Colchicine for coronary disease: teaching an old dog new tricks

Podcast developed by the Canadian Collaborative Research Network

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Faculty Disclosures

Faculty: John Eikelboom

Relationships with financial sponsors:

- **Honoraria:** CCRN, CCRN, Astra-Zeneca, Bayer, Boehringer-Ingelheim, BMS, Daiichi-Sankyo, Eli-Lilly, GSK, Janssen, Pfizer, Sanofi-Aventis, Servier
- **Funded grants/research/clinical trials:** Astra-Zeneca, Bayer, Boehringer-Ingelheim, BMS, GSK, Janssen, Pfizer, Sanofi-Aventis
- **Advisory boards/speakers' bureaus:** none
- **Patents:** none
- **Other:** none

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Presenter Disclosures

Faculty: Milan Gupta (Moderator)

Relationships with financial sponsors:

- **Honoraria:** CCRN
- **Funded grants/research/clinical trials:** none
- **Advisory boards/speakers' bureaus:** none
- **Patents:** none
- **Other:** none

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Disclosure of Financial Support

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Mitigating Potential Bias

Bias in this program has been mitigated using independent content validation as follows:

- All content has been reviewed by a representative physician steering committee.
- All data have been sourced from clinically accepted evidence.
- All support used in justification of patient care recommendations conforms to generally accepted standards and the most recently available clinical data.

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CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Interleukin-1β Inhibition

- ↓ IL-1β
- ↓ IL-6
- ↓ hsCRP
- ↓ 17% reduction in MACE+

CIRT | Cardiovascular Inflammation Reduction Trial

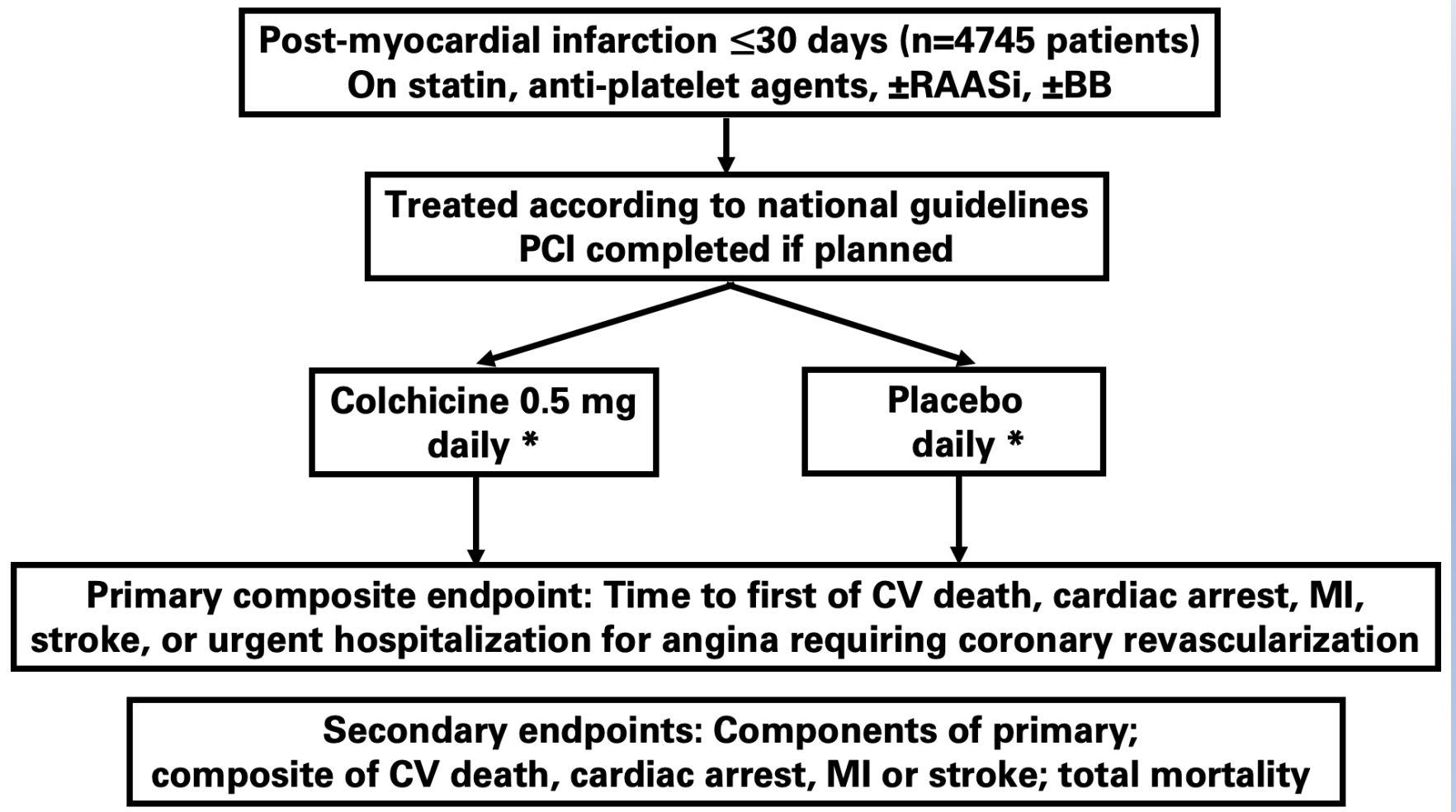
Low-Dose Methotrexate

- ↔ IL-1β
- ↔ IL-6
- ↔ hsCRP
- ↔ No reduction in MACE+

Ridker, PM et al. N Engl J Med 2017; 377:1119-1131 DOI: 10.1056/NEJMoa1707914

Ridker, PM et al. N Engl J Med. 2019; 380:752–762. doi: 10.1056/NEJMoa1809798

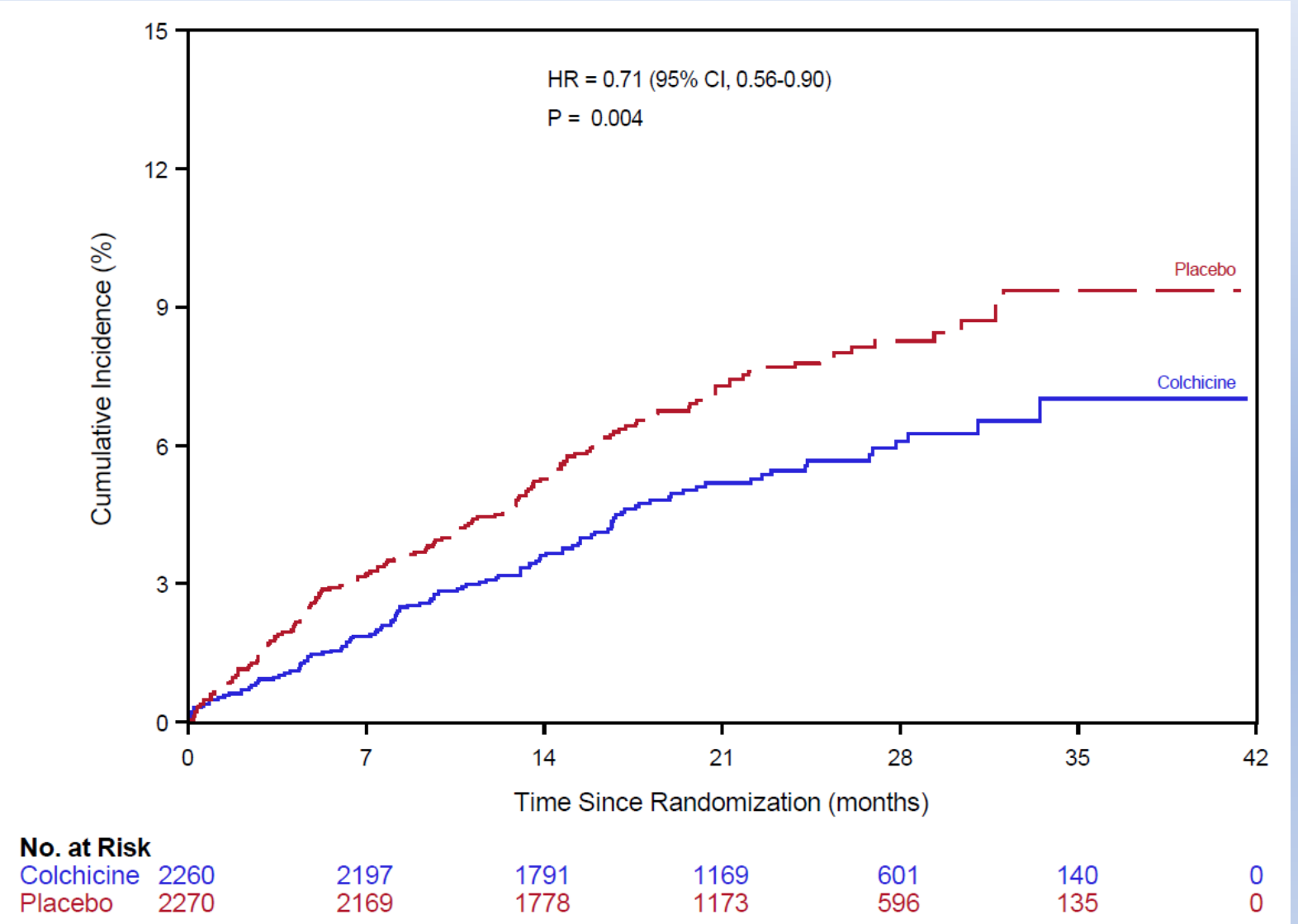
COLCOT- Study design



*provided by Pharmascience (Montreal)

Tardif, JC et al. N Engl J Med 2019; 381:2497-2505 DOI: 10.1056/NEJMoa1912388

COLCOT- Primary Composite Outcome



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COLCOT- Major Clinical Outcomes

Clinical Outcome Intent-to-treat population	Colchicine N=2366	Placebo N=2379	Hazard Ratio (95% CI)	P Value
Primary composite endpoint - no. (%)	131 (5.5%)	170 (7.1%)	0.77 (0.61-0.96)	0.02
CV death - no. (%)	20 (0.8%)	24 (1.0%)	0.84 (0.46-1.52)	
Resuscitated cardiac arrest - no. (%)	5 (0.2%)	6 (0.3%)	0.83 (0.25-2.73)	
Myocardial infarction - no. (%)	89 (3.8%)	98 (4.1%)	0.91 (0.68-1.21)	
Stroke - no. (%)	5 (0.2%)	19 (0.8%)	0.26 (0.10-0.70)	
Urgent hospitalization for angina requiring revascularization - no. (%)	25 (1.1%)	50 (2.1%)	0.50 (0.31-0.81)	
Secondary composite endpoint - no. (%)	111 (4.7%)	130 (5.5%)	0.85 (0.66-1.10)	
Death - no. (%)	43 (1.8%)	44 (1.8%)	0.98 (0.64-1.49)	
DVT or pulmonary embolus - no. (%)	10 (0.4%)	7 (0.3%)	1.43 (0.54-3.75)	
Atrial fibrillation - no. (%)	36 (1.5%)	40 (1.7%)	0.93 (0.59-1.46)	

COLCOT- Conclusion

- **Colchicine 0.5 mg/day significantly reduces the risk of first and total ischemic cardiovascular events by 23% and 34% respectively compared to placebo in patients with a recent myocardial infarction.**

- **Rates of adverse effects were low, including a small increase in pneumonias (0.9 vs. 0.4%) but no significant increase in diarrhea with colchicine, on background therapy with aspirin, a 2nd antiplatelet agent and a statin in 99, 98 and 99% of patients.**

- **The COLCOT results apply to patients who have recently suffered a myocardial infarction. Further research is needed to assess the benefits of colchicine in other high-risk patients.**

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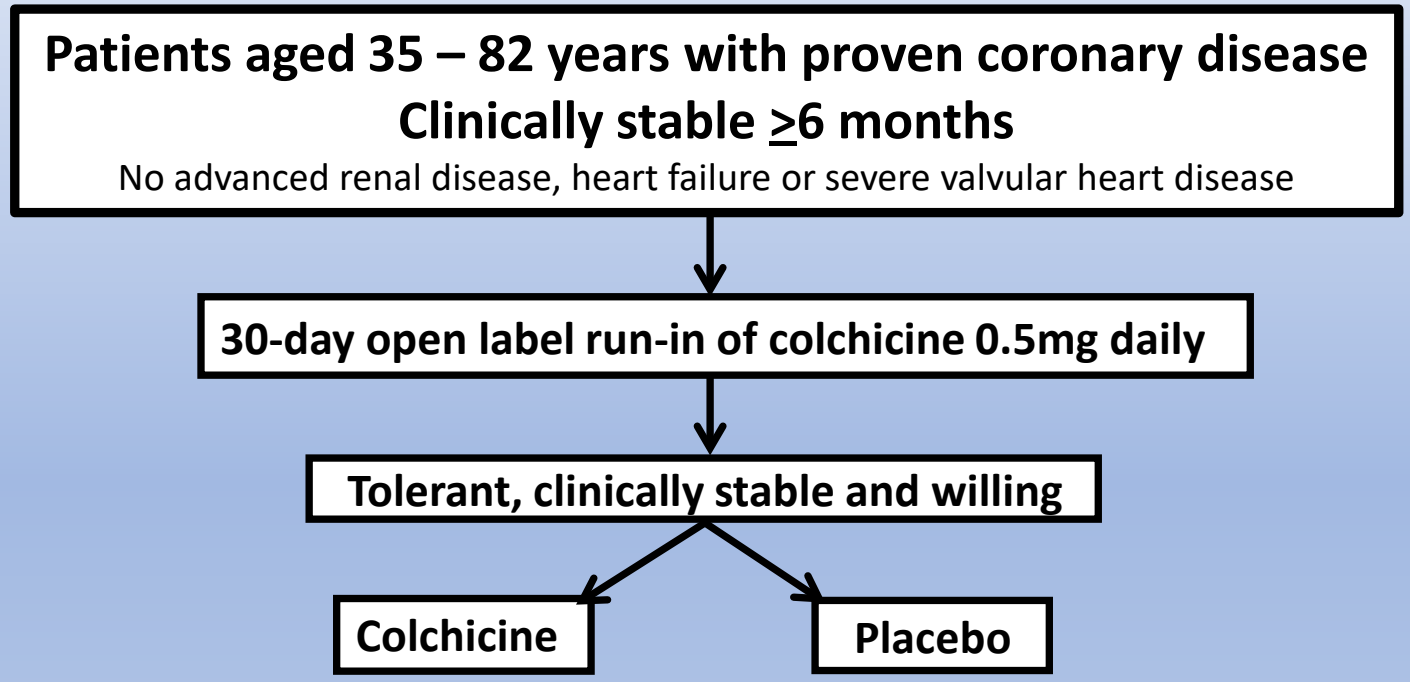
LODOCO2 - Study design



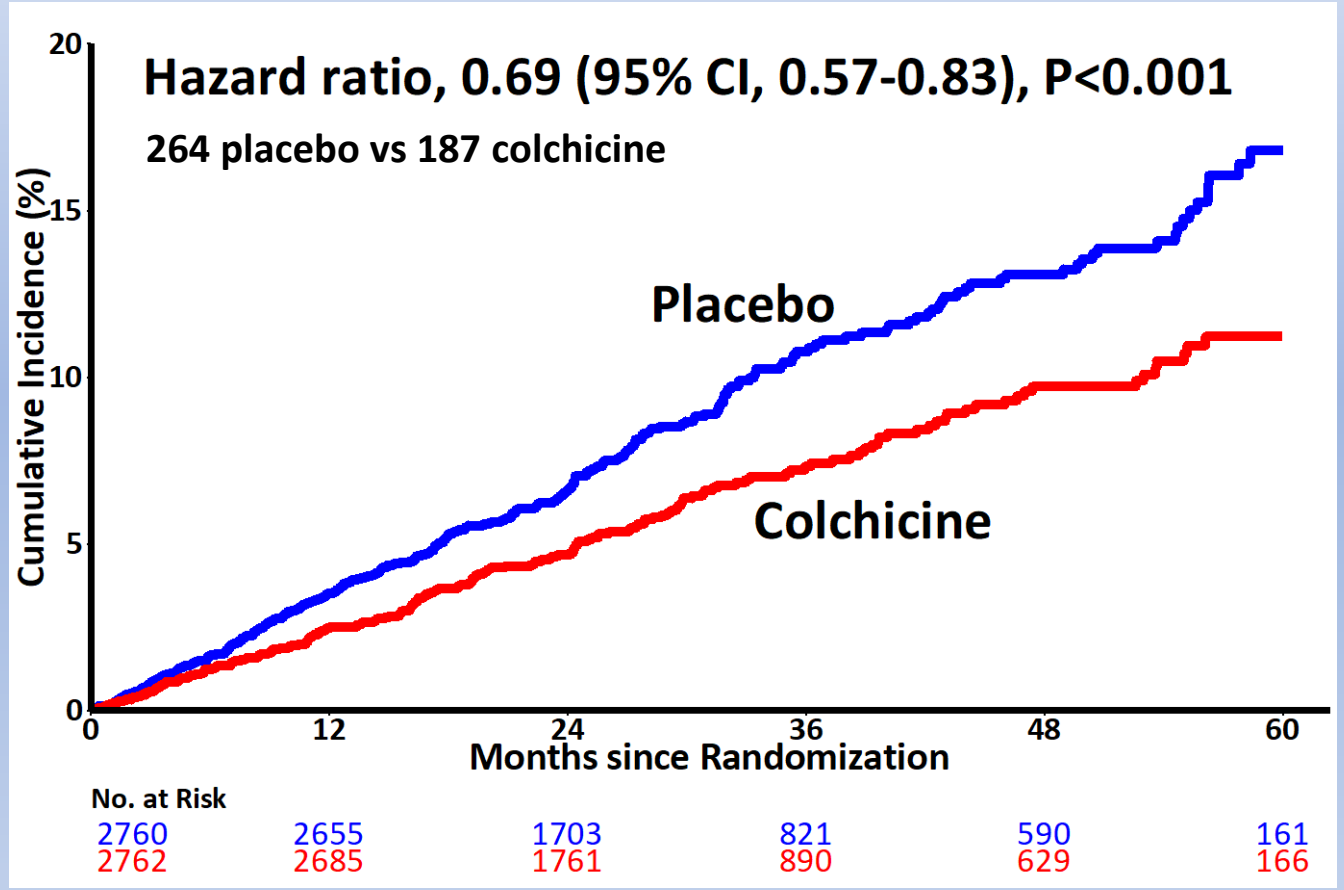
Planned to begin close-out 12 months after the last participant had been randomized*

** If 331 primary events had accrued – sufficient to detect a 30% effect of therapy with 90% power*

Nidorf SM et al. N Engl J Med 2020; 383:1838-1847 DOI: 10.1056/NEJMoa2021372

LODOCO2- Primary end point

Cardiovascular death, Myocardial infarction, Ischemic stroke or Ischemia-driven coronary revascularization



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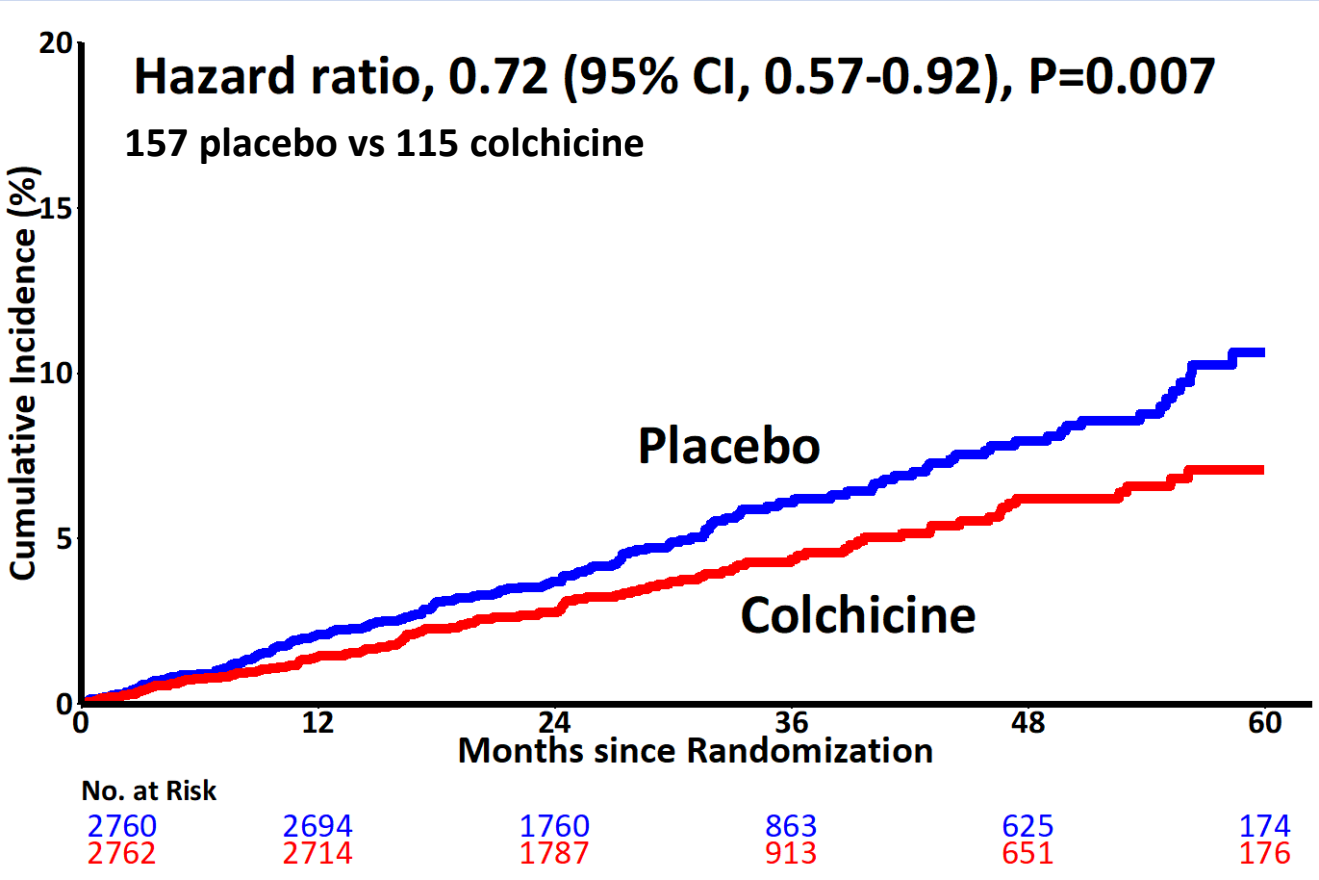
LODOCO2- Key secondary end point

Cardiovascular death, Myocardial infarction or Ischemic stroke



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LODOCO2- Ranked secondary end points

	Colchicine (N = 2762)	Placebo (N = 2760)	Hazard Ratio (95% CI)	P Value
1. Cardiovascular death, Myocardial infarction, or Ischemic stroke	115(4.2)	157(5.7)	0.72(0.57-0.92)	**0.007**
2. Myocardial infarction or Ischemia-driven coronary revascularization	155(5.6)	224(8.1)	0.67(0.55-0.83)	**<0.001**
3. Cardiovascular death or Myocardial infarction	100(3.6)	138(5.0)	0.71(0.55-0.92)	**0.010**
4. Ischemia-driven coronary revascularization	135(4.9)	177(6.4)	0.75(0.60-0.94)	**0.012**
5. Myocardial infarction	83(3.0)	116(4.2)	0.70(0.53-0.93)	**0.014**
6. Ischemic stroke	16(0.6)	24(0.9)	0.66(0.35-1.25)	0.198
7. Death from any cause	73(2.6)	60(2.2)	1.21(0.86-1.71)	
8. Cardiovascular death	20(0.7)	25(0.9)	0.80(0.44-1.44)	

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LODOCO2- Summary

In patients with chronic coronary disease, low-dose colchicine

1) Reduced the risk of;

- The primary composite end point

  Cardiovascular death, myocardial infarction, ischemic stroke or ischemia-driven coronary revascularization.

- Key secondary composite end points

  Cardiovascular death, myocardial infarction or ischemic stroke.

- Individual secondary end points

  Myocardial infarction & Ischemia-driven coronary revascularization.
  … with broadly consistent effects across a range of clinical subgroups

2) Was well tolerated and appeared safe

The incidence of premature discontinuation & serious adverse events were both low & equivalent to placebo.

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COLCOT- Adverse Events

Safety population	Colchicine (N=2330)	Placebo (N=2346)	P Value
Any related AE - no. (%)	372 (16.0%)	371 (15.8%)	0.89
Any SAE - no. (%)	383 (16.4%)	404 (17.2%)	0.47
Gastro-intestinal AE - no. (%)	408 (17.5%)	414 (17.6%)	0.90
Gastro-intestinal SAE – no. (%)	46 (2.0%)	36 (1.5%)	0.25
Diarrhea AE - no. (%)	225 (9.7%)	208 (8.9%)	0.35
Nausea AE - no. (%)	43 (1.8%)	24 (1.0%)	0.02
Flatulence AE - no. (%)	15 (0.6%)	5 (0.2%)	0.02
GI haemorrhage AE - no. (%)	7 (0.3%)	5 (0.2%)	0.56
Infection SAE - no. (%)	51 (2.2%)	38 (1.6%)	0.15
Pneumonia SAE - no. (%)	21 (0.9%)	9 (0.4%)	0.03
Septic shock SAE - no. (%)	2 (0.1%)	2 (0.1%)	0.99
HF hospitalization - no. (%)	25 (1.1%)	17 (0.7%)	0.21
Cancer - no. (%)	43 (1.8%)	46 (2.0%)	0.77
Anemia - no. (%)	14 (0.6%)	10 (0.4%)	0.40
Leukopenia - no. (%)	2 (0.1%)	3 (0.1%)	0.66
Thrombocytopenia - no. (%)	3 (0.1%)	7 (0.3%)	0.21

LODOCO2- Serious adverse events

	Colchicine (N = 2762)	Placebo (N = 2760)
Non-cardiovascular death	53(1.9)	35(1.3)
Diagnosis of new cancer	120(4.3)	122(4.4)
Hospitalization for infection	137(5.0)	144(5.2)
Hospitalization for pneumonia	46(1.7)	55(2.0)
Hospitalization for gastro-intestinal reason	53(1.9)	50(1.8)
Neutropenia	3(0.1)	3(0.1)
Myotoxicity	4(0.1)	3(0.1)

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References – Clinical trials

CANTOS: Ridker, PM et al. N Engl J Med 2017; 377:1119-1131 DOI: 10.1056/NEJMoa1707914

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COLCOT: Tardif, JC et al. N Engl J Med 2019; 381:2497-2505 DOI: 10.1056/NEJMoa1912388

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LODOCO2: Nidorf SM et al. N Engl J Med 2020; 383:1838-1847 DOI: 10.1056/NEJMoa2021372