Inflammation and CVD: Understanding new pathways

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MONTREAL HEART INSTITUTE

Disclosures

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Patent:	**Pharmacogenomics-guided CETP inhibition**

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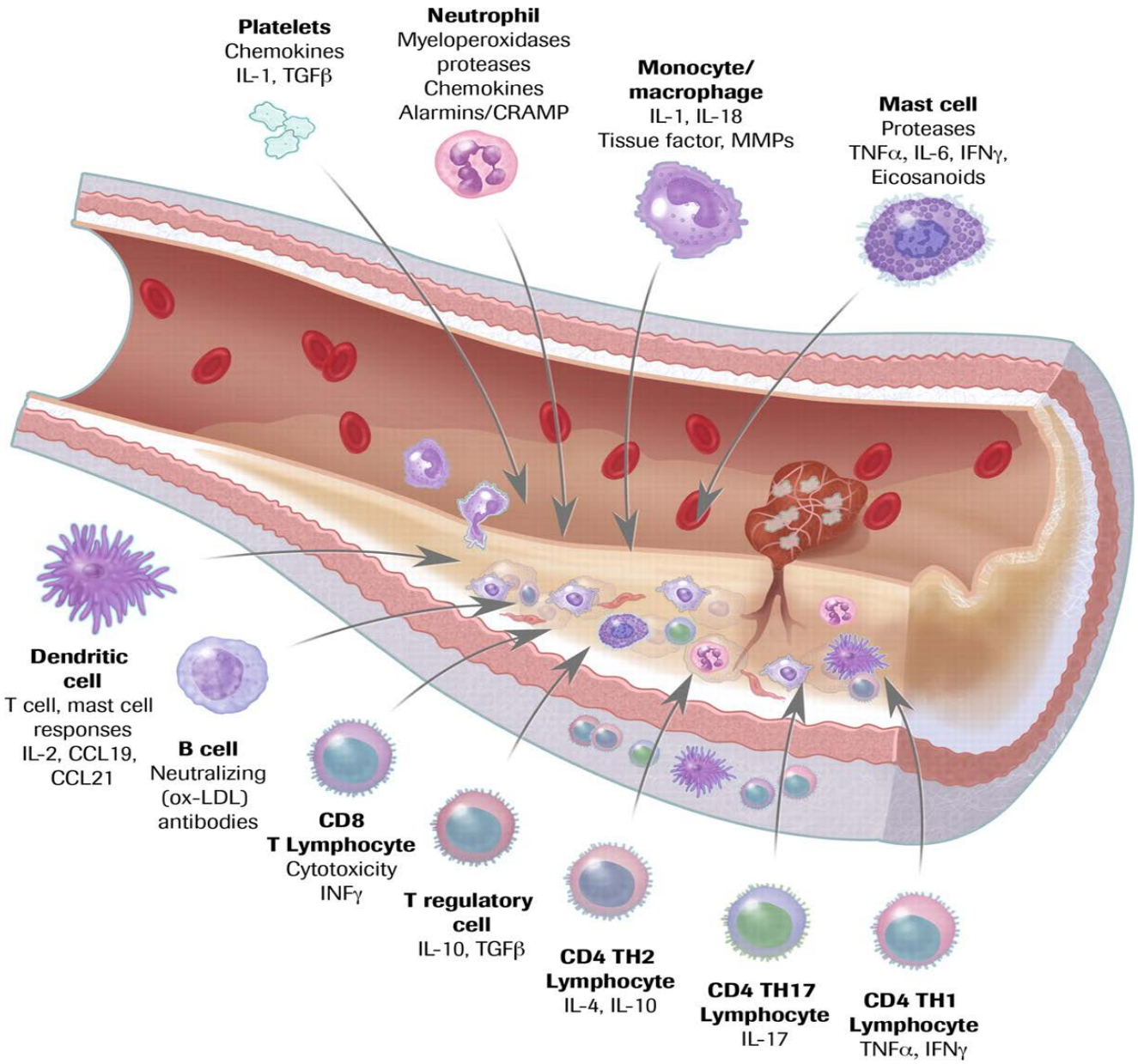
Inflammation and immunity in atherosclerosis



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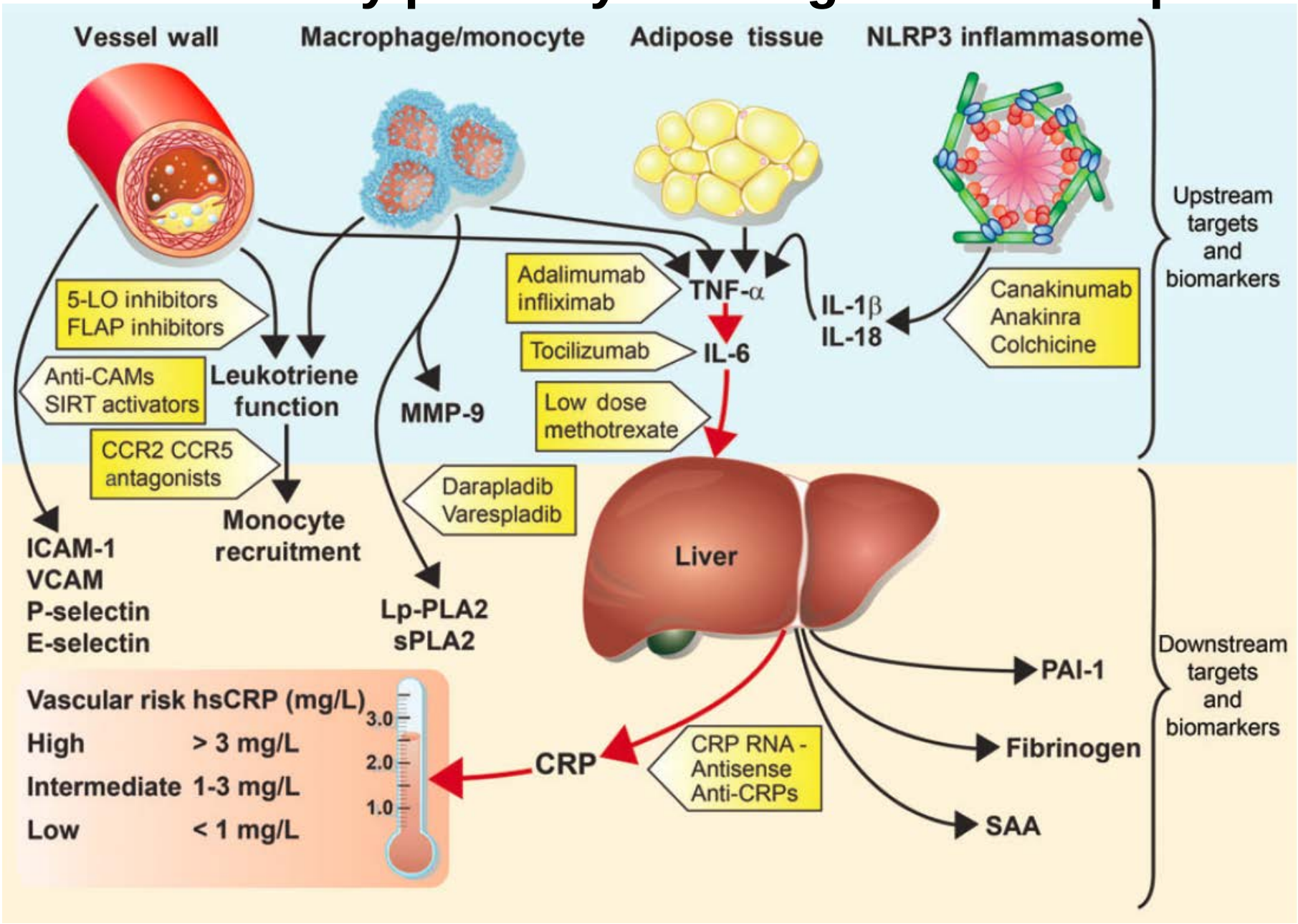
Inflammatory pathways as targets for therapies



Ridker PM, Luscher TF. Eur Heart J 2014;35:1782-1791

Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI)
On Statin, ACE/ARB, BB, ASA
Persistent Elevation
of hsCRP (≥ 2 mg/L)

N = 10,000

Randomized Canakinumab 50 mg SC q 3 months	Randomized Canakinumab 150 mg SC q 3 months	Randomized Canakinumab 300 mg SC q 3 months	Randomized Placebo SC q 3 months

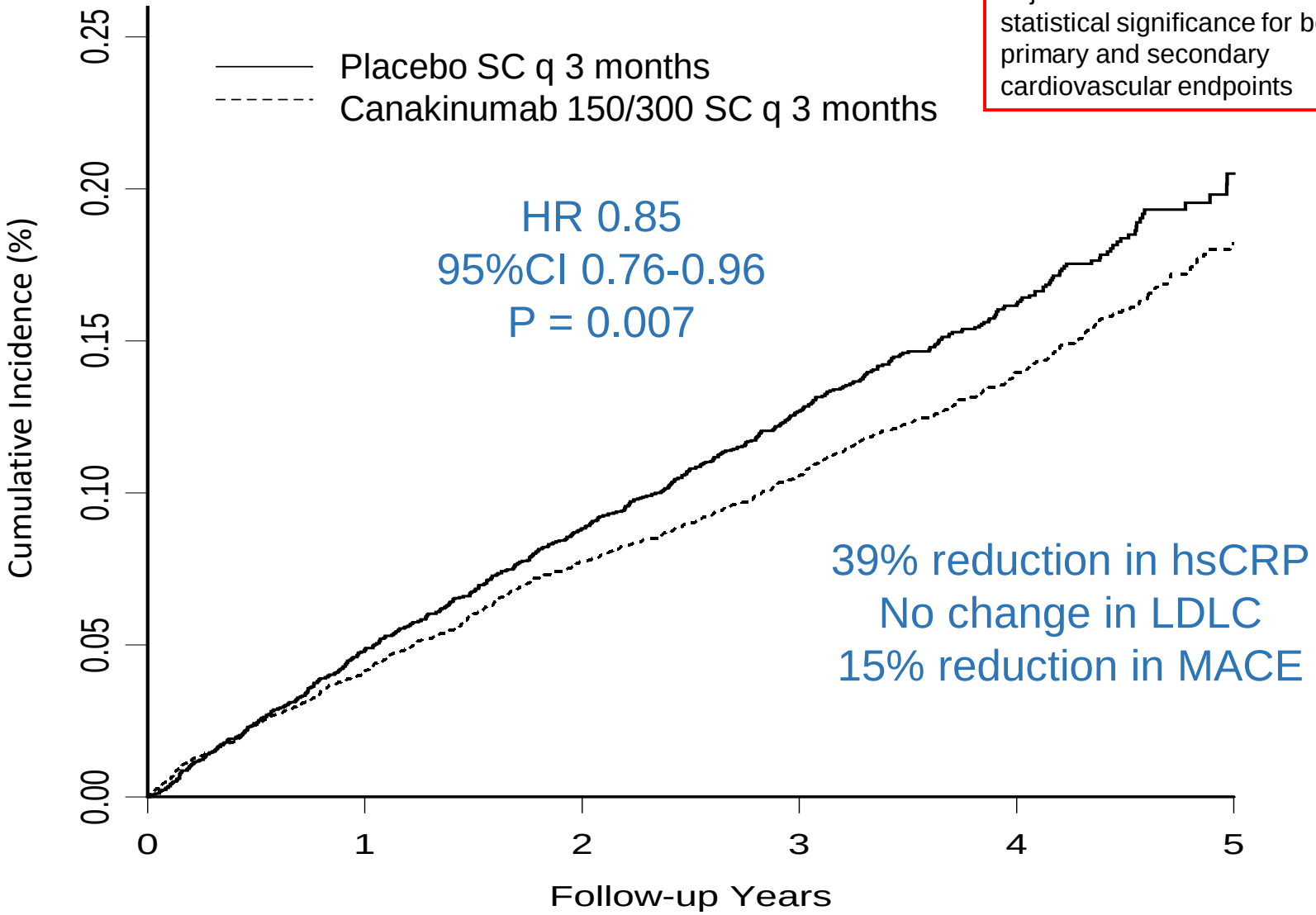
Primary Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death

Secondary Endpoints: Total Mortality, New Onset Diabetes, Other Vascular Events

Exploratory Endpoints: DVT/PE; SVT; hospitalizations for CHF; PCI/CABG; biomarkers

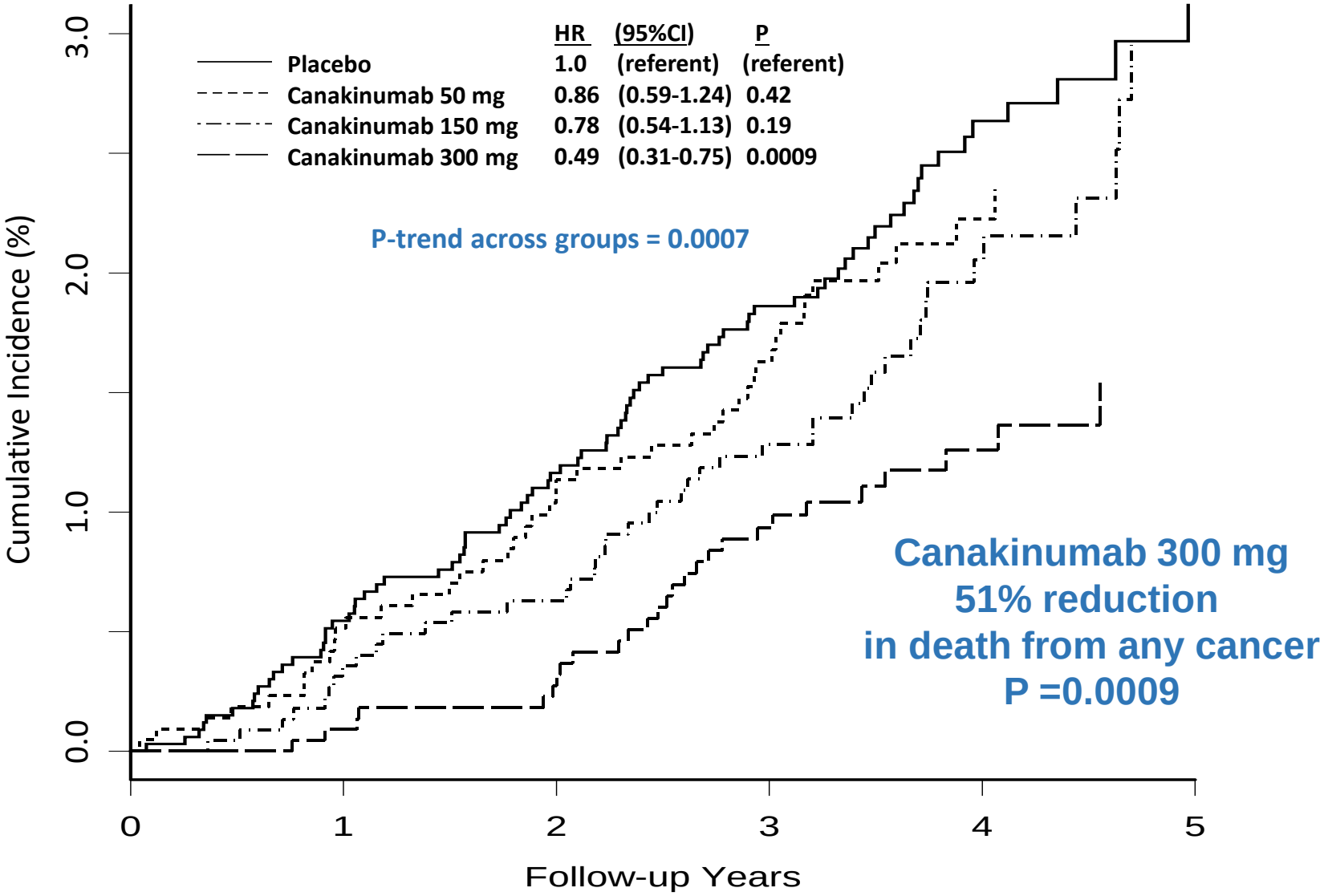
CANTOS: Primary Cardiovascular Endpoint (MACE)

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints



Ridker PM et al, N Engl J Med 2017;377:1119-1131

CANTOS: Additional Non-Cardiovascular Clinical Benefits Cancer Mortality



Ridker PM et al, Lancet 2017;390:1833-1842

CANTOS: Additional Outcomes (per 100 person years of exposure)

		Canakinumab SC q 3 months			
Adverse Event	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	P-trend
Any SAE	12.0	11.4	11.7	12.3	0.43
Leukopenia	0.24	0.30	0.37	0.52	0.002
Any infection	2.86	3.03	3.13	3.25	0.12
Fatal infection	0.18	0.31	0.28	0.34	0.09/0.02*
Injection site reaction	0.23	0.27	0.28	0.30	0.49
Any Malignancy	1.88	1.85	1.69	1.72	0.31
Fatal Malignancy	0.64	0.55	0.50	0.31	0.0007
Arthritis	3.32	2.15	2.17	2.47	0.002
Osteoarthritis	1.67	1.21	1.12	1.30	0.04
Gout	0.80	0.43	0.35	0.37	0.0001
ALT > 3x normal	1.4	1.9	1.9	2.0	0.19
Bilirubin > 2x normal	0.8	1.0	0.7	0.7	0.34

* P-value for combined canakinumab doses vs placebo

Ridker PM et al, N Engl J Med 2017;377:1119-1131

The LODOCO study with orally administered colchicine

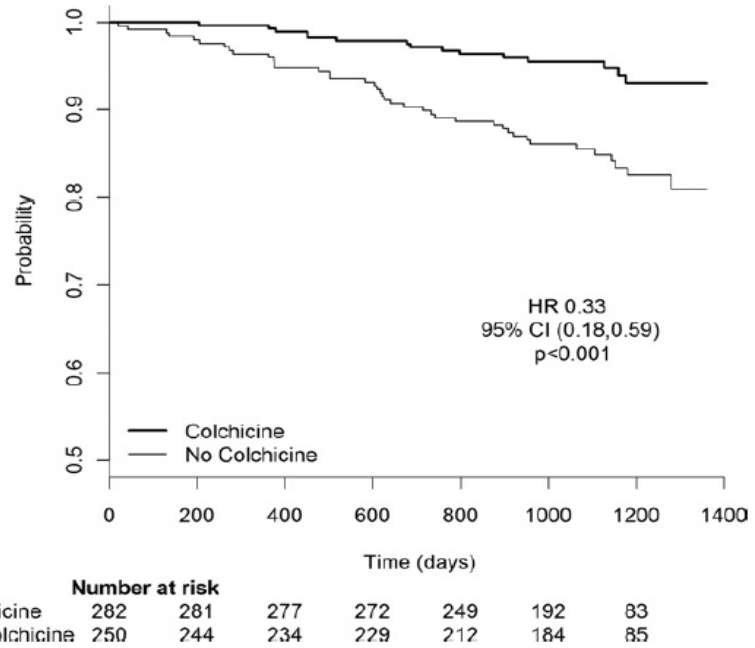


Figure 2 Freedom From the Primary Outcome

Freedom from the primary outcome (acute coronary syndrome, out-of-hospital cardiac arrest, or noncardioembolic ischemic stroke) by treatment. CI = confidence interval; HR = hazard ratio.

Table 3 Primary Outcome and Its Components

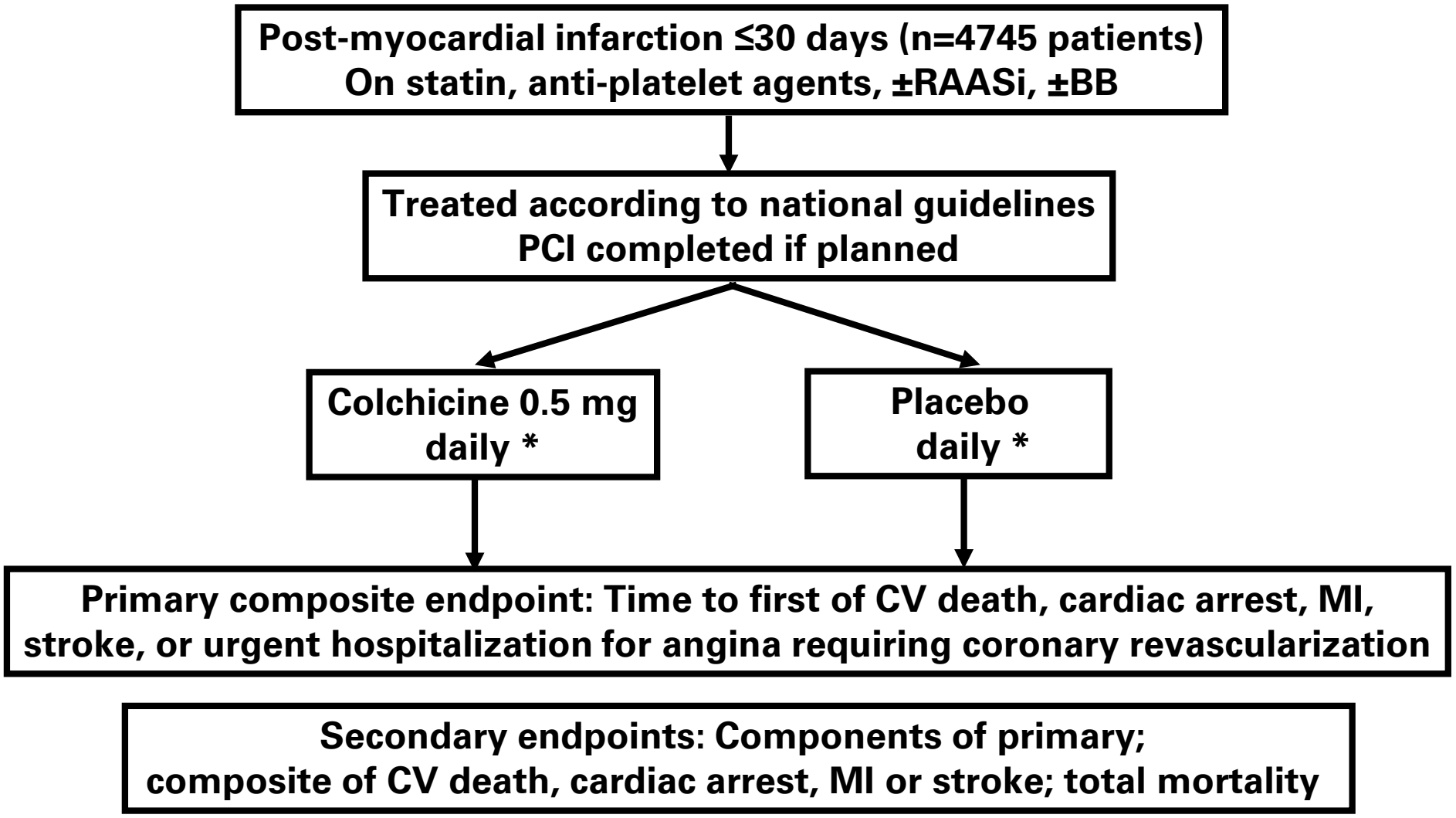
	Control (n = 250)	Treatment (n = 282)	HR (95% CI)	p Value
Primary outcome	40 (16)	15 (5.3)	0.33 (0.18–0.59)	<0.001
Components of primary outcome				
Acute coronary syndrome	34 (13.6)	13 (4.6)	0.33 (0.18–0.63)	<0.001
OOH cardiac arrest	2 (0.8)	1 (0.35)*	0.47 (0.04–5.15)	0.534
Noncardioembolic stroke	4 (1.6)	1 (0.35)	0.23 (0.03–2.03)	0.184
Components of ACS				
Stent-related	4 (1.6)	4 (1.4)		NS
Nonstent-related	30 (12)	9 (3.2)	0.26 (0.12–0.55)	<0.001
Nonstent-related AMI	14 (5.6)	4 (1.6)	0.25 (0.08–0.76)	0.014
Nonstent-related UA	16 (12)	5 (2.4)	0.27 (0.10–0.75)	0.011

Values are n (%). *Nonfatal.
ACS = acute coronary syndrome; NS = nonsignificant; OOH = out of hospital; other abbreviations as in Table 1.

The effect of colchicine became evident early, continued to accrue over time, and was largely driven by a reduction in ACS unrelated to stent disease.

Nidorf SM et al. J Am Coll Cardiol 2013;61:404-410

Study design



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*provided by Pharmascience (Montreal)

Patient characteristics

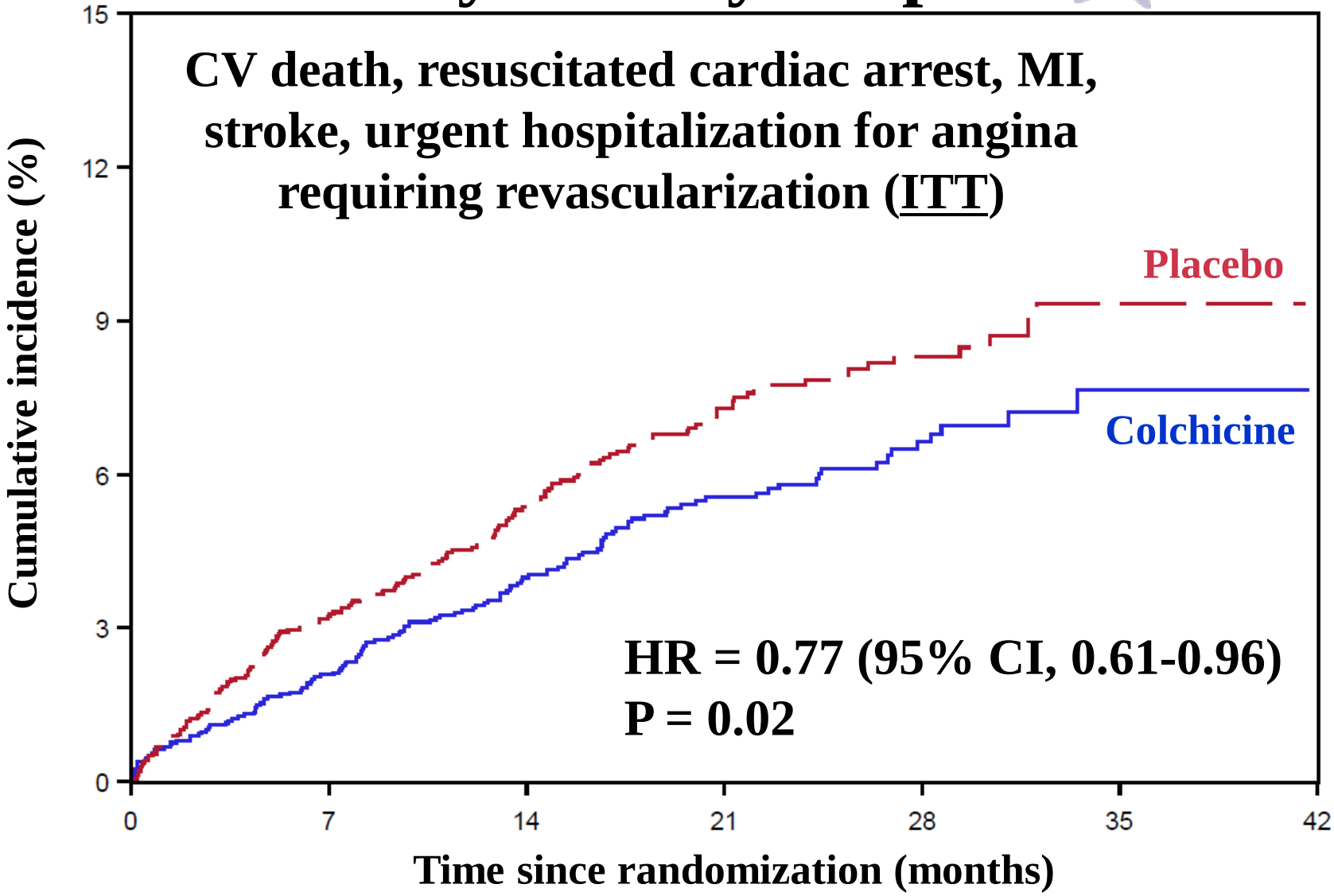
	Colchicine (N=2366)	Placebo (N=2379)
Age - years	60.6±10.7	60.5±10.6
Female sex - no. (%)	472 (19.9%)	437 (18.4%)
Caucasian - no. (%)	1350/1850 (73.0%)	1329/1844 (72.1%)
Body-mass index - kg/m^2	28.2±4.8	28.4±4.7
Smoking - no. (%)	708 (29.9%)	708 (29.8%)
Hypertension - no. (%)	1185 (50.1%)	1236 (52.0%)
Diabetes - no. (%)	462 (19.5%)	497 (20.9%)
Prior MI - no. (%)	370 (15.6%)	397 (16.7%)
Prior PCI - no. (%)	392 (16.6%)	406 (17.1%)
Prior CABG - no. (%)	69 (2.9%)	81 (3.4%)

Patient characteristics

	Colchicine (N=2366)	Placebo (N=2379)
Index MI to randomization - days	13.4 ± 10.2	13.5 ± 10.1
PCI for index MI - no. (%)	2192/2364 (92.7%)	2216/2375 (93.3%)
Aspirin - no. (%)	2334 (98.6%)	2352 (98.9%)
Other anti-platelet agent - no. (%)	2310 (97.6%)	2337 (98.2%)
Statin - no. (%)	2339 (98.9%)	2357 (99.1%)
Beta-blocker - no. (%)	2116 (89.4%)	2101 (88.3%)

Tardif et al. N Engl J Med 2019;381:2497-2505

Primary efficacy endpoint



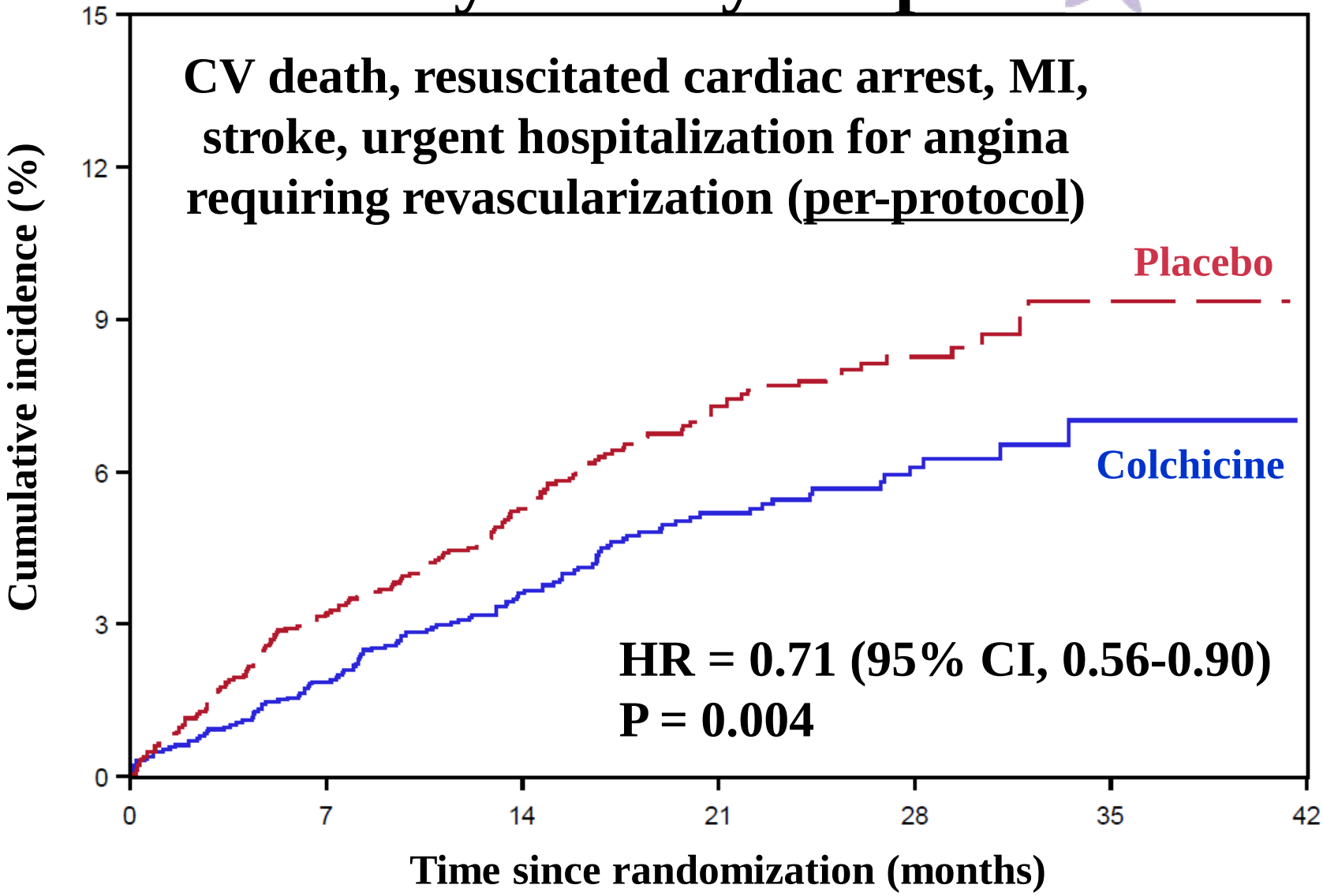
No. at Risk							
Colchicine	2366	2284	1868	1230	628	153	0
Placebo	2379	2261	1854	1224	622	144	0

Tardif et al. N Engl J Med 2019;381:2497-2505

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)	

Primary efficacy endpoint



No. at Risk							
Colchicine	2260	2197	1791	1169	601	140	0
Placebo	2270	2169	1778	1173	596	135	0

Tardif et al. N Engl J Med 2019;381:2497-2505

Major Clinical Outcomes

Clinical Outcome Per-protocol population	Colchicine N=2260	Placebo N=2270	Hazard Ratio (95% CI)	P Value
Primary composite endpoint - no. (%)	115 (5.1%)	162 (7.1%)	0.71 (0.56-0.90)	0.004
CV death - no. (%)	19 (0.8%)	23 (1.0%)	0.83 (0.45-1.53)	
Resuscitated cardiac arrest - no. (%)	5 (0.2%)	5 (0.2%)	1.00 (0.29-3.46)	
Myocardial infarction - no. (%)	77 (3.4%)	92 (4.1%)	0.84 (0.62-1.14)	
Stroke - no. (%)	5 (0.2%)	19 (0.8%)	0.26 (0.10-0.71)	
Urgent hospitalization for angina requiring revascularization - no. (%)	22 (1.0%)	47 (2.1%)	0.47 (0.28-0.78)	

Tardif et al. N Engl J Med 2019;381:2497-2505

Total (First + Recurrent) Primary Endpoint Events (ITT)

Endpoint / Model		Colchicine N=2366	Placebo N=2379	Hazard / Rate Ratio (95% CI)
Total number of primary endpoint events		154	223	
Rate of primary endpoint events per 100 patient-months		0.29	0.42	
Negative binomial model				0.66 (0.51; 0.86)
Andersen-Gill model				0.69 (0.54; 0.88)
Wei-Lin-Wessfeld model	1st event			0.77 (0.61; 0.96)
Wei-Lin-Wessfeld model	2nd event			0.73 (0.48; 1.11)
Wei-Lin-Wessfeld model	3rd event			0.64 (0.37; 1.10)
Wei-Lin-Wessfeld model	Average			0.77 (0.61; 0.96)

Tardif et al. N Engl J Med 2019;381:2497-2505

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

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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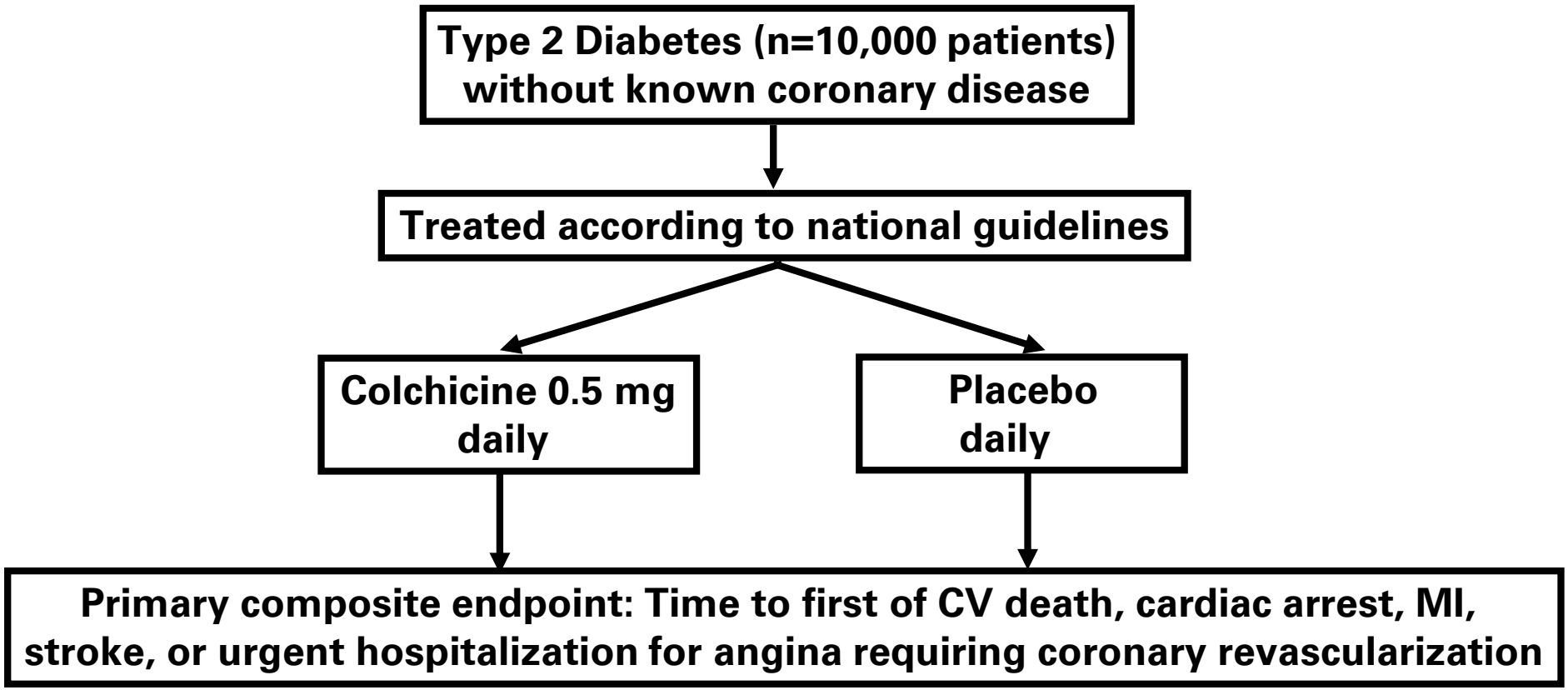
COLCOT-T2D – Study design



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