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Original Article

Smoking, Colchicine and Postoperative Outcomes in Thoracic Surgery: Post Hoc Analysis of the COP-AF Randomized Controlled Trial

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ABSTRACT

Background: To determine, among patients who underwent major noncardiac thoracic surgery, the association between smoking and perioperative atrial fibrillation (AF) and myocardial injury after noncardiac surgery (MINS), and whether the effect of colchicine use on these outcomes varied by smoking status.

RÉSUMÉ

Contexte : Déterminer le lien entre le tabagisme, la fibrillation auriculaire (FA) periopératoire et les lésions myocardiques après une chirurgie non cardiaque chez des patients ayant subi une chirurgie thoracique majeure non cardiaque, et établir si l'effet de la colchicine sur ces paramètres varie en fonction du statut tabagique.

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See page 868 for disclosure information.

Although cigarette smoking is a well established risk factor for postoperative pulmonary and wound complications[1,2] and readmission after thoracic surgery,[3-5] the evidence of its association with perioperative atrial fibrillation (AF) and myocardial injury after noncardiac surgery (MINS) remains unclear. Smoking may increase the risk of AF and myocardial ischemia through multiple pathophysiological pathways,

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Methods: This study is a subgroup analysis of the Colchicine for the Prevention of Perioperative Atrial Fibrillation (COP-AF) randomized clinical trial. A total of 3209 participants who underwent major noncardiac thoracic surgery were randomized to receive colchicine, 0.5 mg twice daily, or identical placebo, for 10 days starting 2-4 hours before surgery. The co-primary outcomes were clinically significant perioperative AF and MINS during the 14-day follow-up.
Results: A total of 687 (21.4%) were current smokers, 1577 (49.1%) were former smokers, and 945 (29.5%) were never smokers. AF occurred in 7.7%, 7.6%, and 5.3%, and MINS occurred in 21.0%, 19.7%, and 17.6% of current, former, and never smokers, respectively. Compared to never smokers, the adjusted hazard ratio for AF was 1.72 (95% confidence interval [CI] 1.07-2.77, $P = 0.02$) in current smokers and 1.46 (95% CI 0.99-2.16, $P = 0.06$) in former smokers, and the adjusted hazard ratio for MINS was 1.16 (95% CI 0.87-1.54, $P = 0.32$) in current smokers and 1.02 (95% CI 0.81-1.28, $P = 0.88$) in former smokers. No interaction occurred between smoking status and colchicine allocation for AF (interaction *P,* 0.82) or MINS (interaction *P*, 0.08).
Conclusions: Current smoking was associated with a small but increased risk of perioperative AF but not MINS after thoracic surgery. The effect of colchicine use on either outcome was not modified by smoking status.
Clinical Trial Registration: NCT03310125

Méthodologie : Il s'agit d'une analyse de sous-groupes de l'essai clinique COP-AF (Colchicine for the Prevention of Perioperative Atrial Fibrillation) dans le cadre de laquelle 3 209 participants ayant subi une chirurgie thoracique majeure non cardiaque ont été répartis aléatoirement pour recevoir de la colchicine à raison de 0,5 mg deux fois par jour ou un placebo identique pendant 10 jours, à compter de 2 à 4 heures avant l'intervention chirurgicale. Les paramètres d'évaluation principaux conjoints étaient une FA périopératoire et les lésions myocardiques cliniquement significatives pendant un suivi de 14 jours.
Résultats : Au total, 687 participants (21,4 %) étaient fumeurs; 1 577 (49,1 %) étaient des ex-fumeurs et 945 (29,5 %) n'avaient jamais fumé. Une FA a été observée chez 7,7 %, 7,6 % et 5,3 %, et des lésions myocardiques chez 21,0 %, 19,7 % et 17,6 % des fumeurs, des ex-fumeurs et des participants n'ayant jamais fumé, respectivement. Comparativement aux participants n'ayant jamais fumé, le rapport de risques ajusté (RRA) pour la FA a été de 1,72 (intervalle de confiance [IC] à 95 % : 1,07-2,77; $p = 0{,}02$) chez les fumeurs et de 1,46 (IC à 95 % : 0,99-2,16; $p = 0{,}06$) chez les ex-fumeurs, et le RRA pour les lésions myocardiques, de 1,16 chez les fumeurs (IC à 95 % : 0,87-1,54; $p = 0{,}32$) et de 1,02 chez les ex-fumeurs (IC à 95 % : 0,81-1,28; $p = 0{,}88$). Aucune interaction n'a été observée entre le statut tabagique et l'affectation au groupe traité par la colchicine pour une FA (valeur *p* de l'interaction = 0,82) ou une lésion myocardique (valeur *p* de l'interaction = 0,08).
Conclusion : Chez les fumeurs, le risque de FA périopératoire était légèrement plus élevé, ce qui n'était pas le cas pour les lésions myocardiques après une chirurgie thoracique. L'effet de la colchicine sur l'un ou l'autre de ces paramètres n'a pas été modifié par le statut tabagique.
Enregistrement de l'essai clinique : ClinicalTrials.gov, NCT03310125

including oxidative stress, endothelial dysfunction, disruption of cardiac ion channels, and microDNA changes that lead to cardiac fibrosis and accelerated atherosclerosis.[6] A meta-analysis of 36 studies involving patients having cardiac surgery showed a pooled odds ratio for perioperative AF of 0.89 (95% confidence interval [CI]: 0.79-1.02) among smokers, indicating no significant association with smoking.[7] Reports regarding noncardiac thoracic surgery are conflicting.[8,9] Similarly, the association between smoking and MINS is inconsistent among several studies.[10-13]

Smoking induces a proinflammatory state,[14,15] and colchicine, an anti-inflammatory drug, has been shown to reduce major cardiovascular outcome events in randomized controlled trials (RCTs) of nonsurgical patients.[16,17] The Colchicine for the Prevention of Perioperative Atrial Fibrillation (COP-AF) trial, a large, multicentre, international RCT evaluated the effect of colchicine use, compared to placebo, on the risk of perioperative atrial fibrillation (AF) and MINS at 14 days in 3209 adults undergoing noncardiac thoracic surgery.[18] The results showed no significant difference between colchicine and placebo in reducing the incidence of either AF or MINS. Whether colchicine's effects on postoperative AF and ischemic events after surgery differ according to smoking status is unknown. Given the proinflammatory effects of smoking, the effect of colchicine use on these outcomes may differ according to smoking status.

In this post hoc analysis of the COP-AF trial, we aimed to evaluate the association between smoking status and AF and MINS among patients undergoing major noncardiac thoracic surgery and examine whether smoking status affects the relative efficacy and safety of colchicine use, vs placebo, at the 14-day follow-up evaluation.

Methods

Trial description

We previously published the study design, protocol, and primary results of the COP-AF trial.[18,19] Briefly, COP-AF was an RCT conducted at 45 sites in 11 countries. Patients aged $\geq$ 55 years who underwent major noncardiac thoracic surgery with general anesthesia were randomly assigned (1:1) to receive oral colchicine, 0·5 mg twice daily, or matching placebo, starting within 4 hours before surgery and continuing for 10 days. Recruitment into the COP-AF trial occurred after patients provided informed consent, and local ethics board approval was obtained from all participating sites. Randomization was performed using a computerized, Web-based system, and stratification by centre was performed. Participants were randomized from February 14, 2018 to June 27, 2023. Healthcare providers, patients, data collectors, and adjudicators of AF and MINS were blinded to the treatment assignment. The follow-up duration was 14 days.

Cigarette smoking history was obtained at baseline on all 3209 study participants in the COP-AF trial. We defined smoking status as "current" if patients reported active smoking

$\leq$ 6 weeks before randomization, as "former" if they previously smoked but had ceased smoking > 6 weeks before randomization, or as "never" if they reported no previous smoking.

Study outcomes

The co-primary efficacy outcomes were as follows: clinically important perioperative AF (defined as AF or atrial flutter that resulted in angina, heart failure, or symptomatic hypotension, or that required treatment with a rate-controlling drug, antiarrhythmic drug, or electrical cardioversion); and separately, MINS (defined as myocardial infarction (MI), or an elevated postoperative troponin level judged to be due to myocardial ischemia). The main safety outcomes were as follows: (i) a composite of sepsis or infection and (ii) noninfectious diarrhea.

The secondary outcomes included the following: (i) a composite of AF or MINS; (ii) a composite of vascular death, nonfatal MINS, nonfatal stroke, or clinically important perioperative AF; (iii) a composite of all-cause mortality, nonfatal MINS, or nonfatal stroke; (iv) a composite of all-cause mortality, nonfatal MI, or nonfatal stroke; (v) MINS not fulfilling the 4th universal definition of MI; and (vi) MI.

The tertiary outcomes included the following: (i) time to chest-tube removal; (ii) duration of stay in the intensive care unit, step-down (ward/unit in hospitals that provide an intermediate level of care between an intensive care unit and a general surgical/medical ward), and in-hospital; (iii) all-cause mortality; (iv) venous thromboembolism (ie, deep vein thrombosis or pulmonary embolism); (v) acute heart failure; (vi) number of days alive and at home; (vii) stroke; and (viii) life-threatening or major bleeding. All outcomes are defined in Supplemental Appendix I.

Statistical analysis

For all outcomes, patients were analyzed in the treatment group to which they were randomized, regardless of treatment received or duration of trial participation, according to the intention-to-treat principle. We compared baseline characteristics, medical history, and clinical outcome events by smoking status using the χ^2 test or Fisher's exact test for binary variables and the Student *t* test or the Wilcoxon rank-sum test for continuous variables, as appropriate.

For the analyses pertaining to the associations of smoking status with perioperative AF and MINS, we estimated time-to-event rates by smoking status using the Kaplan-Meier method and compared them using the log-rank test. Adjusted multivariable Cox proportional hazards regression models were used to adjust for potential confounders, including age, sex, coronary artery disease, history of stroke, peripheral vascular disease, chronic obstructive pulmonary disease, and surgical approach (open or thoracoscopic). We included smoking as a 3-level categorical variable (with "never smoker" as the reference group) in the models.

To determine whether the effect of colchicine use, vs placebo, differed according to smoking status, we incorporated interaction terms between the treatment strategy and smoking status into separate nonstratified Cox regression models that were unadjusted given the randomized comparison. In cases in which the test for interaction was not significant, we considered the overall COP-AF trial result as the most likely best estimate of the effect for all patients, regardless of their smoking status. Our a priori hypothesis was that colchicine use would demonstrate a smaller reduction in hazard of AF and MINS among patients who are current smokers, given the multiple proinflammatory pathways through which smoking exerts its effects on tissues beyond pathways targeted by colchicine.

We reported the hazard ratios (HRs) with 95% CIs based on Cox regression for time-to-event outcomes. We used the Wilcoxon rank-sum test for continuous outcomes, such as length of hospital stay. For all analyses, we considered a 2-sided *P*-value of < 0.05 statistically significant. We did not adjust the analyses for multiple testing, as they were considered exploratory. All analyses were performed using R (version 4.4.0; R Foundation, Vienna, Austria) and SAS 9.4 (SAS Institute, Cary, NC).

Results

Of the 3209 patients enrolled in the COP-AF trial, at baseline, 687 (21.4%) were current smokers, 1577 (49.1%) were former smokers, and 945 (29.5%) were never smokers (Fig. 1). Some baseline characteristics differed across the 3 groups (Table 1). Current smokers were younger, had a lower body mass index, and more frequently underwent lobe resection surgeries than did never and former smokers. Current smokers included fewer women and had more comorbid conditions, including coronary artery disease, MI, peripheral vascular disease, and chronic obstructive airway disease. Former smokers had higher rates of hypertension and diabetes than did current smokers and never smokers. Current smokers had significantly more pack-years (ie, the number of cigarettes smoked per day × the number of years smoked) than did former smokers, with a mean of 41 pack-years (standard deviation = 27) vs 33 pack-years (standard deviation = 26) for former smokers. Very few patients received smoking-cessation medications in the 7 days preceding randomization—95 (13.8%) among current smokers and 30 (1.9%) among former smokers.

Co-primary efficacy outcomes

At 14 days, clinically important AF had occurred in 7.7% of current smokers (53 of 687), 7.6% of former smokers (120 of 1577), and 5.3% of never smokers (50 of 945). MINS had occurred in 21.0% of current smokers (144 of 687), 19.7% of former smokers (310 of 1577), and 17.6% of never smokers (166 of 945; Table 2). In the adjusted models, current smokers had a higher risk of clinically important AF than did never smokers (adjusted hazard ratio [aHR] 1.72, 95% CI 1.07-2.77, *P* = 0.02), whereas the difference between former smokers and never smokers was not statistically significant (aHR 1.46, 95% CI 0.99-2.16, *P* = 0.06; Table 2). The adjusted risk of MINS was not significantly different between current smokers and never smokers (aHR 1.16, 95% CI 0.87-1.54, *P* = 0.32) or between former smokers and never smokers (aHR 1.02, 95% CI 0.81-1.28, *P* = 0.88; Table 2).

No statistically significant interactions occurred between smoking status and treatment assignment to colchicine vs placebo with respect to clinically important AF (*P* for

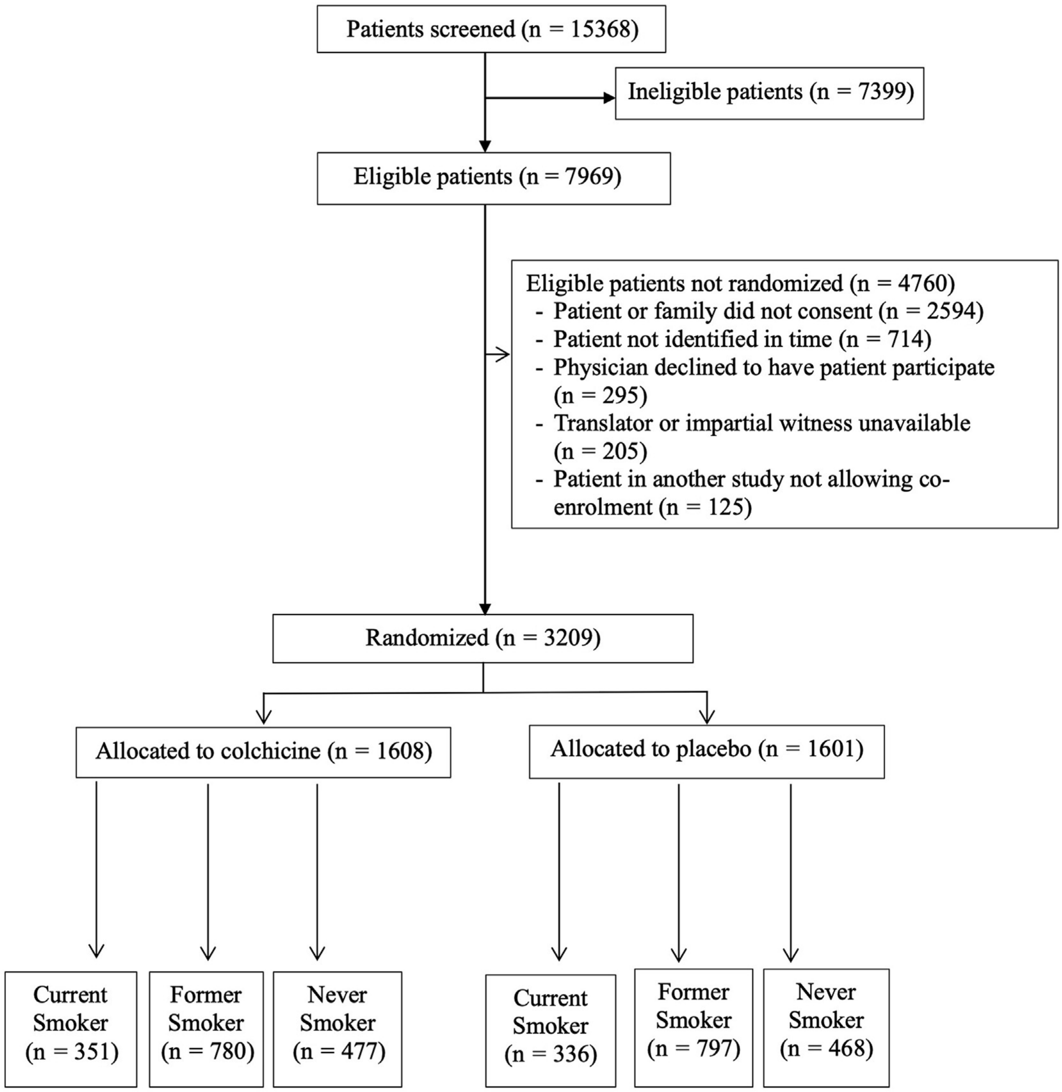

Figure 1. Patient flow diagram.

interaction = 0.82) or MINS (P = 0.08; Table 3; Fig. 2, A and B).

Safety outcomes

The composite outcome of sepsis or infection occurred in 7.6% of current smokers (52 of 687), 5.8% of former smokers (92 of 1577), and 4.6% of never smokers (43 of 945; Table 2). In the adjusted models, compared to never smokers, current smokers had an aHR of 1.31 (95% CI 0.79-2.16; P = 0.30), and former smokers had an aHR of 1.02 (95% CI 0.66-1.57, P = 0.93). The noninfectious diarrhea rates were 4.2% in current smokers, 5.5% in former smokers, and 5.9% in never smokers (Table 2). Compared to never smokers, the aHR for noninfectious diarrhea was 0.80 (95% CI 0.46-1.40, P = 0.44) and 0.98 (95% CI 0.65-1.48, P = 0.94) for current and former smokers, respectively (Table 2).

No significant interactions occurred between smoking status and treatment assignment to colchicine vs placebo with respect to the composite outcome of sepsis or infection (P for interaction 0.81) or noninfectious diarrhea (P for interaction 0.14; Table 3; Fig. 2, A and B).

Secondary and tertiary outcomes

Compared to never smokers, current smokers had a longer median time to chest-tube removal, whereas former smokers had a shorter median time to chest-tube removal, fewer median days in the hospital, and more days alive at home (Supplemental Table S1).

We found directionally consistent but nonsignificant higher hazard levels for all the other secondary and tertiary outcomes, except stroke, among current smokers compared to never smokers and among former smokers compared to never smokers. No statistical interactions occurred between smoking status and treatment assignment to colchicine vs placebo, with respect to all secondary and tertiary outcomes (Supplemental Table S2).

Table 1. Baseline characteristics of patients by smoking status

	Never	Former	Current	Total	
N	945 (29.4)	1,577 (49.1)	687 (21.4)	3,209 (100.0)	*P**
Age, y	68.3 (7.4)	68.9 (7.2)	66.8 (6.7)	68.3 (7.2)	< 0.001
BMI, kg/m^2	26.8 (5.2)	27.9 (5.4)	25.8 (5.1)	27.1 (5.4)	< 0.001
SBP, mm Hg	137.2 (17.8)	138.3 (19.4)	136.2 (19.1)	137.5 (18.9)	0.048
DBP, mm Hg	77.4 (10.7)	76.8 (10.6)	75.6 (10.6)	76.7 (10.7)	0.004
Heart rate, bpm	76.1 (12.3)	76.7 (13.2)	77.0 (13.6)	76.6 (13.1)	0.320
Cockcroft-Gault creatinine clearance, mL/min^2	81.7 (26.7)	84.0 (27.5)	83.9 (27.2)	83.3 (27.2)	0.094
Male	403 (42.6)	876 (55.5)	377 (54.9)	1656 (51.6)	< 0.001
Ethnicity					
White/Caucasian	649 (69.4)	1386 (90.6)	628 (93.5)	2663 (84.9)	< 0.001
Black/African	9 (1.0)	11 (0.7)	5 (0.7)	25 (0.8)	
Hispanic/Latino	47 (5.0)	39 (2.5)	11 (1.6)	97 (3.1)	
Asian	222 (23.7)	78 (5.1)	23 (3.4)	323 (10.3)	
Middle Eastern	8 (0.9)	16 (1.0)	5 (0.7)	29 (0.9)	
Medical History					
Stroke	19 (2.0)	44 (2.8)	22 (3.2)	85 (2.6)	0.297
Congestive heart failure	5 (0.5)	16 (1.0)	12 (1.7)	33 (1.0)	0.055
CAD	52 (5.5)	162 (10.3)	72 (10.5)	286 (8.9)	< 0.001
Myocardial infarction	13 (1.4)	98 (6.2)	52 (7.6)	163 (5.1)	< 0.001
Peripheral vascular disease	18 (1.9)	83 (5.3)	69 (10.0)	170 (5.3)	< 0.001
Hypertension	438 (46.3)	874 (55.4)	356 (51.8)	1668 (52.0)	< 0.001
COPD	51 (5.4)	400 (25.4)	280 (40.8)	731 (22.8)	< 0.001
Diabetes	170 (18.0)	303 (19.2)	122 (17.8)	595 (18.5)	0.625
Smoking pack-years	.	33.2 (26.3)	40.6 (26.9)	35.5 (26.7)	< 0.001
Medications taken < 24 h before surgery					
Aspirin	81 (8.7)	144 (9.2)	71 (10.4)	296 (9.3)	0.474
ACEI	70 (7.5)	200 (12.8)	72 (10.6)	342 (10.7)	< 0.001
Beta-blocker	124 (13.3)	239 (15.3)	93 (13.7)	456 (14.3)	0.328
ARB	87 (9.3)	137 (8.7)	49 (7.2)	273 (8.6)	0.309
Rate-controlling CCB	8 (0.9)	29 (1.9)	14 (2.1)	51 (1.6)	0.090
Statin	271 (29.0)	545 (34.8)	233 (34.2)	1049 (33.0)	0.008
Use of smoking-cessation medication	1 (0.11)	30 (1.9)	95 (13.8)	126 (3.9)	< 0.001
Type of surgery					
Wedge resection	175 (18.6)	354 (22.5)	122 (17.8)	651 (20.3)	0.011
Segment resection	121 (12.8)	257 (16.3)	109 (15.9)	487 (15.2)	0.052
Lobe resection	568 (60.2)	991 (62.9)	483 (70.5)	2042 (63.7)	< 0.001
Pneumonectomy	17 (1.8)	56 (3.6)	15 (2.2)	88 (2.7)	0.020
Decortication	35 (3.7)	57 (3.6)	26 (3.8)	118 (3.7)	0.978
Mediastinal mass resection	78 (8.3)	69 (4.4)	32 (4.7)	179 (5.6)	< 0.001
Pericardium resected	21 (2.2)	18 (1.1)	8 (1.2)	47 (1.5)	0.069
Pericardium entered	7 (0.7)	15 (1.0)	6 (0.9)	28 (0.9)	0.861
Surgical approach					
MIS	715 (76.5)	1163 (74.3)	519 (76.2)	2397 (75.4)	0.134
MIS-converted to open	45 (4.8)	110 (7.0)	49 (7.2)	204 (6.4)	
Open	175 (18.7)	292 (18.7)	113 (16.6)	580 (18.2)	
Type of anesthesia in addition to general anesthesia					
Thoracic epidural	191 (20.3)	357 (22.7)	202 (29.4)	750 (23.5)	< 0.001
Paravertebral	228 (24.2)	395 (25.1)	192 (27.9)	815 (25.4)	0.200
Intercostal	345 (36.5)	608 (38.6)	226 (32.9)	1179 (36.8)	0.036
Local	115 (12.2)	209 (13.3)	87 (12.7)	411 (12.8)	0.725
General anesthesia only	161 (17.1)	260 (16.5)	103 (15.0)	524 (16.3)	0.524
Surgery performed on scheduled date					
No, rescheduled	8 (0.8)	23 (1.5)	6 (0.9)	37 (1.2)	0.486
Yes	927 (98.1)	1543 (97.8)	675 (98.3)	3145 (98.0)	
No, surgery never performed	10 (1.1)	11 (0.7)	6 (0.9)	27 (0.8)	
Surgery not performed within 14 d of randomization	10 (1.0)	11 (0.7)	6 (0.9)	27 (0.8)	.

Values are n (%), unless otherwise indicated.

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; bpm, beats per minute; CAD, coronary artery disease; CCB, calcium channel blocker; COPD, chronic obstructive pulmonary disease; DBP, diastolic blood pressure; MIS, minimally invasive surgery; SBP, systolic blood pressure.

* *P* values are included as these are nonrandomized comparisons.

Discussion

In this post hoc analysis of the COP-AF trial, which compared colchicine to placebo in 3209 patients undergoing major noncardiac thoracic surgery, patients who reported smoking within 6 weeks before surgery had a higher adjusted risk for clinically important AF, but not for MINS. We observed no evidence of effect modification with regard to colchicine vs placebo among current, former, and never smokers concerning the primary efficacy and safety outcomes or the secondary or tertiary outcomes.

Table 2. Association between smoking status and postoperative primary efficacy and safety outcomes (n = 3209)

Outcome	Total events	Never smoker (n = 945)		Former smoker (n = 1577)		Current smoker (n = 687)		Former vs never smoker		Current vs never smoker	
		Events	%	Events	%	Events	%	HR (95% CI)	*P*	HR (95% CI)	*P*
Co-primary:											
Clinically important perioperative atrial fibrillation											
Unadjusted	223	50	5.3	120	7.6	53	7.7	1.46 (1.05−2.04)	0.03	1.47 (1.00−2.17)	0.05
Adjusted								1.46 (0.99−2.16)	0.06	1.72 (1.07−2.77)	0.02
Myocardial injury after noncardiac surgery											
Unadjusted	620	166	17.6	310	19.7	144	21.0	1.13 (0.93−1.37)	0.22	1.22 (0.96−1.53)	0.09
Adjusted								1.02 (0.81−1.28)	0.88	1.16 (0.87−1.54)	0.32
Safety											
Composite infection or sepsis											
Unadjusted	187	43	4.6	92	5.8	52	7.6	1.30 (0.91−1.87)	0.15	1.70 (1.14−2.55)	0.01
Adjusted								1.02 (0.66−1.57)	0.93	1.31 (0.79−2.16)	0.30
Noninfectious diarrhea											
Unadjusted		56	5.9	87	5.5	29	4.2	0.93 (0.67−1.31)	0.69	0.71 (0.45−1.11)	0.13
Adjusted								0.98 (0.65−1.48)	0.94	0.80 (0.46−1.40)	0.44

The adjusted model included the following covariates: age, sex (male vs female), history of coronary artery disease (yes vs no), history of stroke (yes vs no), history of peripheral vascular disease (yes vs no), history of chronic obstructive pulmonary disease (yes vs no), type of surgery (open vs thoracoscopic), smoking pack-years, and current use of smoking-cessation pharmacotherapy (use vs no use).

CI, confidence interval; HR, hazard ratio.

Table 3. Effect of colchicine on primary efficacy outcome incidence at 14 days, according to smoking status (n = 3209)

Co-primary outcome	Colchicine (n = 1608)			Placebo (n = 1601)					
	Events/patients	%	Rate/100 person-y	Events/patients	%	Rate/100 person-y	HR (95% CI)	*P*	*P* for Interaction
Clinically important perioperative atrial fibrillation									
Overall	103/1608	6.4	164.0	120/1601	7.5	193.4	0.85 (0.65−1.10)	0.217	
Never smoker	23/477	4.8	122.0	27/468	5.8	146.6	0.83 (0.48−1.46)	0.521	0.82
Current smoker	27/351	7.7	198.1	26/336	7.7	199.9	0.98 (0.57−1.69)	0.956	
Former smoker	53/780	6.8	174.8	67/797	8.4	218.8	0.80 (0.55−1.15)	0.222	
Myocardial injury after noncardiac surgery									
Overall	295/1608	18.3	525.9	325/1601	20.3	594.7	0.89 (0.76−1.05)	0.159	
Never smoker	69/477	14.5	401.0	97/468	20.7	609.8	0.67 (0.49−0.93)	0.015	0.08
Current smoker	69/351	19.7	568.4	75/336	22.3	666.8	0.86 (0.61−1.20)	0.375	
Former smoker	157/780	20.1	586.9	153/797	19.2	556.5	1.05 (0.83−1.32)	0.674	

CI, confidence interval; HR, hazard ratio.

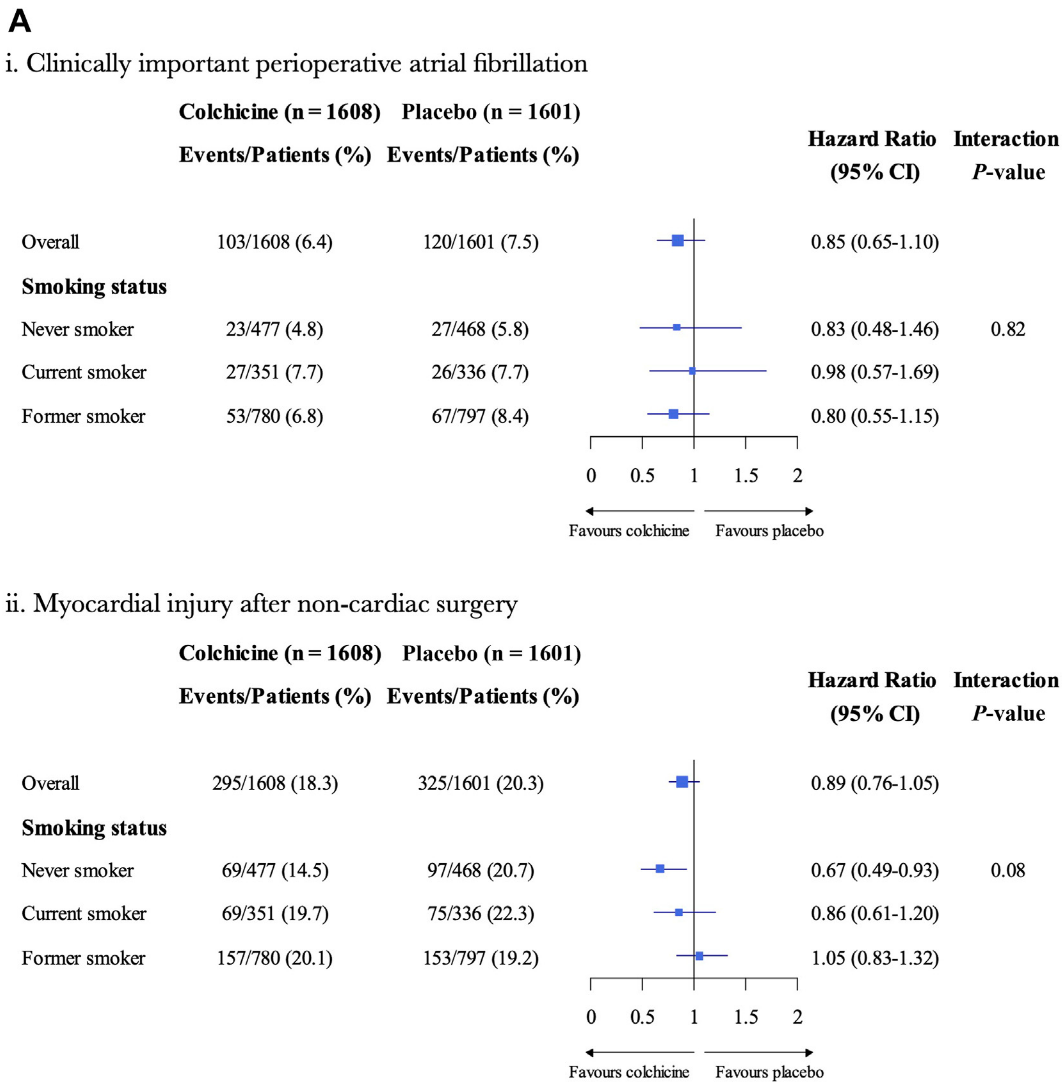

Figure 2. Subgroup analysis of smoking status on (**A**) the 2 co-primary outcomes, and (**B**) the safety outcomes. CI, confidence interval.

Our results revealed an association between current smoking and risk of perioperative AF. Smoking induces cardiac myocyte fibrosis, production of proinflammatory cytokines, and increased activation of the sympathetic system.[20] Although current smokers were younger, they had more cardiovascular disease burden, including coronary artery disease, prior history of MI, and peripheral vascular disease, than did never smokers. After adjusting for baseline differences, the adjusted hazard of clinically important perioperative AF in current smokers was 1.72-fold higher compared with that in never smokers. However, in absolute terms, this difference was very small; the wide CI surrounding this estimate suggests that the study is underpowered, and we infer no causal association, as unmeasured confounders likely influence this association. The trend toward a higher rate of AF in former smokers than in never smokers could highlight the persistent influence of smoking history or the late consequences of smoking on other comorbidities that may be linked to perioperative AF, but this remains to be determined.

Perioperative AF is associated with adverse outcomes in some observational studies. In the **P**eri**o**perative **Is**chemic **E**valuation (POISE) 1 and 2 trials, patients with perioperative AF (new AF within 30 days following noncardiac surgery) had significantly higher 1-year incidences of stroke, death, and MI, compared to those without perioperative AF.[21] Up to 5 years after noncardiac surgery, the risk of clinically overt AF and stroke remains higher among individuals who experience perioperative AF.[22] Among individuals with AF, smoking is associated with an increased risk of stroke and death,[23] underscoring the importance of addressing smoking cessation in the perioperative period. Our findings differ from those of a recent state-of-the-art review on predictors of AF after thoracic surgery, in which smoking was not identified as an independent risk factor.[24] This result may be due at least partially to the retrospective nature of the included studies in that review, in which the definition of current smoking was often unclear.[25-27] Such variability in defining smoking status makes the separation of noise from the true signal of the effect of current smoking on postoperative AF difficult.

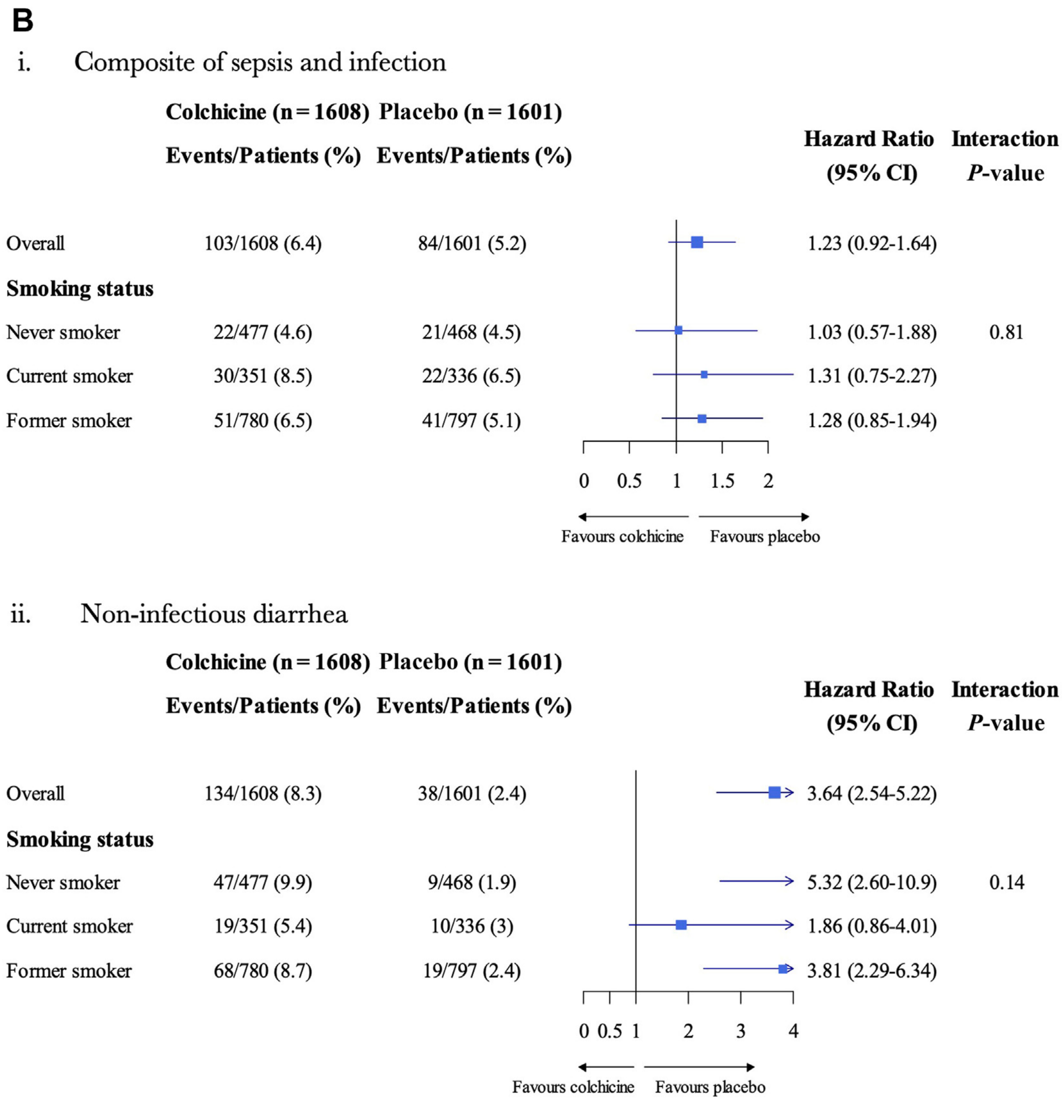

Figure 2. (*continued*).

Smoking is an established risk factor for ischemic heart disease and MI in both general and surgical populations. A large retrospective database study has identified a strong association between smoking and postoperative MI.[28] Other studies that prospectively measured troponin levels and utilized the MINS diagnostic criteria have not consistently identified smoking as an independent risk factor for MINS across various types of noncardiac surgeries.[12,13] However, in patients undergoing thoracic surgery specifically, a small study of 177 patients demonstrated an association between smoking and an increased risk of MINS.[11] In our study of thoracic surgery patients, current smokers had a 16% increase in the hazard of MINS, compared to never smokers. An inverse association appears to be present between smoking and serum levels of high-sensitivity troponin (hs-cTn) in individuals with stable cardiovascular disease, and even in healthy populations.[29-31] The extent to which this relationship influences the inconsistency in the association between smoking and MINS remains unclear.

Smoking also increases the risk of postoperative infection, and smoking cessation reduces this risk.[32,33] Our finding of a nominally increased hazard for most ischemic outcomes, as well as sepsis and infection among current smokers, is consistent with the existing literature. Smoking impacts lung function and expansion, wound healing, and infection. These effects can result in prolonged air leak or ongoing chest-tube output, leading to a longer time to chest-tube removal.[34] Consistent with our findings, other studies also have identified smoking as a risk factor for delayed chest-tube removal and suggest that preoperative smoking cessation could reduce this outcome, important for both patients and healthcare providers.[35,36]

Inflammation is associated with cardiovascular events, including myocardial injury and atrial fibrillation after surgery.[37,38] In the COP-AF trial, use of colchicine did not reduce the incidence of AF or MINS, but it did reduce the composite outcome of AF and MINS (HR 0·84, 95% CI 0·73-0·97).[18] Our a priori hypothesis in this study was that smoking would attenuate the efficacy of colchicine, and our findings indicate a nonsignificant trend toward less benefit with colchicine use, on AF and MINS, among current smokers than among never smokers. With MINS, the *P*-value for interaction was 0.08, and our study likely was underpowered to detect significant differences. The effect of colchicine in causing diarrhea, a recognized side effect, was less severe among current and former smokers, compared to never smokers. This finding supports the theory that smoking exerts its inflammatory effects through multiple pathways; therefore, the impact of a medication, such as colchicine, that targets specific inflammatory pathways, may be diminished among smokers. Further studies are needed in this area.

The role of colchicine use in reducing cardiovascular events has been challenged by recent trials. Several major trials have evaluated colchicine use in cardiovascular disease. The **Col**chicine **C**ardiovascular **O**utcomes **T**rial (COLCOT) (n = 4745) found that a 23% relative reduction in major adverse cardiovascular events occurred when colchicine use was initiated within 30 days post-MI.[16] The Low-dose Colchicine 2 (LoDoCo 2) trial in stable coronary artery disease showed that a 31% reduction in major adverse cardiovascular events occurred with colchicine use.[17] This finding led to US Food and Drug Administration approval and a class IIa guideline recommendation for atherosclerotic cardiovascular disease.[39] In contrast, the **C**olchicine in Patients with Acute Ischaemic Stroke or Transient Ischaemic Attack (CHANCE-3) trial (n = 8345) in acute ischemic stroke or transient ischemic attack found no benefit of a 90-day course of colchicine on vascular events.[40] Similarly, the long-term colchicine for the prevention of vascular recurrent events in non-cardioembolic stroke (CONVINCE) trial (n = 3154) in patients with ischemic stroke showed no significant reduction in vascular events with colchicine use over a median of 34 months.[41] Most recently, the Colchicine in Acute Myocardial Infarction (CLEAR) trial (n = 7062) did not show benefit of colchicine use started soon after MI and continued for a median of 3 years.[42]

Strengths and limitations

To our knowledge, this study is the first to specifically explore the relationship between smoking status and the effectiveness of colchicine as an anti-inflammatory agent for preventing postoperative cardiovascular events. Smoking data were complete for all patients at baseline. Our study has some limitations. This is a post hoc subgroup analysis, and our findings are exploratory. Unmeasured confounding factors, such as each individual's detailed smoking history and the reasons former smokers quit, which may be related to their unmeasured health status, may have influenced the association between smoking status and the study outcomes. We arbitrarily chose a 6-week cutoff to define current smokers, aiming to capture recent active smoking. The wide CIs around some effect estimates likely indicate that our study was underpowered for some of the outcomes. Finally, we included only those patients who underwent noncardiac thoracic surgery, limiting the generalizability of our findings.

Conclusion

In the COP-AF trial, current smoking was associated with a higher risk of perioperative AF but not MINS. No significant interactions occurred between the effects of colchicine vs placebo, and smoking status, on any of the study outcomes. Overall, smoking cessation remains an important goal in perioperative medicine.

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Data Access Statement

The Population Health Research Institute (PHRI) is the sponsor of this trial. The PHRI believes the dissemination of clinical research results is vital and that sharing of data is important. The PHRI prioritizes access to data analyses to researchers who have worked on the trial for a significant duration, have played substantial roles, and have participated in raising the funds to conduct the trial. The PHRI balances the length of the research study and the intellectual and financial investments that made it possible with the need to allow wider access to the data collected. Data will be disclosed only upon request and approval of the proposed use of the data by a review committee. Data requests from other non-COP-AF investigators will not be considered until 5 years after the close of the trial. All data requests should be made to the corresponding author.

Ethics Statement

Recruitment into the COP-AF trial occurred after patients provided informed consent, and local ethics board approval was obtained from all participating sites.

Patient Consent

The authors confirm that individual patient consent forms were obtained for the COP-AF trial.

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Supplementary Material

To access the supplementary material accompanying this article, visit *CJC Open* at https://www.cjcopen.ca/ and at https://doi.org/10.1016/j.cjco.2025.04.008.