel is metabolized by cytochrome P450s to its active compound that irreversibly binds platelet P2Y12 receptors. Recent data suggest that current smokers may have enhanced P2Y12 blockade after clopidogrel from up-regulation of its metabolizing CYP1A2 enzyme, thereby augmenting its clinical effects.[1-4] In the CLARITY-TIMI 28 trial of patients presenting with ST elevation myocardial infarcts, smokers treated with clopidogrel had better clinical outcomes.[5] Similarly, among patients at high vascular risk in the CHARISMA trial, a reduction in mortality associated with clopidogrel use was only seen among smokers in a post hoc analysis.[6] No data about this interaction exist in patients across the full spectrum of acute coronary syndrome (ACS) in a nonclinical trial, "real-world" setting.

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The primary objective of this observational study is to examine the association between clopidogrel use and in-hospital outcomes (death, in-hospital myocardial infarction [MI], and major bleeding) among patients with ACS in relation to smoking status before hospitalization. We hypothesize that clopidogrel use is independently associated with a greater reduction in adverse cardiovascular events but a higher risk of bleeding among smokers compared with non-smokers.

Methods

The details and rationale for the Global Registry of Acute Coronary Events (GRACE) and expanded GRACE have been published elsewhere.[7,8] In brief, 247 hospitals from 30 countries participated in a prospective observational registry of patients with ACS. Patients were eligible if they were older than 18 years with a presumptive diagnosis of ACS, defined as symptoms compatible with cardiac ischemia, and at least one of the following: positive biomarkers of myocardial necrosis, electrocardiographic (ECG) changes consistent with ACS, or documented evidence of coronary artery disease. Patients were classified as current smokers if they reported cigarette smoking in the month before admission, former smokers if they had reported quitting more than 1 month before admission, and nonsmokers if they reported never smoking. Cigar and pipe smoking was not included. Early medication use was defined as medication given within 24 hours of presentation to hospital. Patients with ACS precipitated by or concomitant with trauma or surgery were excluded. Demographics, clinical presentation, laboratory results, relevant treatment, and in-hospital outcome were recorded on case report forms. Ethics approval was sought from relevant hospital or institutional boards where required.

Forty-five thousand eight-hundred fourteen patients were enrolled from 1999 to 2007 using case report forms that collected data on clopidogrel use within 24 hours of hospital presentation. Three percent were excluded because data on early clopidogrel use (n = 389) or smoking history (n = 999) were missing, resulting in a final cohort of 44,426 patients with a final ACS diagnosis. Six-month follow-up data were available for 30,580 of these patients. Patients were divided into 4 groups based on their prehospitalization smoking status and early clopidogrel use. Former smokers were considered as non-smokers for the purpose of this analysis.

Outcomes assessed included death and reinfarction both in-hospital. Reinfarction was defined as a clinically documented event with re-elevation of creatine kinase-MB (CK-MB) above the upper limit of normal (ULN) and an increase of at least 50% more than the previous value 24 hours after the index MI. If CK-MB was unavailable, CK reelevation of $\geq$2 times the ULN with an increase of 25% more than the previous value or $\geq$ 1.5 times the ULN with an increase of 50% more than the previous value was required. After percutaneous coronary intervention (PCI), CK-MB needed to be $\geq$3 times the ULN and at least 50% increased from previous. After coronary artery bypass graft (CABG), both CK-MB elevation of $\geq$3 times the ULN and at least 50% increase from previous as well as ECG changes consistent with MI were required.[9]

Unadjusted odds ratios (ORs) for early clopidogel use versus non-use stratified by smoking status were calculated for each outcome. Continuous data are summarized as medians with interquartile ranges, and categorical data are reported as frequencies and percentages. χ^2 and Kruskal-Wallis tests were used to compare categorical and continuous variables, respectively.

Multivariable analysis using a logistic regression model was constructed using smoking status and early clopidogrel use as covariates. An interaction term of smoking status and early clopidogrel use was added. A first model adjusted for all independent predictors of in-hospital death in the GRACE risk score.[10,11] Because medication use varied significantly among early clopidogrel users compared with nonusers, a second model was constructed that also adjusted for early medication use. A third model was constructed for major bleeding controlling for known independent predictors of bleeding, including age, gender, history of bleeding, systolic blood pressure, creatinine, in-hospital cardiac catheterization, in-hospital percutaneous coronary intervention, low-molecular-weight heparin use, thrombolytic use, and glycoprotein IIb/IIIa inhibitor use.[12]

A propensity score was devised for the probability of clopidogrel use adjusted for independent predictors of in-hospital mortality in the GRACE risk score and medical history (angina, MI, congestive heart failure, coronary artery disease, PCI, CABG, hypertension, dyslipidemia, prosthetic valve replacement, atrial fibrillation, transient ischemic attack/stroke, diabetes, renal insufficiency, major surgery, and major bleeding). The propensity score (probability of clopidogrel use) was categorized into quintiles. Matching of clinical characteristics between patients receiving clopidogrel and those not receiving clopidogrel across quintiles of propensity score was verified. In an ancillary analysis to examine the relationship clopidogrel use, smoking and outcomes, additional logistic regression models were constructed to adjust for independent predictors (of GRACE risk score or major bleeding), medication use, and propensity quintiles. We performed statistical analyses using SAS version 9.1 (SAS Inc, Cary, NC).

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Results

Of the 44,426 patients with ACS in the study cohort, 12,149 (27%) were current smokers. Overall, early use of clopidogrel was 55% and more common among current smokers than non-smokers (61% vs 53%). Current smokers were younger, more likely to be male and less likely to have hypertension, diabetes, or known atherosclerotic disease (prior angina, MI, coronary revascularization, congestive heart failure, transient ischemic attacks, and strokes). Smokers were more likely to present with ST elevation and had lower GRACE risk scores (Table I).

Smokers were more often treated with fibrinolysis, angiography, and angioplasty (Table II). Rates of aspirin, β blocker, statin, and glycoprotein IIb/IIIa inhibitor use were higher among those who received clopidogrel.

Table I. Baseline characteristics of 4 groups

	Nonsmokers (n = 32 277)				Smokers (n = 12 149)				
	No early clopidogrel use		Early clopidogrel use		No early clopidogrel use		Early clopidogrel use		
	n		n		n		n		*P* (4-group comparisons)
Age (y)*	15 072	72 (62, 80)	17 094	69 (59, 77)	4 779	58 (50, 67)	7 326	56 (49, 64)	<.001
Female sex	15 052	40.5%	17 123	33.4%	4 772	23.8%	7 326	21.4%	<.001
Hypertension	15 046	68.8%	17 130	67.4%	4 767	52.9%	7 343	48.5%	<.001
Dyslipidemia	15 005	46.5%	17 117	55.2%	4 766	42.8%	7 335	46.5%	<.001
Diabetes	15 076	28.9%	17 133	28.0%	4 769	18.5%	7 333	16.2%	<.001
History									
Angina	15 066	56.6%	17 130	48.4%	4 767	49.5%	7 343	34.9%	<.0001
MI	15 065	35.0%	17 123	31.7%	4 771	25.8%	7 337	20.9%	<.0001
Peripheral vascular disease	15 035	15.6%	17 125	23.8%	4 768	11.7%	7 325	14.7%	<.0001
CABG	15 054	15.0%	17 125	14.6%	4 773	6.5%	7 323	6.0%	<.0001
CHF	14 997	16.3%	17 065	9.1%	4 768	6.5%	7 321	3.3%	<.0001
TIA/stroke	15 016	10.2%	17 115	8.5%	4 763	6.0%	7 325	4.9%	<.0001
Peripheral vascular disease	15 014	9.9%	17 102	9.1%	4 762	9.3%	7 323	8.0%	.0001
Bleeding	15 039	1.8%	17 112	1.2%	4 765	1.2%	7 327	0.7%	<.0001
Presenting physical exam									
Systolic blood pressure mm Hg*	14 881	140 (120, 160)	16 719	140 (122, 160)	4 699	137 (120, 156)	7 116	138 (120, 157)	<.001
Diastolic blood pressure (mm Hg)*	14 853	80 (69, 90)	16 690	80 (70, 90)	4 694	80 (70, 90)	7 107	80 (70, 92)	<.001
Heart rate (beat/min)*	14 868	78 (66, 92)	16 681	75 (64, 88)	4 690	77 (65, 90)	7 101	76 (65, 89)	<.001
Killip class	14 760		16 815		4 715		7 204		
I		78.6%		85.7%		85.6%		89.4%	<.001
II		14.9%		10.4%		9.8%		7.9%	
III		5.2%		3.3%		3.4%		1.9%	
IV		1.3%		0.7%		1.3%		0.9%	
Presenting ECG and cardiac biomarkers									
ST deviation on presentation	15 110	49.2%	17 167	51.4%	4 791	59.0%	7 358	64.1%	<.001
T wave inversion on presentation	15 110	27.5%	17 167	26.0%	4 791	28.9%	7 358	24.1%	<.001
Positive initial biomarker	14 726	43.9%	16 710	50.0%	4 667	44.9%	7 116	53.2%	<.001
Creatinine (μmol/L)*	14 010	97 (79, 114)	16 315	88 (79, 114)	4 301	88 (79, 106)	6 938	88 (70, 97)	<.001
GRACE risk score*	13 131	137 (110, 165)	15 166	131 (108, 156)	4 034	118 (96, 144)	6 414	116 (95, 139)	<.001
Final diagnosis	15 110		17 167		4 791		7 358		
STEMI		27.9%		35.1%		40.6%		50.9%	<.001
NSTEMI		34.0%		37.3%		28.4%		30.9%	
Unstable angina		38.1%		27.7%		31.0%		18.2%	

CHF Congestive heart failure; TIA transient ischemic attack; STEMI ST elevation myocardial infarction; and NSTEMI non-ST elevation myocardial infarction.
*Median (25th 75th percentiles).

The risk of in-hospital death or (re)infarction adjusted for GRACE risk score and smoking status was lower among patients treated with clopidogrel (OR 0.72, 95% CI 0.65-0.79, $P < .0001$); there was a lower adjusted risk of in-hospital death (OR 0.49, 95% CI 0.43-0.55, $P < .0001$) but not reinfarction (OR 1.08, 95% CI 0.92-1.26, $P = .39$).

When stratified by smoking status, no significant interaction between early clopidogrel use and smoking status was found (Table III). Similarly, no interaction was found in the subanalysis of 43,972 patients who survived the first 24 hours of hospitalization or the 17,767 patients who underwent PCI during the index hospitalization after adjusting for the independent predictors of the GRACE risk score. In propensity score analysis, clopidogrel was also associated with a reduction in the composite risk of death and reinfarction in-hospital and at 6 months across all quintiles. In the propensity model, the interaction term for clopidogrel and smoking was also not significant for the composite endpoint of death and reinfarction ($P = .70$ in-hospital and $P = .99$ at 6 months). *P* values for the interaction terms for in-hospital death and reinfarction were .07 and .86, respectively. Similarly, at 6 months, *P* values for the interaction terms were not significant ($P = .79$ and $P = .99$ for death and death/(re-)MI, respectively).

Overall, the rate of in-hospital major bleeding was low at 2.8%. The association between early clopidogrel use and major bleeding differed by smoking status.

Table II. Inhospital medical and invasive management

	Nonsmokers (n = 32 277)				Smokers (n = 12 149)				
	No early clopidogrel use		Early clopidogrel use		No early clopidogrel use		Early clopidogrel use		*P* (4-group comparisons)
	n		n		n		n		
Medication use within the first 24 h:									
Aspirin	15 101	85.9%	17 158	91.2%	4 786	90.4%	7 357	93.1%	<.0001
β blocker	15 007	68.3%	17 042	77.3%	4 747	71.0%	7 312	79.1%	<.0001
ACE inhibitor	15 017	46.8%	17 029	52.3%	4 767	42.7%	7 315	51.7%	<.0001
Angiotensin receptor blocker	14 918	4.7%	16 895	6.6%	4 735	2.8%	7 247	2.8%	<.0001
Calcium channel blocker	14 941	17.3%	16 959	16.7%	4 745	11.2%	7 271	9.2%	<.0001
Statin	15 047	41.1%	17 106	66.9%	4 779	41.1%	7 333	68.9%	<.0001
Unfractionated heparin	14 983	35.1%	16 943	37.8%	4 745	37.3%	7 272	42.0%	<.0001
Enoxaparin	15 009	40.5%	16 973	49.7%	4 754	38.6%	7 265	49.4%	<.0001
Glycoprotein IIb/IIIa inhibitor	10 109	7.4%	15 796	23.8%	3 122	10.2%	6 831	33.5%	<.0001
Fibrinolytics	14 927	10.7%	16 934	8.7%	4 723	22.4%	7 260	16.2%	<.0001
Inhospital cardiac procedures:									
Coronary angiography	15 008	39.0%	17 092	78.6%	4 767	48.6%	7 333	86.0%	<.0001
PCI	15 041	13.1%	17 109	57.2%	4 772	20.8%	7 330	68.5%	<.0001
Coronary artery bypass surgery	14 986	7.1%	16 964	3.6%	4 743	7.0%	7 262	3.3%	<.0001

ACE indicates angiotensin-converting enzyme.

Clopidogrel use was independently associated with bleeding among non-smokers but not among smokers in both multivariable models (Table III). However, when correcting for quintiles of propensity score, major bleeding was increased among all early clopidogrel users (OR 1.27, 95% CI 1.07-1.51, $P = .007$).

Discussion

This is the first observational study to examine the association between clopidogrel use and outcomes among patients with ACS in relation to smoking status in a non-clinical trial, real-world setting. The key findings are as follows: (1) early clopidogrel use was associated with a decreased event rate among patients with ACS, (2) there was no significant interaction between early clopidogrel use in patients with ACS and smoking status on in-hospital mortality or reinfarction, (3) early clopidogrel use among patients with ACS did not result in a large increase in major bleeding, and (4) there was a significant interaction between early clopidogrel use in patients with ACS and smoking status with respect to major bleeding.

Early clopidogrel use associated with a decreased event rate among patients with ACS

The associated lower incidence of nonfatal MI and mortality among patients with ACS with early clopidogrel use reported in this study is greater than that previously reported. In the CURE trial, early use of clopidogrel in patients with non-ST elevation ACS resulted in a 20% relative risk reduction of a composite endpoint of death, recurrent MI, and stroke after 1 year.[13] A similar 31% odds reduction in composite endpoint of angiographic artery occlusion, in-hospital death, and reinfarction was seen in patients with ST elevation ACS with the addition of clopidogrel to aspirin and fibrinolytic therapy in the CLARITY trial.[14] In the largest randomized study, the ClOpidogrel and Metoprolol in Myocardial Infarction Trial (COMMIT), clopidogrel use was associated with a 9% reduction in death, reinfarction, and stroke along with a 7% proportional reduction in death among patients with ACS at 2 weeks.[15] The augmented "treatment" effect in our observational cohort is likely a result of residual confounding in patients receiving early clopidogrel in a non-randomized setting. A more modest and consistent reduction in endpoints associated with clopidogrel use was observed in the logistic regression modeling of the data with corrections for GRACE risk variables and medication use.

Lack of interaction between smoking and early clopidogrel use in patients with ACS

Smoking is a potent inducer of cytochrome 1A2[16-18] that has been reported to modify in vivo drug levels and efficacy.[5,19-21] This up-regulation of cytochrome 1A2 may lead to enhanced metabolism of clopidogrel to its active metabolite. Bliden et al showed significantly less platelet aggregation and adenosine diphosphate-induced platelet glycoprotein IIb/IIIa expression among smokers who received loading doses of clopidogrel compared with non-smokers at the time of angioplasty. The clinical implications of this effect were explored by Desai et al in a post hoc analysis of the Clopidogrel as Adjunctive Reperfusion Therapy (CLARITY)–Thrombolysis in Myocardial Infarction (TIMI) 28 trial. Smoking 10 or more

Table III. Events with and without early clopidogrel use by smoking status

Inhospital outcomes	Nonsmoker: No clopidogrel n (%)	Nonsmoker: Clopidogrel n (%)	Nonsmoker: Adjusted OR (95% CI, *P*)	Current smoker: No clopidogrel n (%)	Current smoker: Clopidogrel n (%)	Current smoker: Adjusted OR (95% CI, *P*)	*P* for interaction (multivariable model)
Death	1 108 (7.4%)	482 (2.8%)	0.50 (0.44-0.56, $P < .0001$)*	216 (4.5%)	119 (1.6%)	0.44 (0.34-0.58, $P < .0001$)*	.43*
			0.48 (0.34-0.68, $P < .0001$)†			0.60 (0.51-0.70, $P < .0001$)†	.07†
Death/MI	1 289 (8.6%)	828 (4.8%)	0.71 (0.64-0.79, $P < .0001$)*	253 (5.3%)	247 (3.4%)	0.77 (0.62-0.95, $P = .013$)*	.50*
			0.77 (0.60-0.99, $P < .04$)†			0.80 (0.70-0.90, $P < .0004$)†	.70†
Major bleeding	338 (2.3%)	527 (3.1%)	1.63 (1.41-1.90, $P < .0001$)*	94 (2.0%)	144 (2.0%)	1.002 (0.752-1.336, $P = .9873$)*	.0003*
			1.179 (0.986-1.409, $P = .071$)‡			1.024 (0.722-1.450, $P = .90$)‡	.02‡
Death at 6 mo	699 (6.7%)	425 (3.6%)	0.64 (0.56-0.74, $P < .0001$)*	118 (3.4%)	96 (1.9%)	0.67 (0.49-0.90, $P < .009$)*	.79*
			0.74 (0.62-0.87, $P = .0004$)†			0.65 (0.44-0.97, $P = .0333$)†	.87†
Death/MI at 6 mo	70 (5.2%)	271 (4.0%)	0.78 (0.69-0.87, $P < .0001$)*	24 (3.4%)	111 (3.2%)	0.74 (0.59-0.94, $P = .01$)*	.99*
			0.79 (0.68-0.90, $P = .0006$)†			0.69 (0.51-0.92, $P = .01$)†	.91†

* Adjusted for all independent predictors of in-hospital death in GRACE risk score.
† Adjusted for all independent predictors of in-hospital death in GRACE risk score, medication use in the first 24 hours (aspirin, β blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, unfractionated heparin, low-molecular-weight heparins, statins, and glycoprotein IIb/IIIa inhibitors), and propensity score quintiles.
‡ Adjusted for factors significantly associated with major bleeding based on Moscucci et al.[13]

cigarettes a day was associated with a near doubling in clopidogrel-related reduction of 30-day death and reinfarction in patients with ST elevation MI.[5] In a post hoc analysis of the CHARISMA trial, a significant interaction between smoking status and clopidogrel existed.[6] In this placebo-controlled trial of patients at high cardiovascular risk followed on average for 28 months, randomization to clopidogrel was associated with a significant reduction in mortality and increase in major bleeding only among smokers, in contrast with non-significant effects in non- or former smokers.

The findings in the current analysis of the GRACE registry differ from the aforementioned clinical trial data. Although we found no convincing interaction between smoking status and early clopidogrel use, there was a borderline significant interaction term for in-hospital death in our model corrected for GRACE risk score, medication use, and propensity quintiles. It is possible that the interaction between smoking and clopidogrel is less relevant in a less selected group of patients. However, follow-up was shorter and less complete than in either the CHARISMA or CLARITY-TIMI 28 trials.[5,6] In addition, because clopidogrel-related platelet inhibition has been linked to stent-related outcomes,[22,23] differing rates of angiography and angioplasty in these 2 studies may also partly account for this difference. Lastly, quantification of smoking or clopidogrel loading dose was not recorded in GRACE. Significant loading doses might have overcome varied metabolism, especially among light smokers, and may not have reached the necessary threshold for a demonstrable interaction. Nonetheless, the lack of interaction in this large unselected real-world population suggests that the effects of clopidogrel may not be significantly altered by smoking status in a broad ACS patient population.

Clopidogrel-related bleeding

Clopidogrel was associated with a 1.0% absolute increase in CURE major bleeding over 9 months in the CURE trial.[11] In CLARITY, no significant increase in TIMI major bleeding was detected with clopidogrel use during 1-month follow-up; however, the duration of blinded, placebo-control treatment was a maximum of 8 days.[13-15] Similarly, no increase in major bleeding (defined as bleeding that was fatal, intracerebral, or requiring transfusion) was detected during a median follow-up of 14 days in COMMIT.[13-15] In this large real-world registry analysis, early clopidogrel use was associated with a less than 1% increase in major bleeding in hospital. Among smokers, rates of major bleeding were the same among those who used and did not use clopidogrel. This may be because of short follow-up and incomplete statistical correction of bleeding risk factors among smokers. This

evidence supports the safety profile demonstrated in the more selected patients enrolled in randomized trials.

Limitations

Several limitations of the current study need be considered. The duration and degree of the effects of smoking on clopidogrel metabolism is unknown. We could not control for the time from pre-hospital smoking to post-admission clopidogrel administration. Furthermore, we are unable to quantify the number of cigarettes smoked per day that may have been below the threshold of 10 cigarettes per day noted by Desai et al.[6] Lastly, we do not have data on smoking status post-admission; for example, a substantive decrease in smoking rates could make a potential interaction more difficult to detect at 6-month follow-up.

As a large registry-based analysis, uncorrected confounders may still exist despite adjustment for all known prognostic factors. In particular, non-smokers in the GRACE were a higher risk group of patients who may derive greater absolute therapeutic benefit from clopidogrel. Although we attempted to correct for these demographic differences, we recognize the limitations of unmeasured confounders in our registry database. We also recognize the issue of loss to follow-up at 6 months in our data set. It is also possible that the interaction between smoking and clopidogrel use is more significant in ST elevation ACS where treatment with coronary stenting is particularly common and the role of clopidogrel is paramount. In contrast with the clinical trial setting of CLARITY, the patients in GRACE were older with a greater proportion of women and a relatively lower proportion of patients who smoked; thus, our population may differ with respect to underlying genetic cytochrome polymorphisms with resultant differences in susceptibility to the pharmacokinetic alterations because of smoking.[2,4]

In summary, this observational study of patients with ACS suggests similar efficacy and safety of early clopidogrel use in smokers and non-smokers. We speculate that the previously reported interaction between smoking and clopidogrel use may not be as pronounced in the management of a broader spectrum of ACS in the real-world setting.

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Conflicts of Interest

Sanofi-Aventis had no involvement in the collection, analysis, and interpretation of data; in the writing of the manuscript; or in the decision to submit the paper for publication. The design, conduct, and interpretation of the GRACE data are undertaken by an independent steering committee.

Potential conflicts of interest are as follows:

M Sibbald: None

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