TCTAP

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MEET THE EXPERTS | 8’

Is IL-6 a Possible Target to Prevent Post-AMI Cardiovascular Events?

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Financial disclosures

Within the past 12 months, with respect to the content of this presentation, I, **Davide Capodanno**, have had a financial interest/arrangement or affiliation with the organization(s) listed below:

Advisory Board fees

- *Bristol-Myers Squibb, Daiichi Sankyo*

Lecture Fees

- *Novo Nordisk, Sanofi, Terumo*

RESIDUAL CARDIOVASCULAR RISK

Biological issue	Residual Cholesterol Risk	Residual Inflammatory Risk	Residual Thrombotic Risk	Residual Triglyceride Risk	Residual Lp(a) Risk	Residual Diabetes Risk
						
Critical biomarker	LDL-C ≥100 mg/dL	hsCRP ≥2 mg/L	No simple biomarker	Triglyceride ≥150 mg/dL	Lp(a) ≥50 mg/dL	HbA1c Fasting glucose
Potential intervention	Targeted LDL/Apo B reduction	Targeted Inflammation reduction	Targeted Thrombotic reduction	Targeted Triglyceride reduction	Targeted Lp(a) reduction	SGLT2i GLP1 Agonists

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Adapted from Lawler PR, et al. Eur Heart J. 2021;42:113-131

Inflammatory Pathway

Deposition of oxidized LDL and cholesterol in the vessel wall

Post-AMI cell debris and metabolites, ischemia and reperfusion injury

Inflammasome

Pro-IL-18

Pro-IL-1β

Active IL-18

Active IL-1β

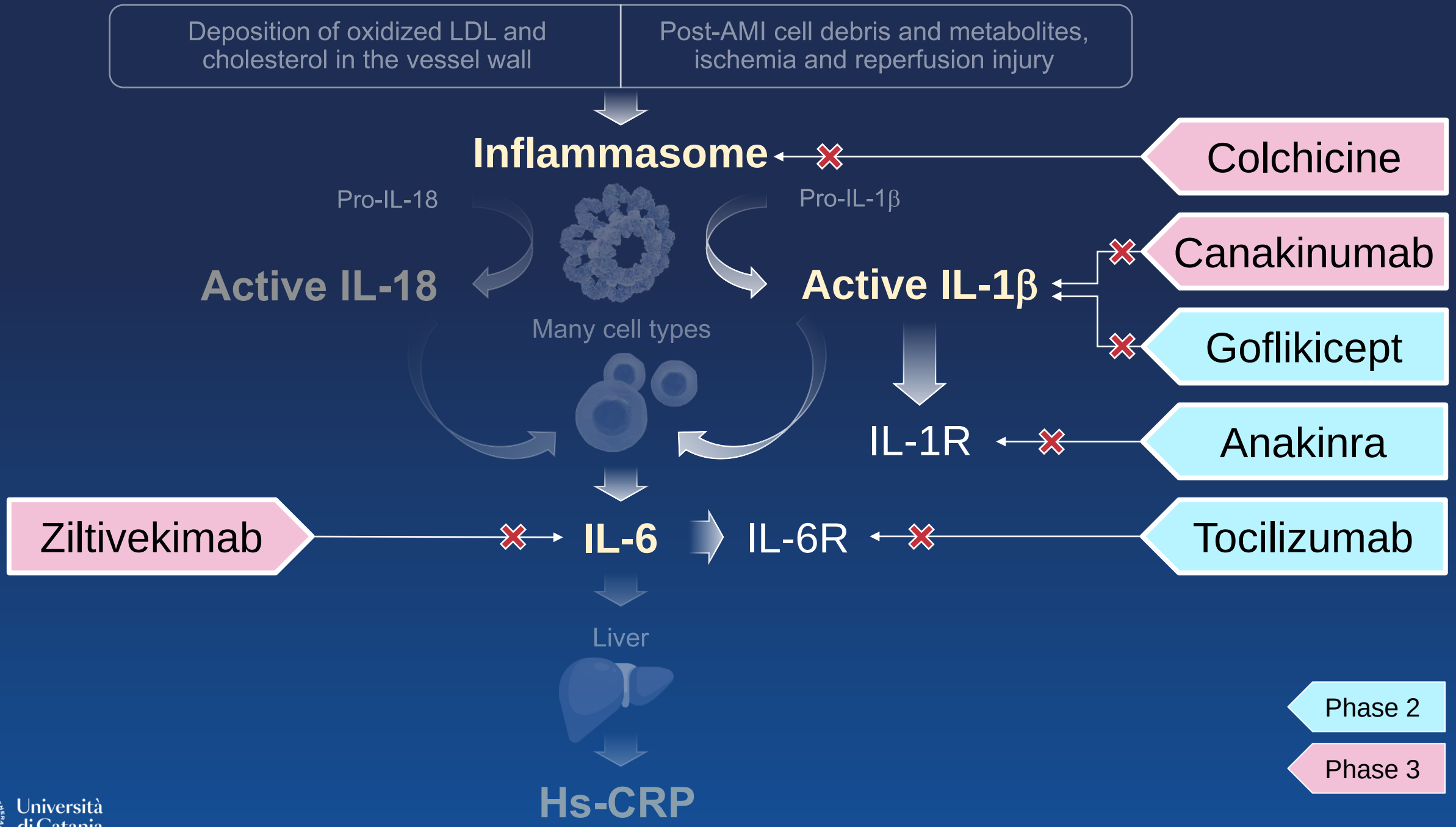
Many cell types

IL-1R

IL-6 → IL-6R

Liver

Hs-CRP



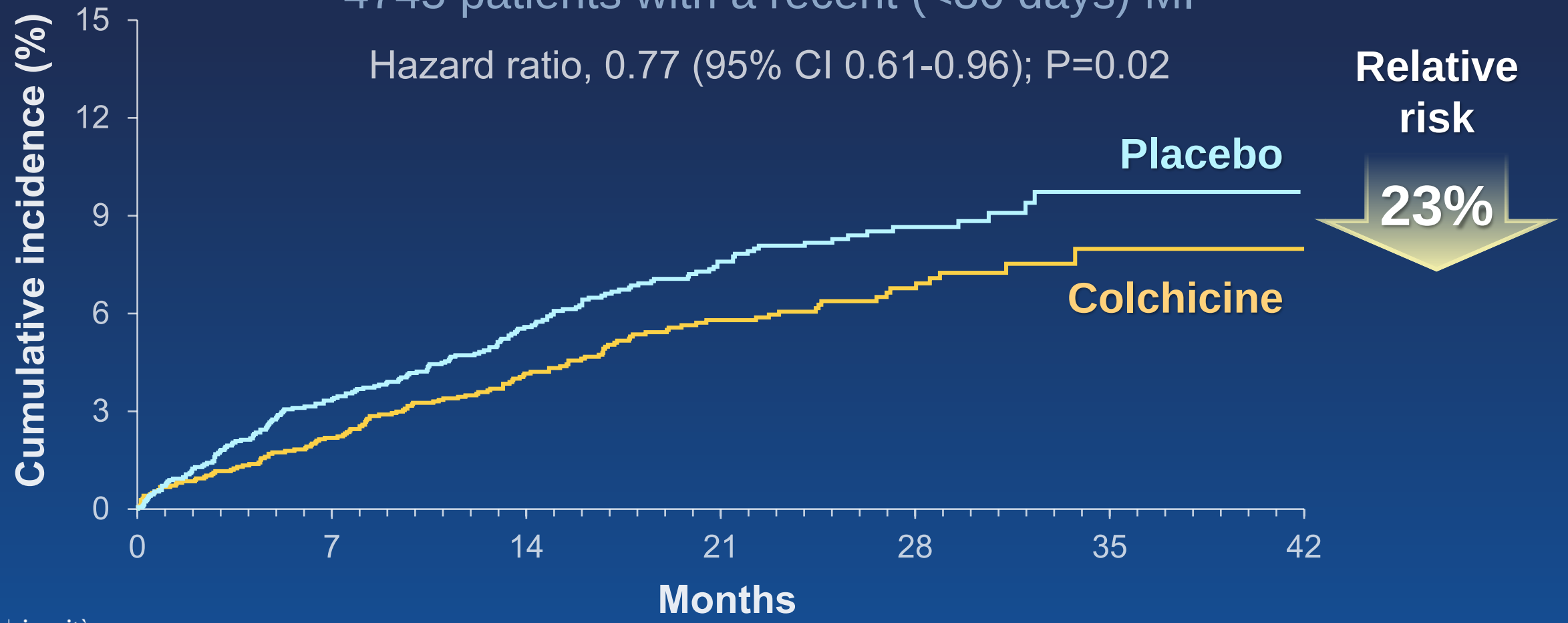
Anti-inflammatory drugs

Colchicine

Major Adverse Cardiac Events

4745 patients with a recent (<30 days) MI

Hazard ratio, 0.77 (95% CI 0.61-0.96); P=0.02



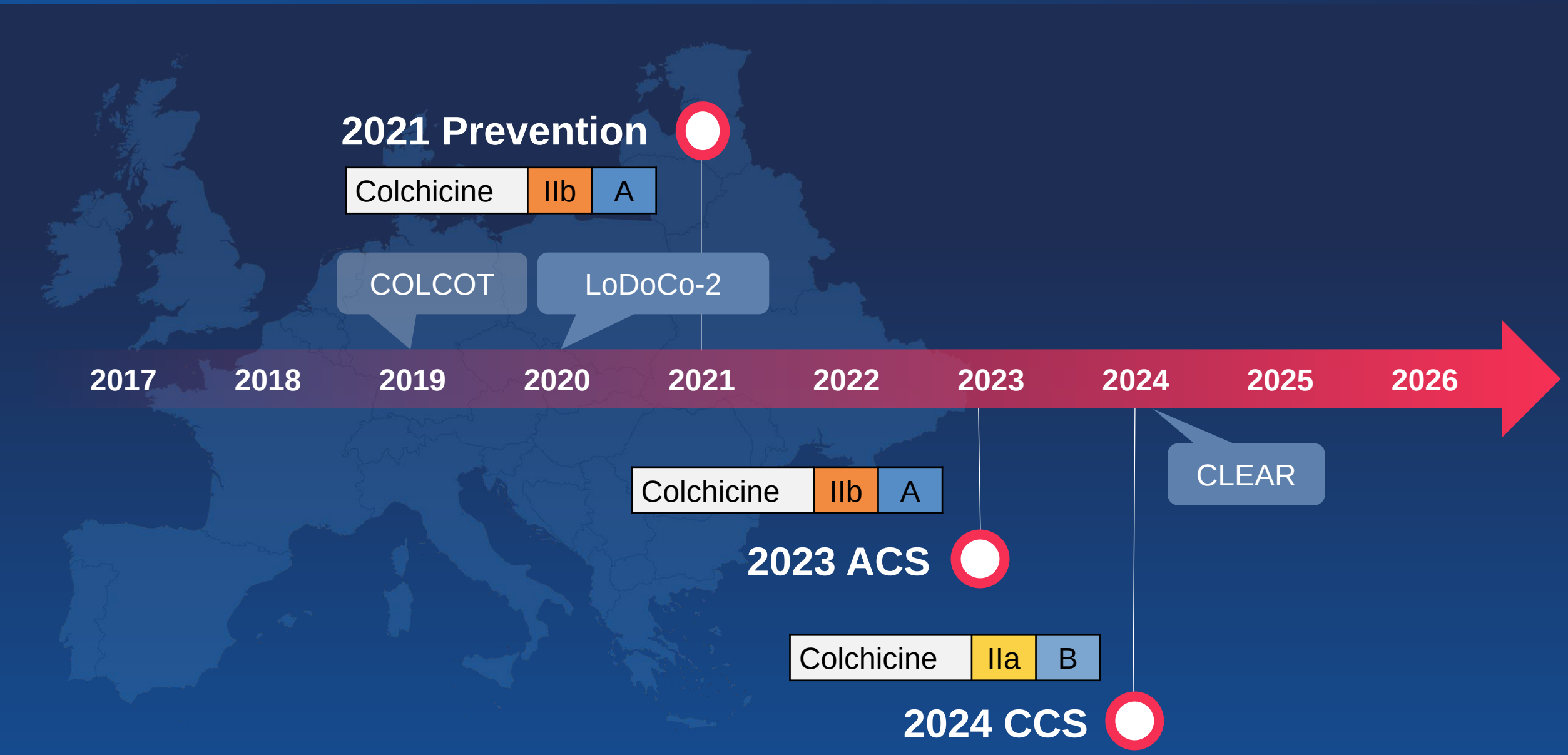
Tardif JC, et al. N Engl J Med 2019;381:2497-2505

Serious Adverse Events at ~23 Months

	Colchicine (N=2330)	Placebo (N=2346)
Any serious adverse events	383 (16.4%)	404 (17.2%)
Gastrointestinal event	46 (2.0%)	36 (1.5%)
Infection	51 (2.2%)	38 (1.6%)
Pneumonia	21 (0.9%)	9 (0.4%)
Septic shock	2 (0.1%)	2 (0.1%)
Hospitalization for heart failure	25 (1.1%)	21 (0.7%)
Cancer	43 (1.8%)	46 (2.0%)

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

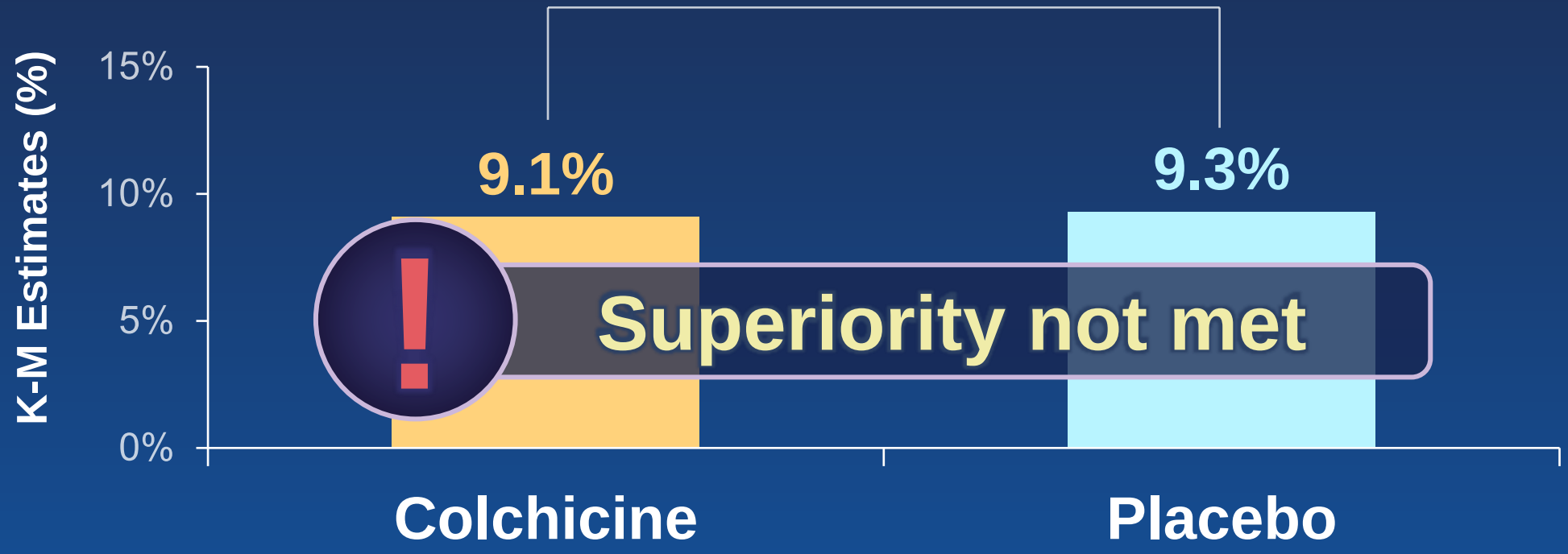
TRIALS AND GUIDELINES RECOMMENDATIONS



Major Adverse Cardiac Events

7062 patients who had a MI at Median 3 Years

Hazard ratio, 0.99 (95% CI 0.85-1.6; P=0.93 for superiority)



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

Serious Adverse Events at ~36 Months

	Colchicine (N=3528)	Placebo (N=3534)
Noncardiovascular death	45 (1.3%)	66 (1.9%)
Death from all causes	162 (4.6%)	179 (5.1%)
Pericarditis	91 (2.6%)	89 (2.5%)
Serious adverse GI event	35 (1.0%)	33 (0.9%)
Serious adverse hematologic event	0 (0%)	8 (0.2%)
Serious infection	87 (2.5%)	101 (2.9%)
Diarrhea	361 (10.2%)	233 (6.6%)

Jolly SS, et al. N Engl J Med 2025;392:633-642

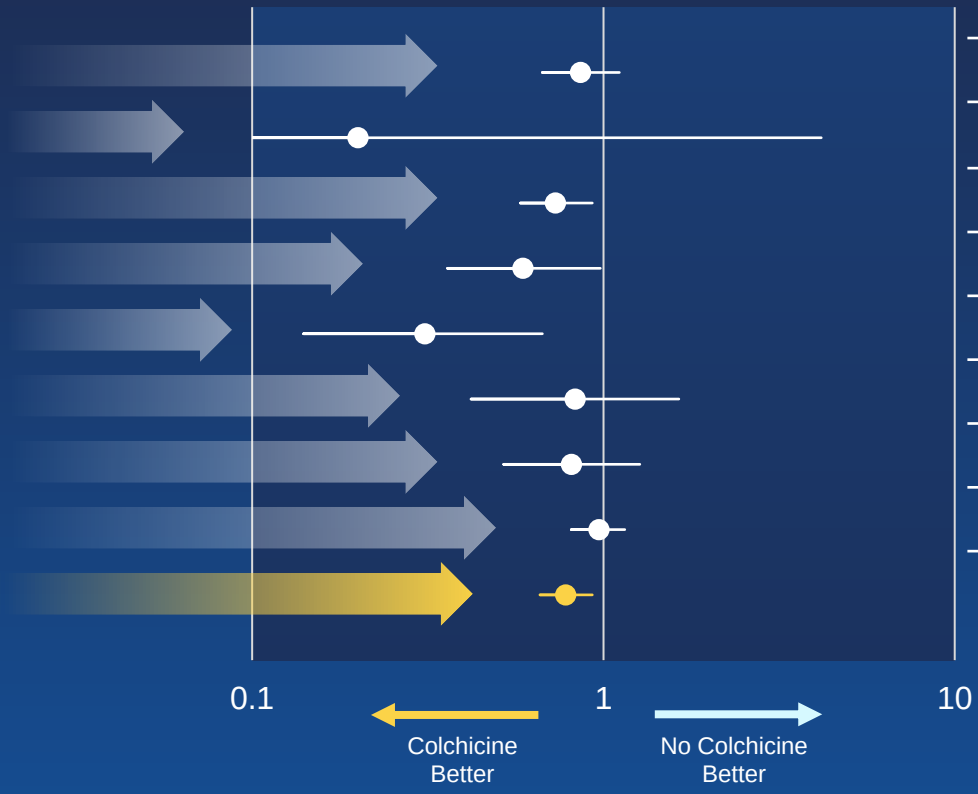
TITIAN META-ANALYSIS

10 Trials, 19304 patients with MI

Mean follow-up 11±15 months

	Colchicine Events / PY	**No Colchicine** Events / PY	
Deftereos et al.	0 (0)	0 (0)	Not calculated
COLIN	0 (0)	0 (0)	Not calculated
COLCOT	111 (8281)	130 (8327)	0.86 (0.67-1.11)
LoDoCo-MI	0 (9)	2 (9)	0.20 (0.01-4.17)
LoDoCo2	115 (6583)	157 (6578)	0.73 (0.58-0.93)
Australian COPS	24 (429)	41 (432)	0.59 (0.36-0.98)
Akrami et al.	8 (60)	28 (65)	0.31 (0.14-0.67)
PODCAST-PCI	15 (161)	18 (160)	0.83 (0.42-1.64)
COVERT-MI	36 (101)	40 (91)	0.81 (0.52-1.27)
CLEAR	241 (10584)	250 (10602)	0.97 (0.81-1.15)
Pooled effect			**0.78 (0.66-0.93)**

3-point MACE (IRR, 95% CI)



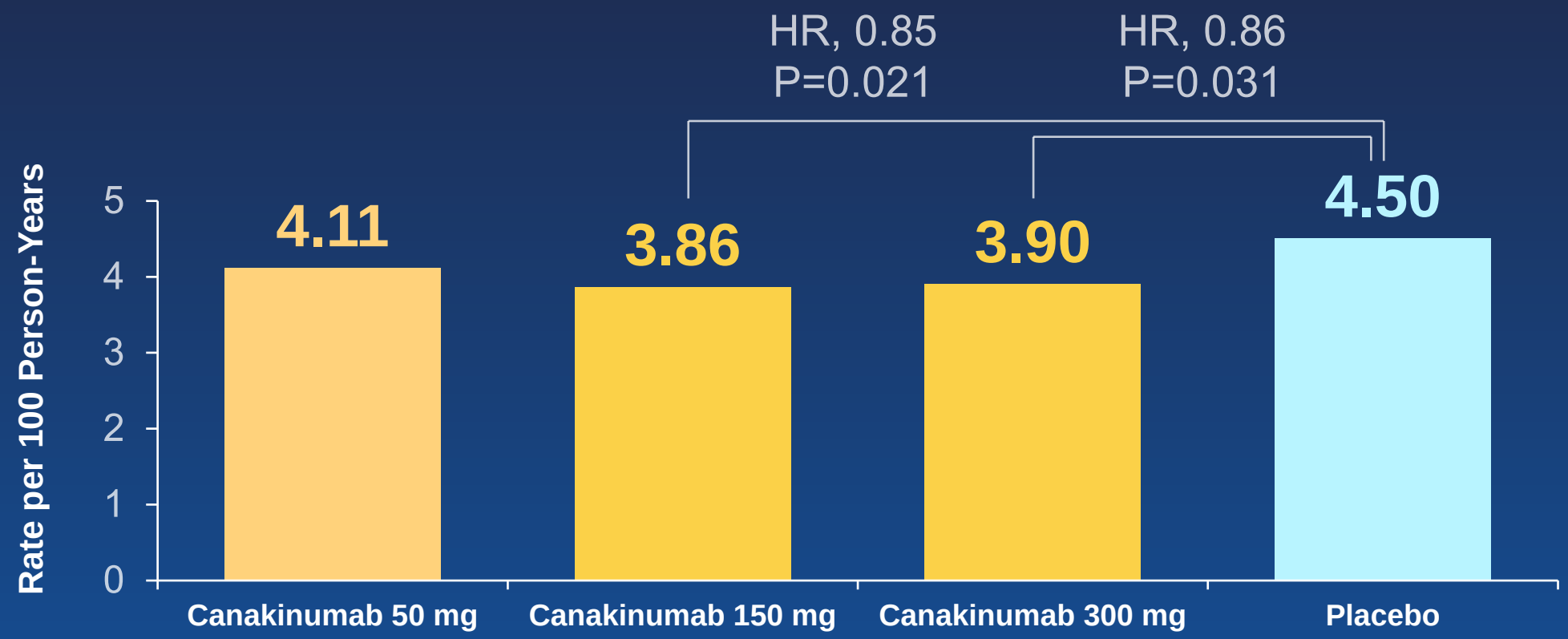
Laudani C, Capodanno D, et al. Eur Heart J Cardiovasc Pharmacother [ePub ahead of print]

Targeting IL-1

Canakinumab

MACE at Median 3.7 Years

10061 patients with previous myocardial infarction and a high-sensitivity C-reactive protein level of 2 mg or more per liter



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

Annualized Incidence of Serious Adverse Events

	Canakinumab (N=6717)	Placebo (N=3344)
Any serious adverse events	2389 (11.8%)	1202 (12.0%)
Fatal cancer	115 (0.5%)	81 (0.6%)
Fatal infection or sepsis	78 (0.3%)	23 (0.2%)
Arthritis	545 (2.3%)	385 (3.3%)
Leukopenia	100 (0.4%)	30 (0.2%)
Thrombocytopenia	150 (0.6%)	53 (0.4%)

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

Major Adverse Cardiovascular Events

According to the achievement of on-treatment interleukin-6 levels above or below the trial median of 1.65 mg/L at 3 months among those allocated to canakinumab

P < 0.0001 for interaction

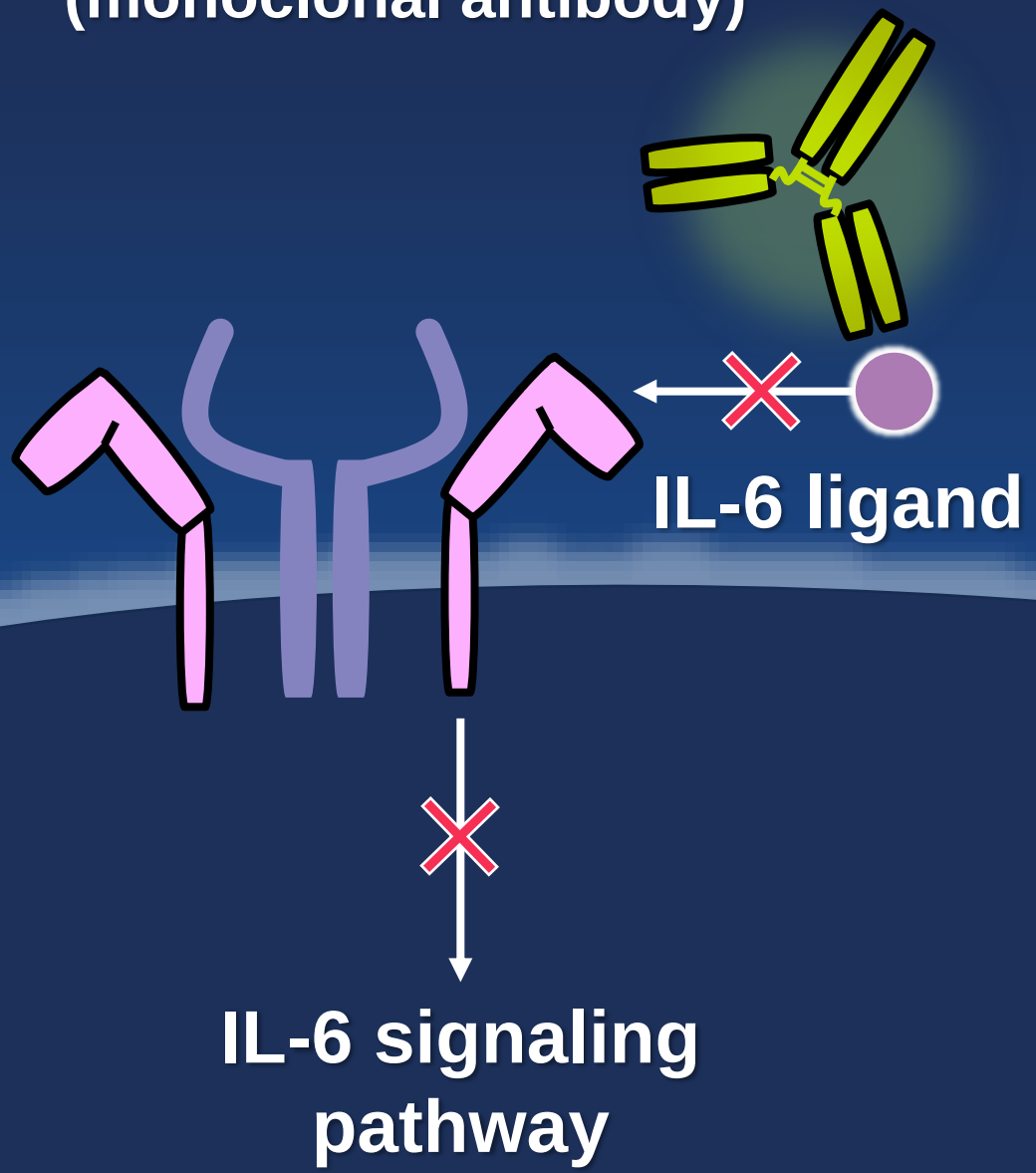
	Hazard ratio (95% CI)
Placebo	Reference
Canakinumab, IL-6 ≥ median value (1.65 mg/L)	HR, 1.06; 95% CI, 0.90-1.25
Canakinumab, IL-6 < median value (1.65 mg/L)	HR, 0.64; 95% CI, 0.54-0.77

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

Targeting IL-6

Ziltivekimab

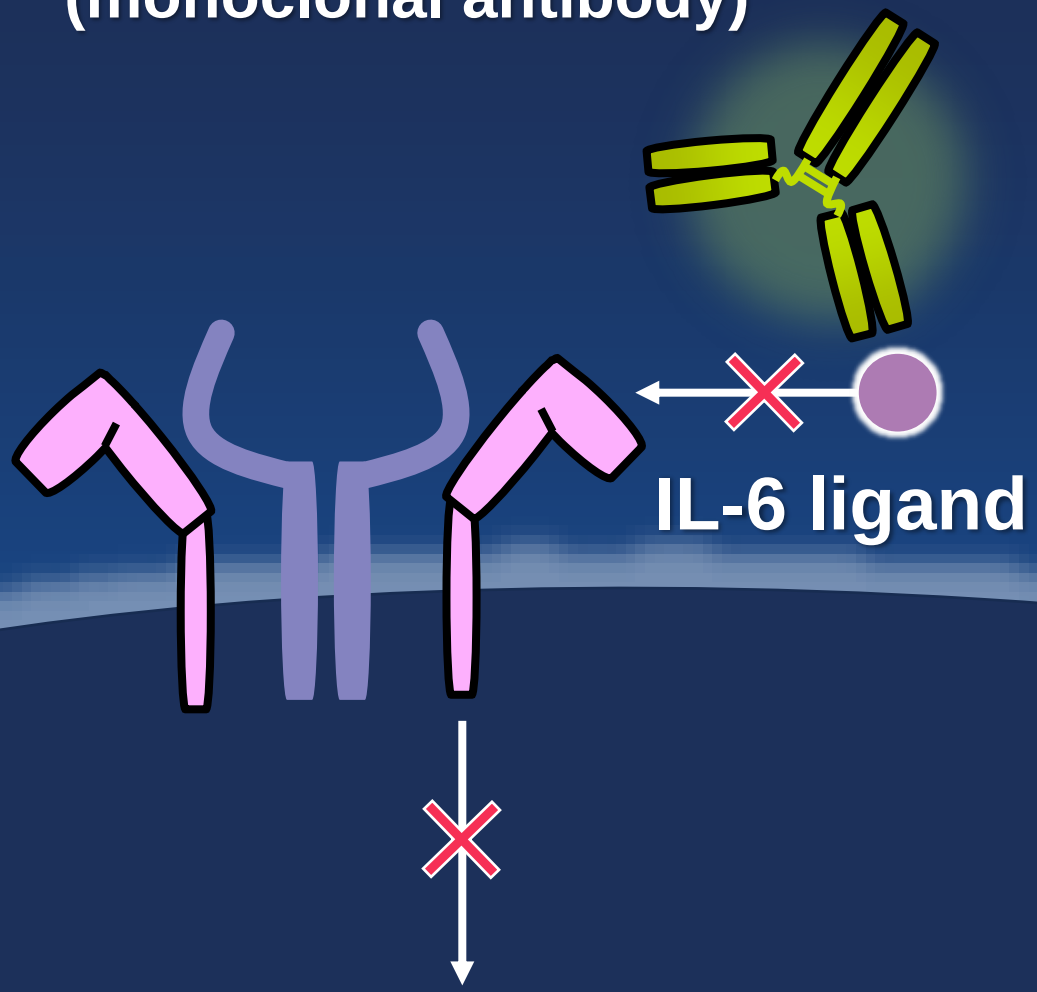
Ziltivekimab
(monoclonal antibody)



A human monoclonal antibody directed against the IL-6 ligand

Given once monthly as a subcutaneous injection

Ziltivekimab
(monoclonal antibody)



2021 2022 2023 2024 2025 2026 2027

Phase 3 ZEUS – ASCVD + CKD
(n=6200 / 38 countries)

Phase 3 HERMES – HFpEF/HFmrEF
(n=5600 / 46 countries)

Phase 3 ATHENA – Functional study
HFpEF/HFmrEF (n=680 / 15 countries)

Phase 3 ARTEMIS – AMI
(n=10000 / 24 countries)

POSEIDON – hsCRP prevalence study
ASCVD (+/- CKD), HF (HFrEF and HFpEF/HFmrEF)
(n=22000 / 19 countries)

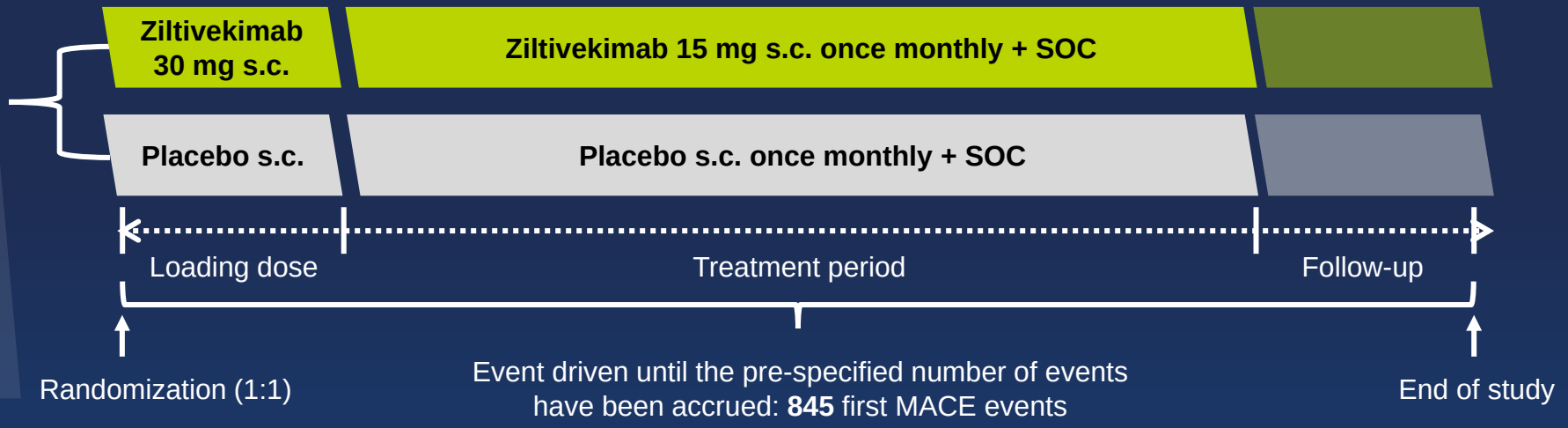
Healthy volunteer comparability study
(n=267)

China PK (n=24)

ARTEMIS TRIAL

10000 Participants

- AMI (STEMI or NSTEMI)
- Angiographic evidence of type 1 MI
- ≥1 enrichment criteria
- Randomization as early as possible and latest within 36 h from STEMI or 48 h from NSTEMI



Study objective

To demonstrate the superiority of a loading dose of ziltivekimab 30 mg s.c. versus placebo s.c. followed by 15 mg s.c. once monthly vs placebo s.c. both added to SOC, in reducing the risk of MACE in participants with angiographic evidence type 1 MI.

Primary endpoint

Time to first occurrence of 3-point MACE

- CV death
- Non-fatal MI
- Non-fatal stroke

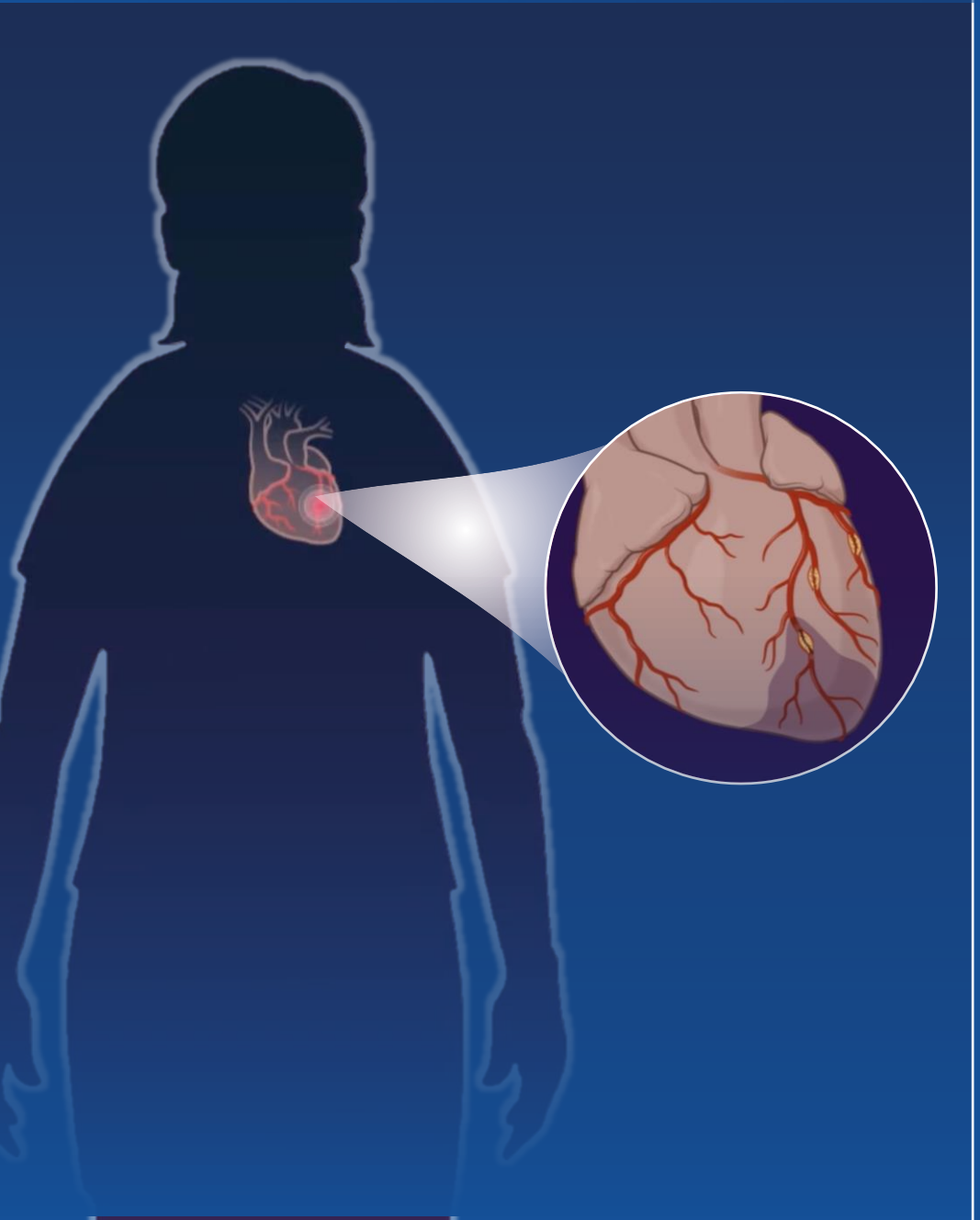
Confirmatory secondary endpoints (hierarchy)

Time to first occurrence of

- Coronary MACE (CV-death, non-fatal MI, ischemia-driven coronary revascularization)
- Expanded MACE (CV death, non-fatal MI, non-fatal stroke, ID-CR, HFH, urgent HF)
- Expanded HF (CV death, HFH, urgent HF, or outpatient HF visit)
- All-cause death

Clinicaltrials.gov identifier NCT06118281

CLOSING REMARKS



- Low-dose colchicine is class IIa in the CCS guidelines and class IIb in the ACS guidelines, but recently failed to show benefit in a large trial of patients with AMI.
- I still consider colchicine in the infrequent CCS-PCI “frequent flyer” patients who meet the LDL-C targets but remain with high hs-CRP.
- The divergent results of the trials of canakinumab and colchicine highlight the need for large trials that target different parts of the inflammatory pathway.
- Trials are in planning or underway evaluating interleukin-6 inhibition in several clinical settings.

X: @DFCapodanno