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Low-Dose Colchicine in Patients With Type 2 Diabetes and Recent Myocardial Infarction in the Colchicine Cardiovascular Outcomes Trial (COLCOT)

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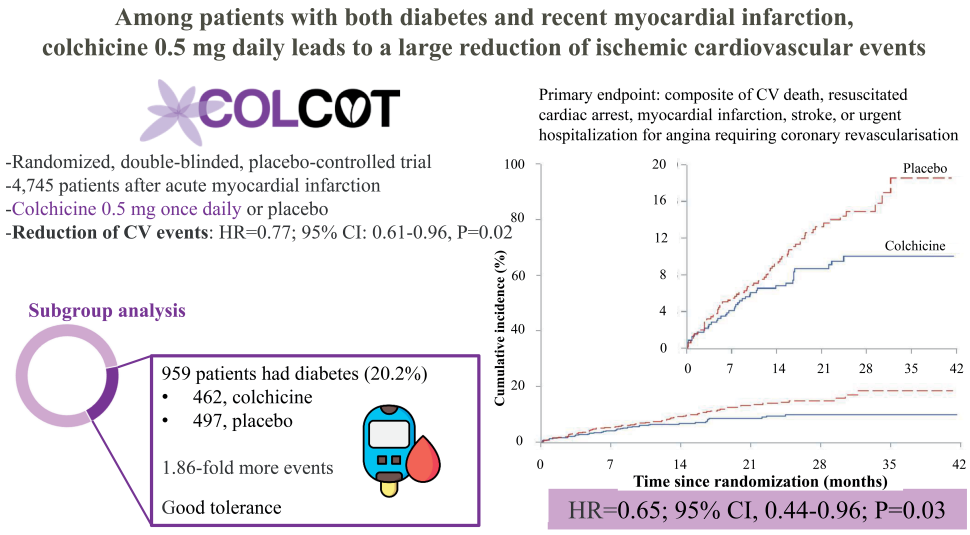

COLCOT, Colchicine Cardiovascular Outcomes Trial; CV, cardiovascular; HR, hazard ratio

ARTICLE HIGHLIGHTS

- **Why did we undertake this study?**
  Patients with type 2 diabetes (T2D) are known to be at higher cardiovascular risk, at least partly due to vascular inflammation. Colchicine has shown its benefits in the Colchicine Cardiovascular Outcomes Trial (COLCOT) trial in 4,745 patients with a recent myocardial infarction.

- **What is the specific question we wanted to answer?**
  We aimed at determining the cardiovascular benefits of low-dose colchicine in the 959 patients with T2D in COLCOT.

- **What did we find?**
  In this prespecified analysis of patients with T2D, the primary end point occurred less often in the colchicine group (hazard ratio 0.65; 95% CI 0.44–0.96; $P = 0.03$).

- **What are the implications of our findings?**
  Patients with both T2D and a recent myocardial infarction derive large cardiovascular benefits from colchicine.

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OBJECTIVE

The cardiovascular benefits of low-dose colchicine have been demonstrated in patients with coronary disease. Its effects were evaluated in this prespecified analysis in patients with type 2 diabetes (T2D) from the Colchicine Cardiovascular Outcomes Trial (COLCOT).

RESEARCH DESIGN AND METHODS

COLCOT was a randomized, double-blinded trial of colchicine, 0.5 mg daily, versus placebo initiated within 30 days after a myocardial infarction.

RESULTS

There were 959 patients with T2D enrolled and monitored for a median of 22.6 months. A primary end point event occurred in 8.7% of patients in the colchicine group and in 13.1% in the placebo group (hazard ratio 0.65; 95% CI 0.44–0.96; *P* = 0.03). Nausea was reported in 2.7% and 0.8% in the study groups (*P* = 0.03), and pneumonia occurred in 2.4% and 0.4% (*P* = 0.008).

CONCLUSIONS

Among patients with T2D and a recent myocardial infarction, colchicine, 0.5 mg daily, leads to a large reduction of cardiovascular events. These results support the conduct of the COLCOT-T2D trial in primary prevention.

Inflammation is involved in the initiation, progression, and destabilization of atherosclerosis (1). Basic studies and clinical trials have demonstrated the benefits of reducing inflammation in atherosclerosis (2,3). Colchicine has been shown to exert beneficial effects, both in the Colchicine Cardiovascular Outcomes Trial (COLCOT) of patients with a recent myocardial infarction (MI) (4) and in the Low-Dose Colchicine-2 (LoDoCo2) trial of patients with stable coronary artery disease (CAD) (5). These results have led to the regulatory approval of low-dose colchicine for prevention of cardiovascular events in patients with atherosclerotic cardiovascular disease.

Type 2 diabetes (T2D) is associated with increased rates of both macrovascular and microvascular disease and cardiovascular events (6). Accumulating evidence suggests that inflammation is an important bridging link between diabetes and atherosclerosis (7). At least one-third of patients with acute coronary syndrome have

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T2D or prediabetes (8). Patients with T2D are at higher risk of presenting a cardiovascular event after an MI (9). This appears to be at least in part due to more pronounced vascular inflammation (7). We hypothesized that patients with both T2D and a recent MI could draw significant benefit from colchicine.

RESEARCH DESIGN AND METHODS

The COLCOT trial was reported in detail elsewhere (4). Briefly, COLCOT was a randomized, double-blind, placebo-controlled, investigator-initiated trial comparing colchicine, 0.5 mg once daily, with placebo in a 1:1 ratio. The protocol was approved by the institutional review board at each of the 167 centers in the 12 countries participating. All study support activities, including project coordination, data management, site monitoring, and statistical analyses, were performed at the Montreal Health Innovations Coordinating Center. Potential study end points were adjudicated by an independent clinical end point committee composed of experienced cardiologists and neurologists who were unaware of the trial group assignments. The study medication and matching placebo were provided by Pharmascience (Montreal, Quebec, Canada), which had no role in the trial design or conduct.

Adult patients were eligible if an MI had occurred within 30 days of enrollment. Patients were excluded if they had class III or IV heart failure, left ventricular ejection fraction <35%; stroke within the past 3 months; type 2 index MI, coronary bypass surgery within the past 3 years or planned, history of noncutaneous cancer within the last 3 years, inflammatory bowel disease or chronic diarrhea, neuromuscular disease, or nontransient creatine phosphokinase greater than three times the upper limit of normal (ULN), significant nontransient hematological abnormalities, severe renal disease with serum creatinine greater than twice the ULN, severe hepatic disease, drug or alcohol abuse, chronic systemic steroid therapy, or history of sensitivity to colchicine.

Written informed consent was obtained from all patients before enrollment. Clinical evaluations occurred at 1 and 3 months following randomization and every 3 months thereafter.

The primary efficacy end point was a composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization in a time-to-event analysis.

The statistical analysis plan of this event-driven trial was published elsewhere (4) and included a prespecified subgroup analysis of the primary end point according to diabetes. The subgroup analysis was conducted according to the statistical analysis plan using positively adjudicated data, according to the intention-to-treat (ITT) principle and using a Cox proportional hazards model with terms for group, diabetes, and group × diabetes interaction. The treatment effect in patients with diabetes, along with its 95% CI, was estimated from this model. Patients with no event were censored at the time last known to be event free. The subgroup analysis of the primary end point was repeated on the per-protocol population of patients without major protocol deviations. To account for the occurrence of multiple primary end point events within patients, a recurrent-event analysis was undertaken in the subgroup of patients with diabetes, with the use of a negative binomial regression model.

All statistical tests were two-sided and conducted at the 0.05 significance level. Statistical analyses were performed using SAS 9.4 software.

RESULTS

COLCOT enrolled 4,745 patients between December 2015 and August 2018. Patients were monitored for a median of 22.6 months. As reported previously, the primary end point occurred less often in patients in the colchicine group than in those allocated to placebo (hazard ratio 0.77; 95% CI 0.61–0.96; $P = 0.02$).

A total of 959 patients (20.2%) had T2D, with 462 and 497 being assigned to the colchicine and placebo groups, respectively. The characteristics of patients with T2D at baseline are shown in Table 1. Patients were enrolled a mean of 14.0 days after the index MI. The mean age was 62.4 years, and 22.2% were women. The mean BMI was 29.9 kg/m^2, and 74.9% of patients presented with hypertension.

Table 1—Characteristics of the patients with diabetes

Characteristic	Colchicine (n = 462)	Placebo (n = 497)
Age, years	62.5 ± 10.4	62.4 ± 10.7
Female sex	106 (22.9)	107 (21.5)
BMI, kg/m^2	29.7 ± 5.1	30.2 ± 5.2
Current smoking	127 (27.5)	122 (24.5)
Hypertension	337 (72.9)	381 (76.7)
History of		
MI	118 (25.5)	122 (24.5)
PCI	127 (27.5)	113 (22.7)
heart failure	20 (4.3)	18 (3.6)
Stroke or transient ischemic attack	18 (3.9)	25 (5.0)
Time from index MI to randomization, days	13.9 ± 9.8	14.0 ± 9.9
PCI for index MI	413 (89.4)	457 (92.1)
Medication use		
Aspirin	452 (97.8)	491 (98.8)
Other antiplatelet agent	448 (97.0)	481 (96.8)
Statin	456 (98.7)	491 (98.8)
β-Blocker	430 (93.1)	448 (90.1)
Diabetes medication use		
Metformin	347 (75.1)	378 (76.1)
Insulin	133 (28.8)	163 (32.8)
Glucagon-like peptide 1 receptor agonist	33 (7.1)	46 (9.3)
Sodium–glucose cotransporter inhibitor	88 (19.0)	78 (15.7)
Dipeptidyl peptidase-4 inhibitor	102 (22.1)	99 (19.9)
Sulfonylurea	84 (18.2)	107 (21.5)

Data are presented as means ± SD or n (%). PCI, percutaneous coronary intervention.

Most patients (90.8%) underwent a percutaneous coronary intervention for their index MI. Aspirin, another antiplatelet agent, a statin, and a β-blocker were taken by 98.3%, 96.9%, 98.7%, and 91.6% of the patients, respectively. Metformin, insulin, a sodium–glucose cotransporter 2 inhibitor, a glucagon-like peptide 1 receptor agonist, and a dipeptidyl peptidase 4 inhibitor were used by 75.6%, 30.9%, 17.3%, 8.2%, and 21.0% of the patients, respectively.

The ITT analysis showed the primary end point occurred in 8.7% of the patients in the colchicine group and in 13.1% of those in the placebo group (hazard ratio, 0.65; 95% CI 0.44–0.96; *P* = 0.03), as presented in Fig. 1 and Table 2. This result is consistent with the per-protocol analysis (hazard ratio 0.63; 95% CI 0.42–0.95; *P* = 0.03).

In the ITT analysis, the total number of primary end point events (first and recurrent) was 50 in the colchicine group and 93 in the placebo group, over periods of 10,311 and 10,847 patient-months of follow-up, respectively. Thus, the primary end point event rates per 100 patient-months were 0.48 in the colchicine group and 0.86 in the placebo group (rate ratio, 0.53; 95% CI 0.33–0.87; *P* = 0.01).

The interaction between history of diabetes (presence or absence) and the study treatment group was not statistically significant (*P* = 0.27). The rate of the primary end point in patients with no diabetes was 4.8% and 5.6% in the colchicine and placebo groups, respectively (hazard ratio 0.85; 95% CI 0.64–1.13).

The incidence of adverse events considered to be related to the study drug in patients with T2D was 14.6% in the colchicine group and 12.8% in the placebo group (Table 3). At least one gastrointestinal adverse event occurred in 15.3% of the patients in the colchicine group compared with 16.1% of those in the placebo group. Diarrhea was reported in 8.0% of the patients in the colchicine group and in 9.8% of those in the placebo group (*P* = 0.34). Nausea was more common in the colchicine group than in the placebo group (2.7% vs. 0.8%; *P* = 0.04). Pneumonia was reported as a serious adverse event in 2.4% of the patients receiving colchicine compared with 0.4% of those receiving placebo (*P* = 0.008).

CONCLUSIONS

In this prespecified subgroup analysis of COLCOT, the risk of the primary efficacy end point, consisting of a composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization, was reduced by 35% in the patients with T2D in the colchicine group compared with those in the placebo group.

Approximately 30–40% of MI patients have T2D or metabolic syndrome (8). Patients with T2D present a very high risk of cardiovascular events after an MI, with an event rate nearly twice as high as in those without T2D (9). In COLCOT, patients with T2D presented a 1.86-fold higher risk of a primary end point cardiovascular event. Inflammation has been shown to contribute to the increased risk of cardiovascular events in patients with T2D (7).

The most common adverse events observed were gastrointestinal. Diarrhea was reported in 8.0% of the patients in the colchicine group and in 9.8% of those in the placebo group, and nausea occurred in 2.7% and 0.8%, respectively. Pneumonia, as a serious adverse event,

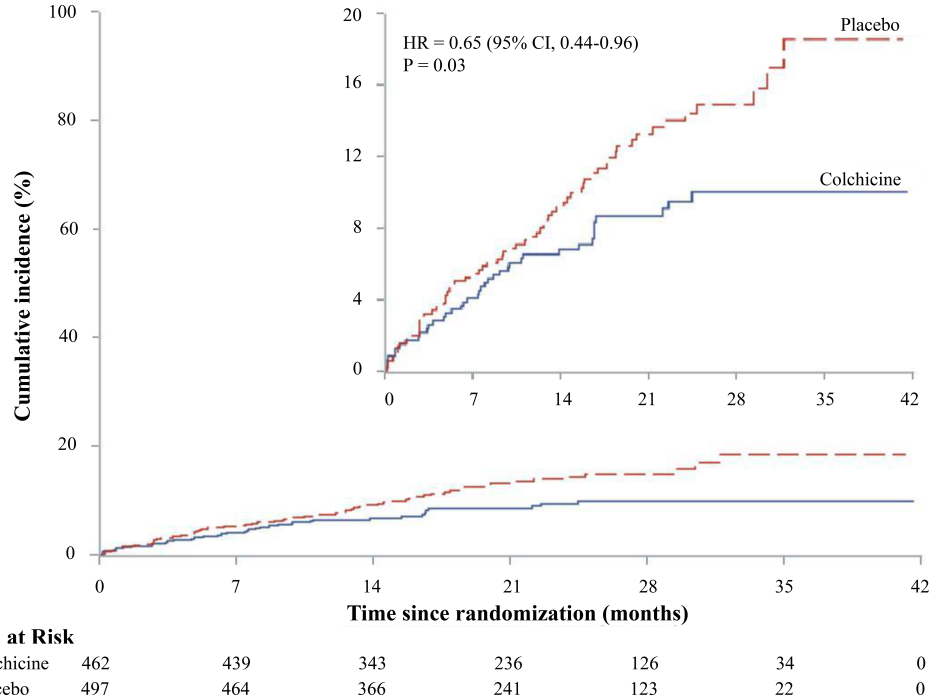

Figure 1—Cumulative incidence of cardiovascular events in patients with diabetes (ITT population). Shown are the Kaplan-Meier event curves for the primary efficacy composite end point of death from cardiovascular causes, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring coronary revascularization in the colchicine group and the placebo group of patients with diabetes, in a time-to-first event analysis. The insert shows the same data on an enlarged *y* axis. HR, hazard ratio.

Table 2—Rates and HR for the primary end point and its components in COLCOT patients with diabetes (ITT population)

End point	Colchicine (*n* = 462)	Placebo (*n* = 497)	Hazard ratio (95% CI)	*P* value
Primary composite end point	40 (8.7)	65 (13.1)	0.65 (0.44–0.96)	0.03
Components of primary end point				
Cardiovascular death	8 (1.7)	14 (2.8)	0.61 (0.26–1.45)	0.26
Resuscitated cardiac arrest	1 (0.2)	2 (0.4)	0.53 (0.05–5.86)	0.61
Myocardial infarction	25 (5.4)	36 (7.2)	0.74 (0.44–1.23)	0.24
Stroke	2 (0.4)	10 (2.0)	0.21 (0.05–0.96)	0.04
Urgent hospitalization for angina requiring revascularization	7 (1.5)	17 (3.4)	0.44 (0.18–1.05)	0.06
Death	18 (3.9)	21 (4.2)	0.90 (0.48–1.69)	0.75

Data are presented as *n* (%).

was more frequent in the colchicine group than in the placebo group (2.4% vs. 0.4%). The latter observation could be due to a play of chance or might reflect altered immunologic responses. This difference in the incidence of infections was not observed in LoDoCo2 (5).

The role of HbA_{1c} or LDL-cholesterol could not be analyzed. The effects of different glucose-lowering medications or possible hypoglycemic episodes could also not be assessed. Finally, patients were not stratified at inclusion for the presence of diabetes.

In conclusion, this subgroup analysis of COLCOT suggests that patients with both T2D and a recent MI derive a large benefit from inflammation-reducing therapy with colchicine.

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Table 3—Adverse events in the patients with diabetes (safety population)

Event	Colchicine (*n* = 451)	Placebo (*n* = 492)	*P* value
Any related adverse event	66 (14.6)	63 (12.8)	0.41
Adverse events			
Gastrointestinal event	69 (15.3)	79 (16.1)	0.75
Diarrhea	36 (8.0)	48 (9.8)	0.34
Nausea	12 (2.7)	4 (0.8)	0.03
Flatulence	1 (0.2)	0	—
Decreased appetite	1 (0.2)	0	—
Gastrointestinal hemorrhage	1 (0.2)	1 (0.2)	0.95
Anemia	5 (1.1)	5 (1.0)	0.89
Leukopenia	1 (0.2)	0	—
Thrombocytopenia	2 (0.4)	2 (0.4)	0.93
Serious adverse events			
Any serious adverse event	92 (20.4)	93 (18.9)	0.56
Gastrointestinal event	7 (1.6)	7 (1.4)	0.87
Infection	19 (4.2)	13 (2.6)	0.18
Severe infection	10 (2.2)	7 (1.4)	0.36
Diabetic foot infection	1 (0.2)	0	—
Pneumonia	11 (2.4)	2 (0.4)	0.008
Septic shock	1 (0.2)	1 (0.2)	0.95
Hospitalization for heart failure	10 (2.2)	11 (2.2)	0.98
Cancer	13 (2.9)	10 (2.0)	0.40

Data are presented as *n* (%).

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