

Discussant review:
- CANTOS -

The Canakinumab Anti-Inflammatory Thrombosis
Outcomes Study

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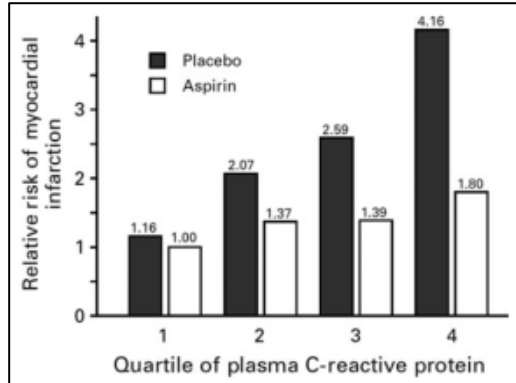
Declaration of interest

- I have nothing to declare

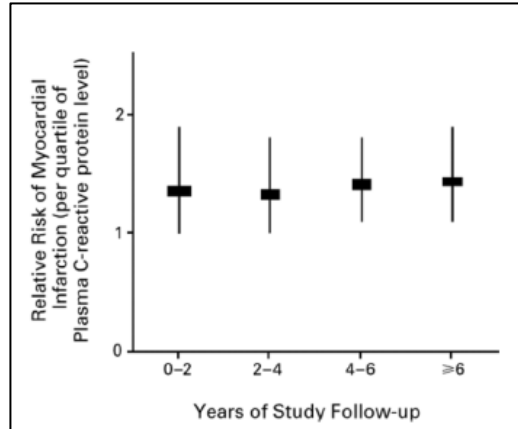
- **Chronic inflammation in atherosclerosis**
- **Patient (and target) population**
- **Effect size, tailoring therapy**
- **Non-cardiovascular effects and safety**

hsCRP reflects inflammation in humans

effect size

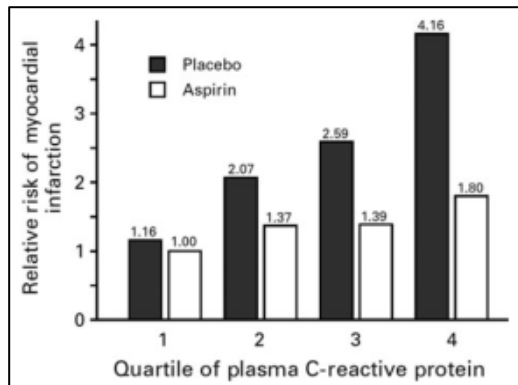


stability

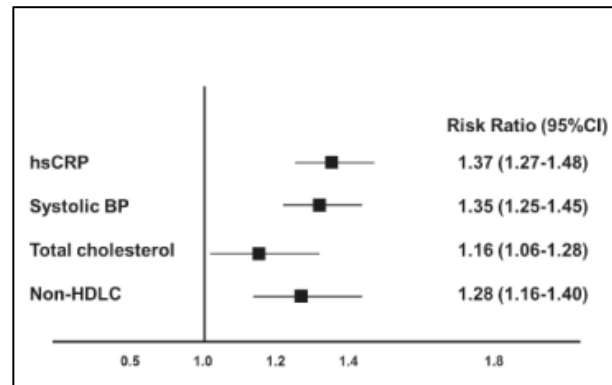


hsCRP reflects inflammation in humans

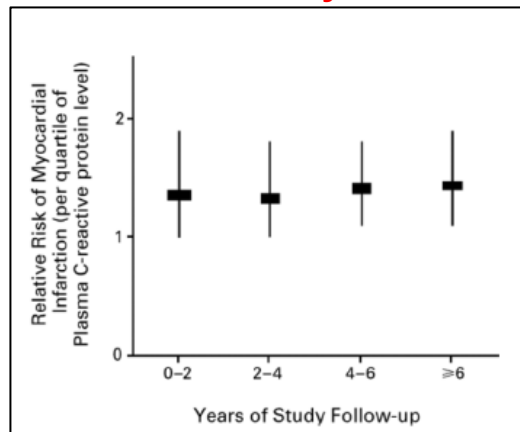
effect size



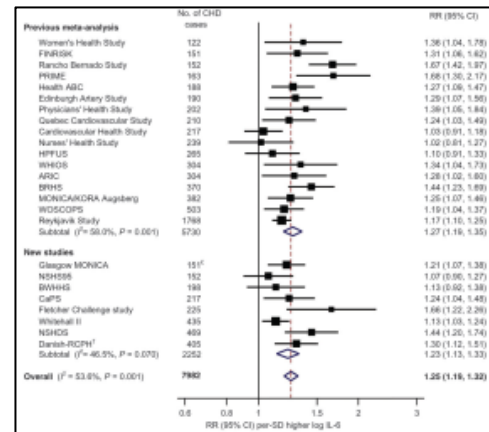
independent risk indication



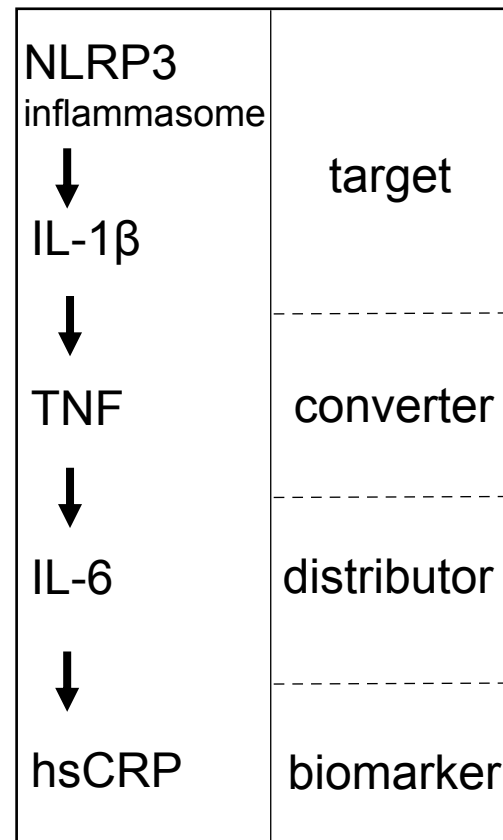
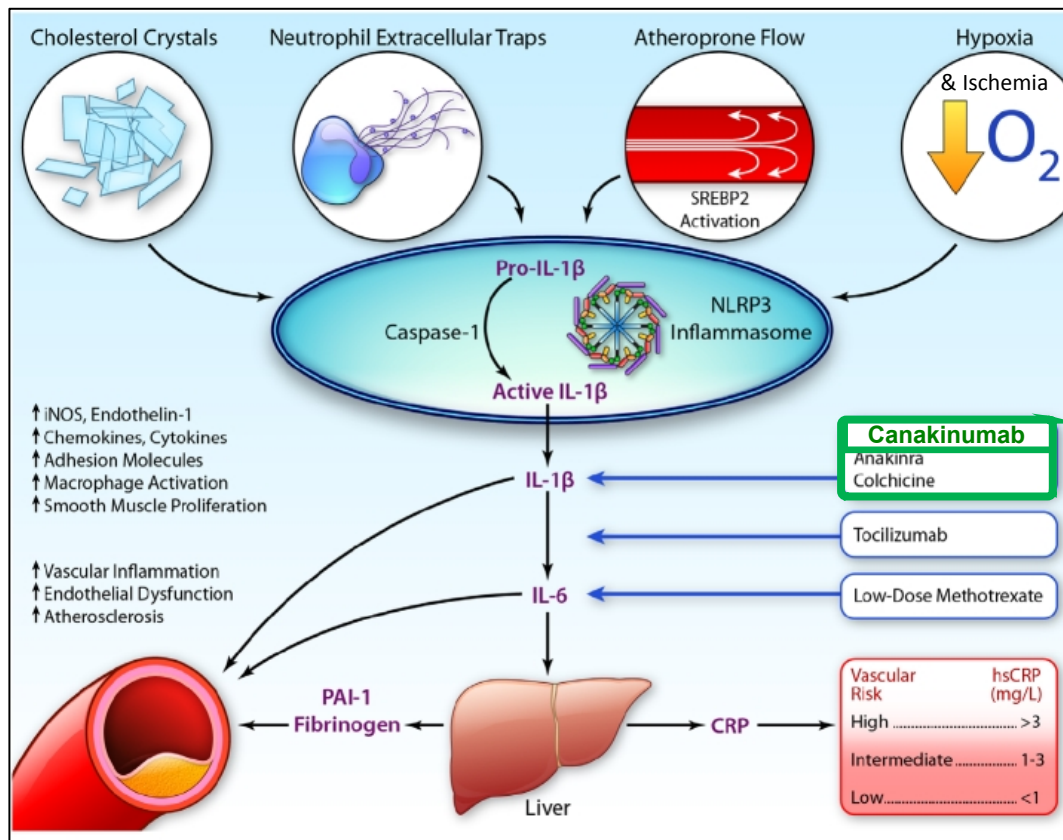
stability



IL6 upstream signalling

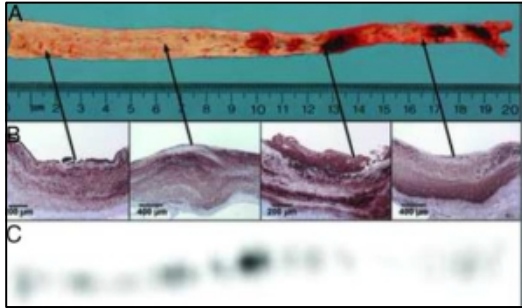


Activation of inflammasome - “clinical utility”

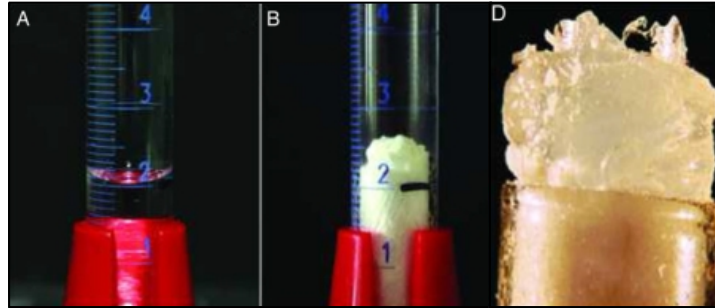


Cholesterol crystals induce local and systemic inflammation

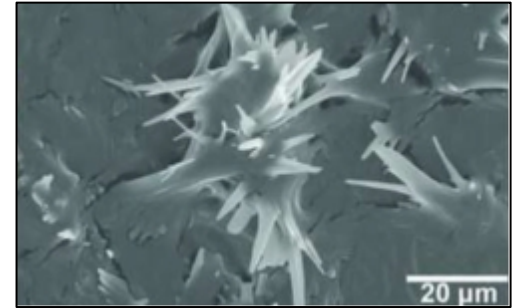
experimental studies



monocytes & macrophages



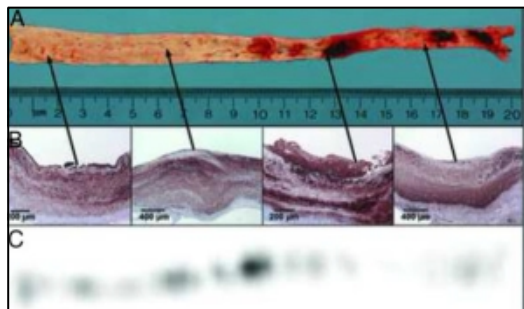
volume expansion



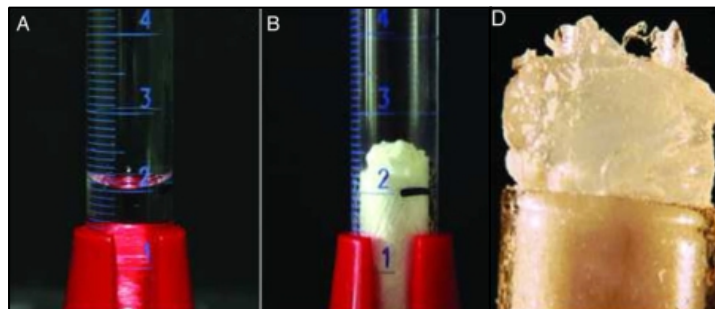
intima perforation

Cholesterol crystals induce local and systemic inflammation

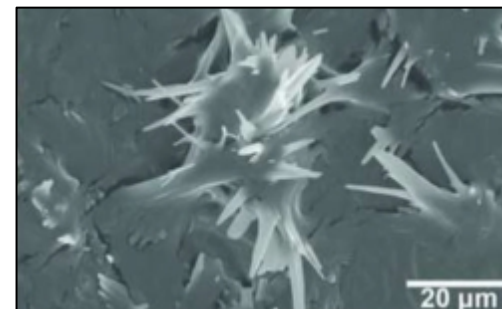
experimental studies



monocytes & macrophages

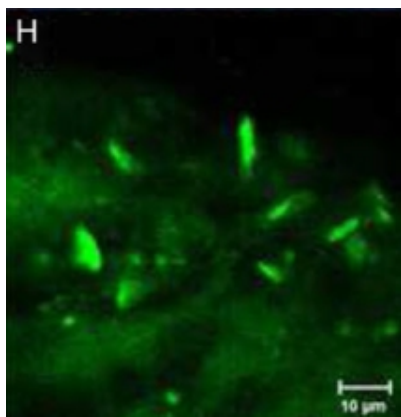


volume expansion

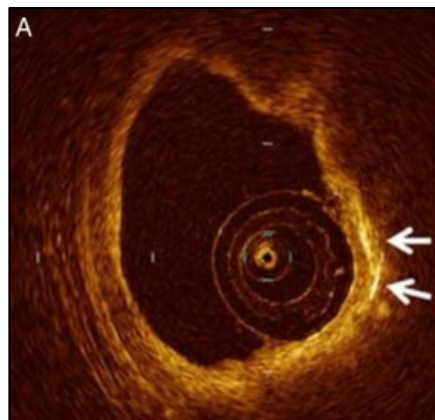


intima perforation

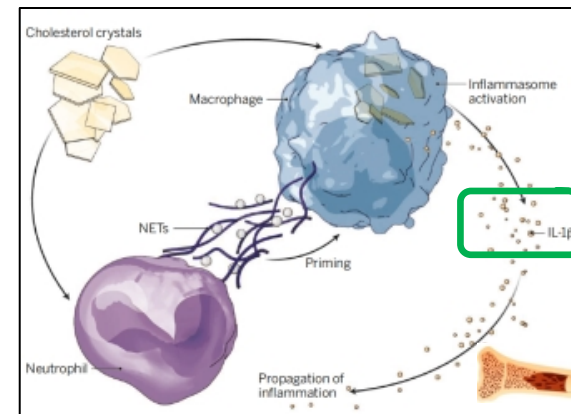
human studies



Carotid artery

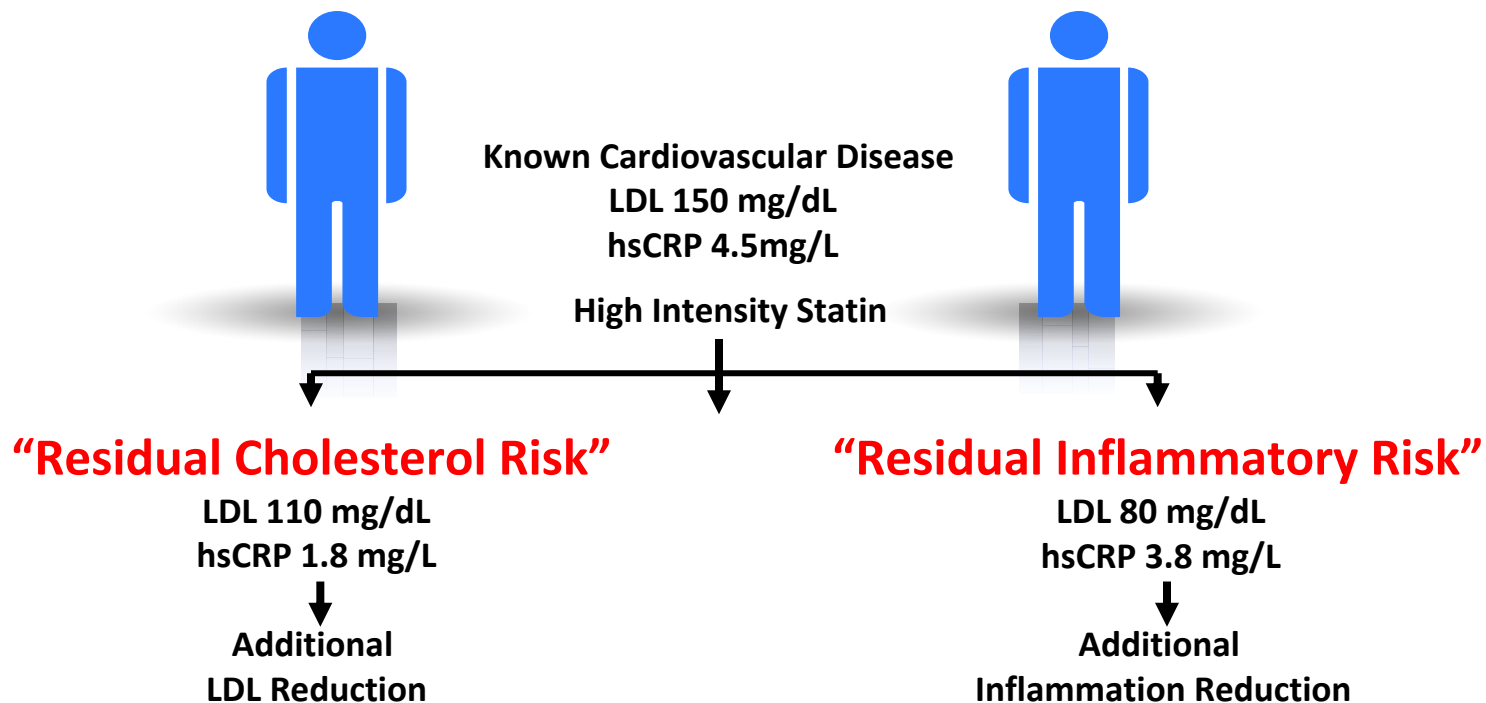


coronary artery



systemic effects

Residual risk in HR-patients with CAD: >50%

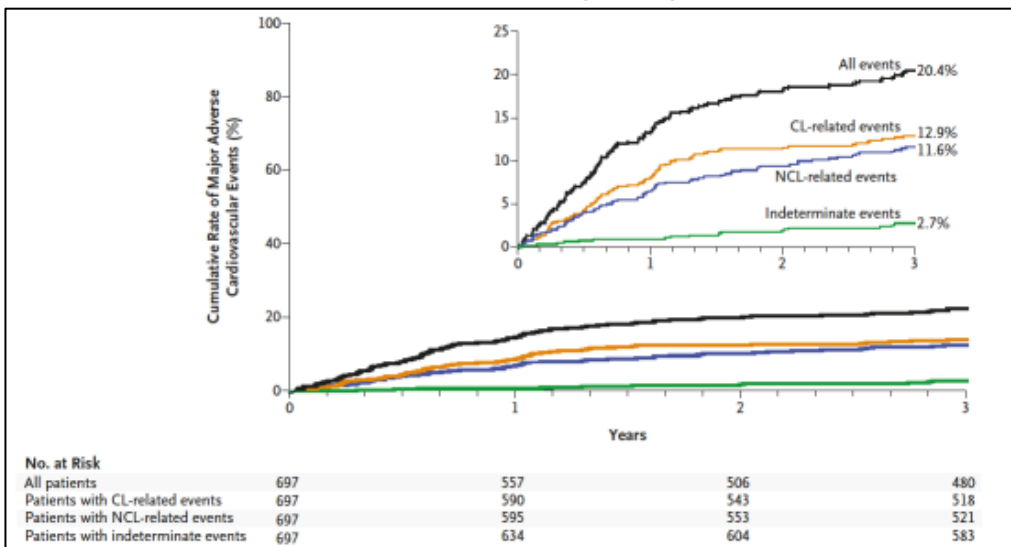


IMPROVE-IT : Ezetimibe 6% RRR

FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

CANTOS: Proof of Concept

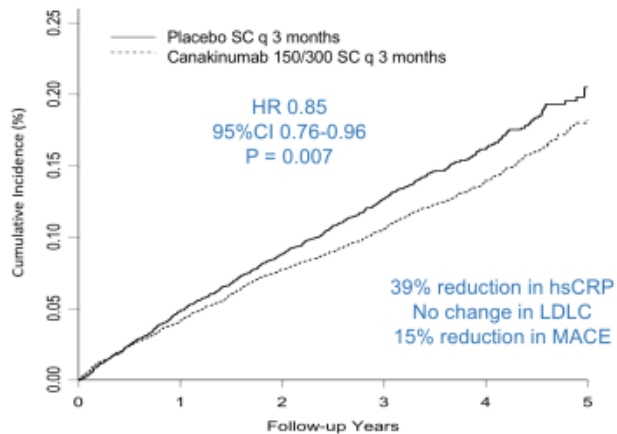
PROSPECT - event rate post pPCI / AMI



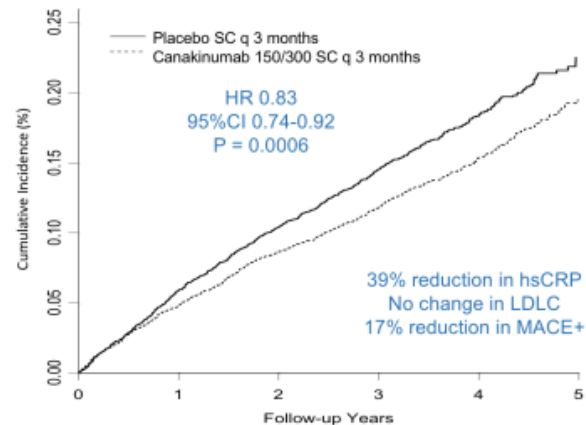
CANTOS - baseline clinical characteristics

Characteristic	Canakinumab SC q 3 months			
	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)
Age (years)	61.1	61.1	61.2	61.1
Female (%)	25.9	24.9	25.2	26.8
Current smoker (%)	22.9	24.5	23.4	23.7
Diabetes (%)	39.9	39.4	41.8	39.2
Lipid lowering therapy (%)	93.7	94.0	92.7	93.5
Renin-angiotensin inhibitors (%)	79.8	79.3	79.8	79.6
Prior Revascularization (%)	79.6	80.9	82.2	80.7
LDL cholesterol (mg/dL)	82.8	81.2	82.4	83.5
HDL cholesterol (mg/dL)	44.5	43.7	43.7	44.0
Triglycerides (mg/dL)	139	139	139	138
hsCRP (mg/L)	4.1	4.1	4.2	4.1

CANTOS: Primary Cardiovascular Endpoint (MACE)



CANTOS: Key Secondary Cardiovascular Endpoint (MACE+)

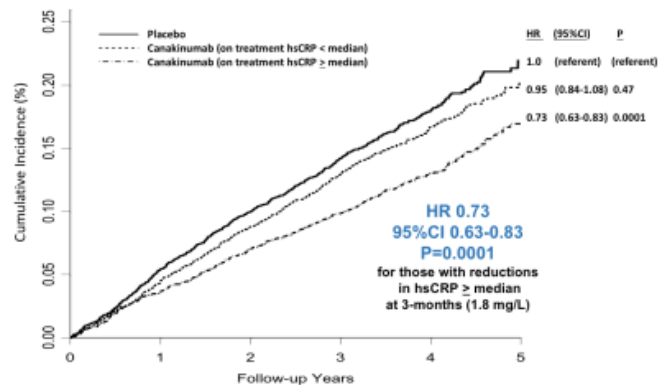


CANTOS: Consistency of HRs Across All Cardiovascular Endpoints

Endpoint	Placebo (N=3347)	Canakinumab SC q 3 months			P-trend
		50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	
Primary	1.00	0.93	0.85	0.86	0.020
Secondary	1.00	0.90	0.83	0.83	0.002
Myocardial Infarction	1.00	0.94	0.76	0.84	0.028
Urgent Revascularization	1.00	0.70	0.64	0.58	0.005
Any Coronary Revascularization	1.00	0.72	0.68	0.70	<0.001
Stroke	1.00	1.01	0.98	0.80	0.17
Cardiac Arrest	1.00	0.72	0.63	0.46	0.035
CV Death	1.00	0.89	0.90	0.94	0.62
All Cause Mortality	1.00	0.94	0.92	0.94	0.39

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CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)



Tailored therapy in CAD



Known Cardiovascular Disease
LDL 150 mg/dL
hsCRP 4.5mg/L



High Intensity Statin



“Residual Cholesterol Risk”

LDL high
hsCRP low



**Additional
LDL Reduction**

“Residual Inflammatory Risk”

LDL low
hsCRP high



**Additional
Inflammation Reduction**



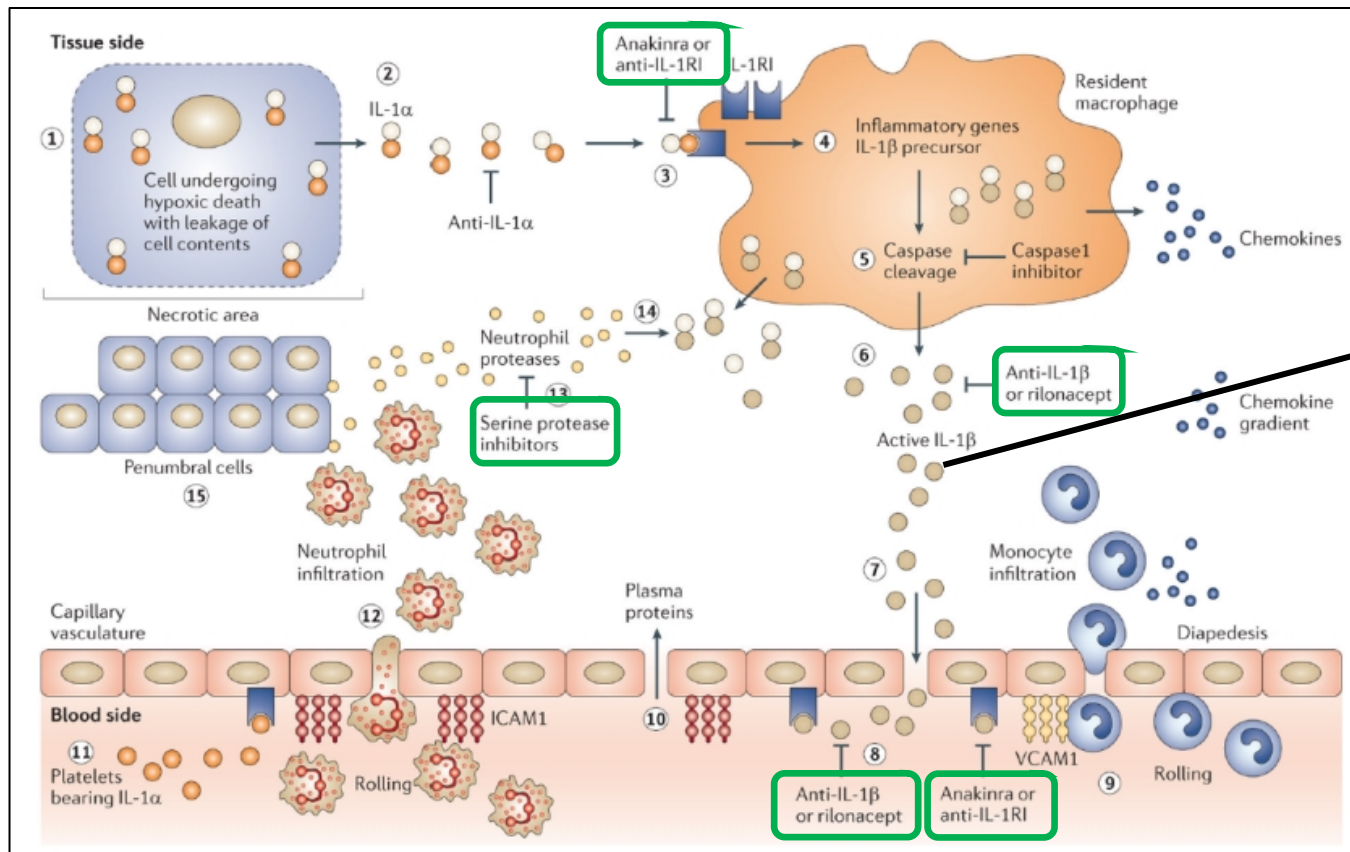
“Residual Thrombotic Risk”

HTPR

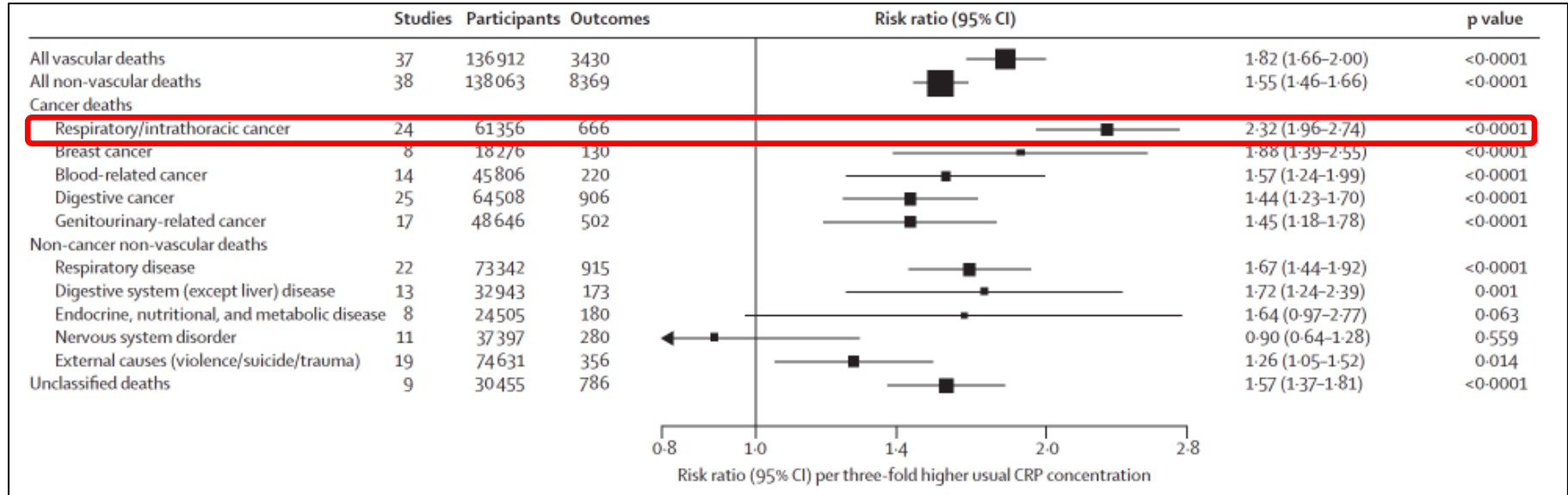


**Additional antiplatelet &
anticoagulant therapy**

IL-1 β in sterile inflammation and non-CVD



CRP & (non) cardiovascular mortality



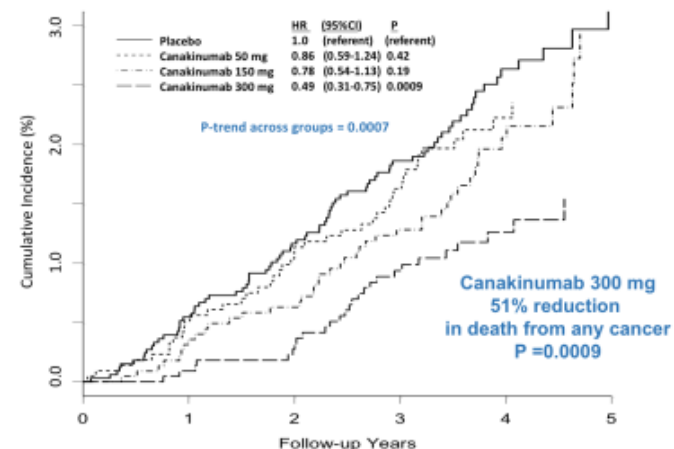
CANTOS: Additional Outcomes (per 100 person years of exposure)

Adverse Event	Canakinumab SC q 3 months				P-trend
	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	
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

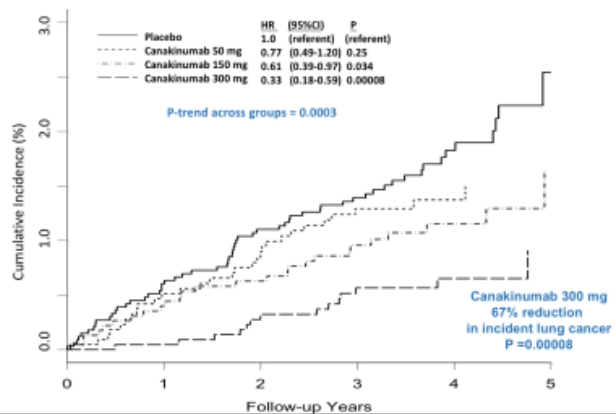
* P-value for combined canakinumab doses vs placebo

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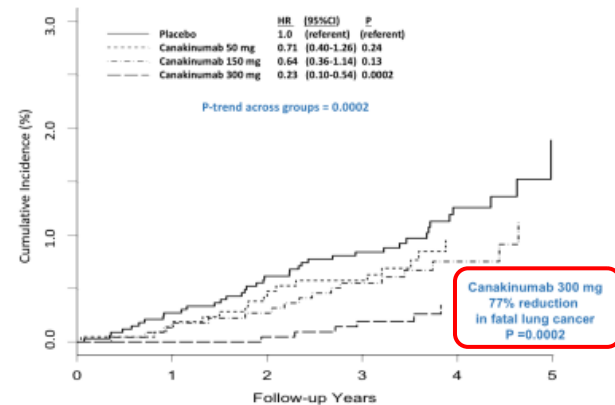
CANTOS: Additional Non-Cardiovascular Clinical Benefits
Cancer Mortality



CANTOS: Additional Non-Cardiovascular Clinical Benefits
Incident Lung Cancer



CANTOS: Additional Non-Cardiovascular Clinical Benefits
Fatal Lung Cancer



CANTOS: Canakinumab **Anti-Inflammatory Thrombosis Outcomes Study**

- supports the concept of causal anti-inflammatory therapy in atherosclerosis
- offers the perspective of tailored indication, treatment & monitoring of anti-inflammatory therapy in secondary prevention in high risk patients
- need to proof the transition of this concept to patients with AMI
- safety has to be further evaluated in post-trial registries in cardiology and oncology, as with other anti-inflammatory agents tested in ongoing trials