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جمعية القلب السعودية
Saudi Heart Association

INFLAMMATION &THROMBOSIS

INSIGHTS FROM CANTOS TRIAL

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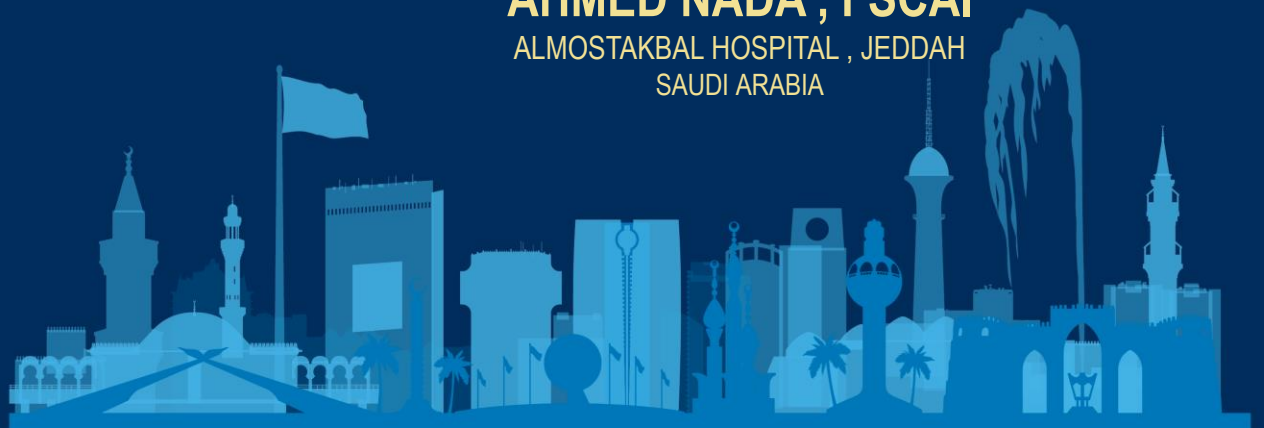


Introduction

- Two or three decades ago, many experts predicted that the modification of risk factors, in particular, the treatment of high blood pressure and lipid disorders, would eliminate CAD in 10 – 20 years. Unfortunately, that prediction turned out to be wrong.
- *Despite current treatments about 40% of heart attack survivors remain at increased risk of recurrent heart attack, stroke or cardiovascular death because of high-risk inflammatory atherosclerosis; 25% experience another event within five years*
- Current drug therapies designed to slow the atherosclerotic process focus almost exclusively on reducing plasma levels of **LDL cholesterol**. However, experimental and clinical research supports that additionally targeting inflammation may be beneficial

[1] Ridker P. How Common Is Residual Inflammatory Risk? *Circ Res. 2017;120:617-619*
[2] Heart Disease and Stroke Statistics-2017 Update: A Report From the American Heart Association. Circulation. 2017;135:e146-e603

Introduction

- Heart attack occurs in about 580,000 people every year in EUR. and 750,000 people in the United States alone

- Despite standard treatment, people with a prior heart attack live with a higher ongoing risk of having another event or dying, and it has been shown that in about four in 10 people, this risk is directly related to increased inflammation associated with atherosclerosis

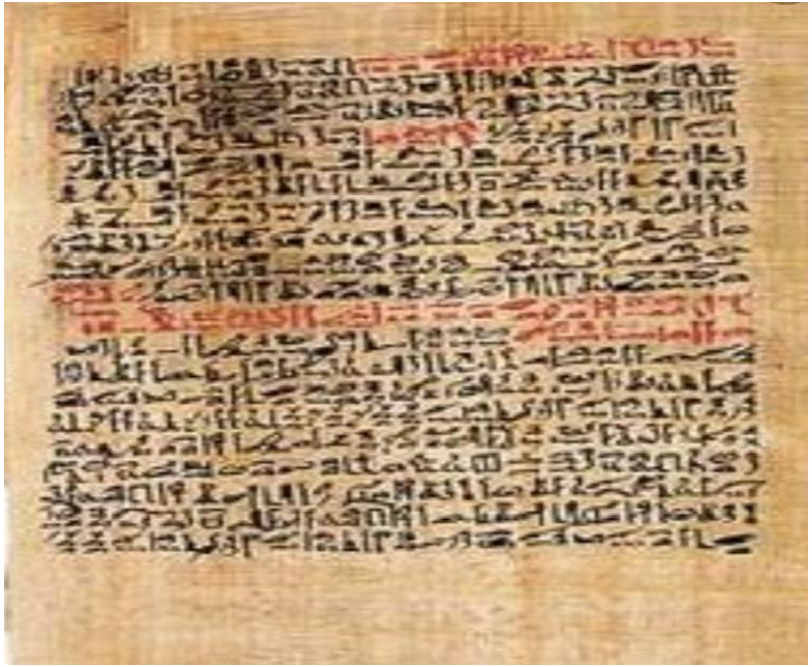
- In FOURIER trial, treatment with the PCSK9 inhibitor Evolocumab (Repatha, Amgen) reduced the risk of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization by 15% when compared with placebo.

- Mozaffarian D, et al. Heart Disease and Stroke Statistics - 2016 Update: A Report From the American Heart Association. *Circulation.* 2017; 135(23):e1-324.
[Roth G, et al. Global, Regional, and National Burden of Cardiovascular Diseases for 10 Causes, 1990 to 2015. *JACC.* Available online May 17, 2017.

Inflammation: an enduring flame

Historical Highlights

- Although clinical features of inflammation were described in an Egyptian papyrus dated around 3000 BC
- Celsus, a Roman writer of the first century AD, first listed the four cardinal signs of inflammation: *rubor* (redness), *tumor* (swelling), *calor* (heat), and *dolor* (pain).



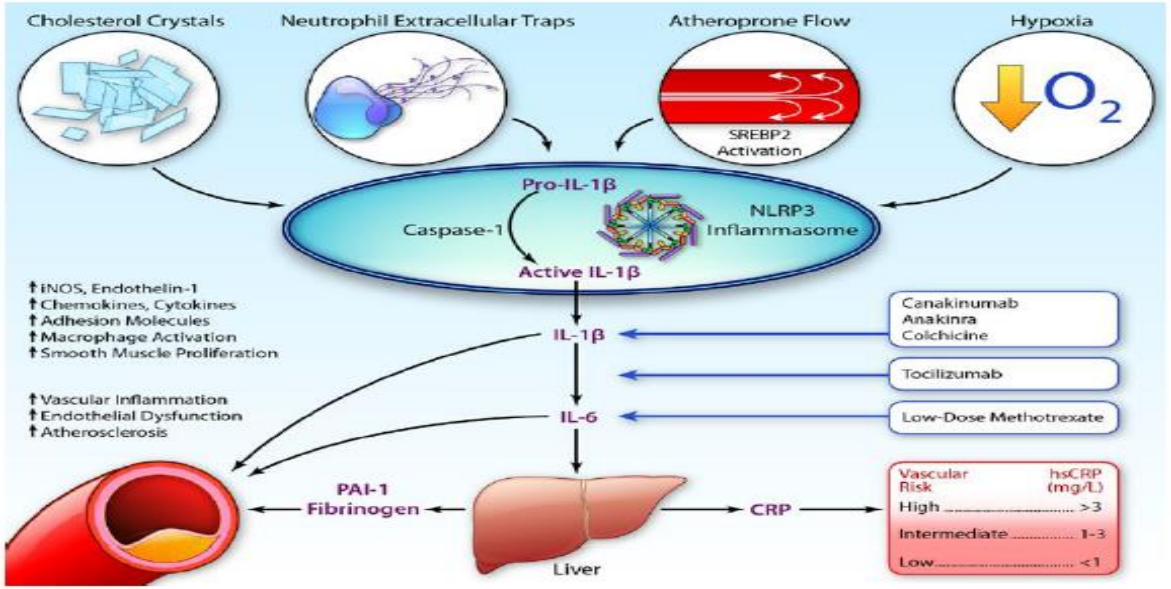
Historical Highlights :

- In the 19th century, keen observers described the diapedesis of leukocytes from the blood into tissues.
- Rudolf Virchow recognized the inflammatory nature of atherosclerotic plaques.
- Virchow also understood atherosclerosis as an active process of tissue reaction, rather than a mere encrustation of thrombus or deposition of fatty material,
- Virchow's concept of atherogenesis, unfortunately yielded to the view of atheroma as a primarily passive lipid collection for more than a century.

Historical Highlights :

- Paul Ehrlich studied antibodies and proposed the concept of complementarity of antigen and antibody, analogous to a key fitting into a lock.
- Ilya Mechnikov discovered phagocytosis at the end of the 19th century, providing the basis of the field we now call innate immunity.
- Ehrlich and Mechnikov shared the Nobel Prize in 1908 for their pioneering studies in immunity and host defenses

Inflammation is the hallmark of atherosclerosis, leading to MI and other CV events



Ridker PM. Circ Res 2016;118:145-156

Interleukin-1β
is instrumental in driving atherosclerosis

ACZ885 (canakinumab),
a human mAb, selectively blocks the IL-1β inflammatory pathway

CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study)

- The CANTOS trial examined whether reducing inflammation with Canakinumab in patients with a history of a prior heart attack can decrease the risk of another cardiovascular event happening in the future.
- Canakinumab is a human monoclonal antibody that neutralizes interleukin-1β ,has proven to be well-tolerated in people with diabetes or arthritis.

CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes Study)

- A total of 10.061 patients with a history of myocardial infarction and hs-CRP equal to or above 2 mg/L were included in the CANTOS trial.
- Patients with a history of chronic or recurrent infections and cancer were excluded from the trial.
- The median follow-up was 3.7 years.
- The trial compared three doses of Canakinumab (50 mg,150 mg, and 300 mg, administered subcutaneously every three months) with placebo.
- Enrollment began in April 2011 and was completed in March 2014. Last trial visit was in June 2017

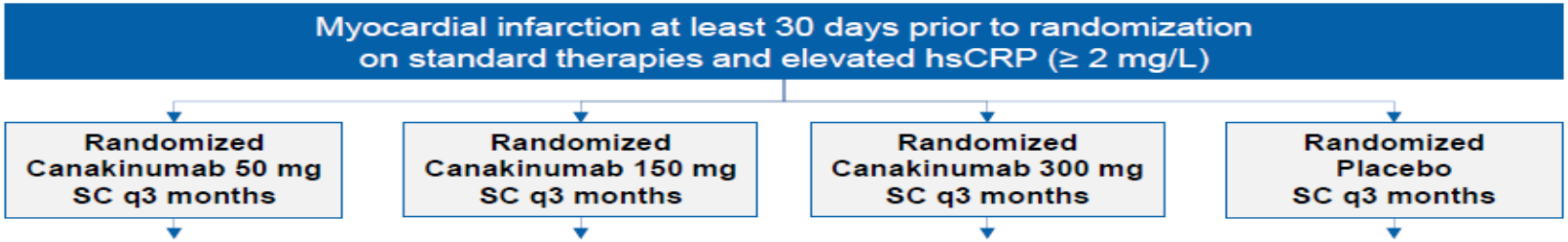
Inclusion criteria:

- History of MI
- hsCRP ≥2 mg/L

Exclusion criteria:

- Chronic or recurrent infection
- High risk for tuberculosis or HIV
- History of cancer
- Immuno-compromised state
- Systemic use of anti-inflammatory treatment

CANTOS study design



Primary Endpoint

- Time to first major cardiovascular event (MACE: CV death, non-fatal MI, or non-fatal stroke) of at least one ACZ885 dose compared to Placebo

Key Secondary Endpoints

- Time to first event of MACE or hospitalization for unstable angina requiring unplanned revascularization
- Time to new onset diabetes among those with pre-diabetes at randomization

Secondary Endpoints

- Time to all cause mortality
- Time to first occurrence of all cause mortality, non-fatal stroke, or non-fatal MI

Key Exploratory Endpoints

- DVT/PE[1], stent thrombosis, hospitalizations for CHF[2], PCI/CABG[3] and biomarkers

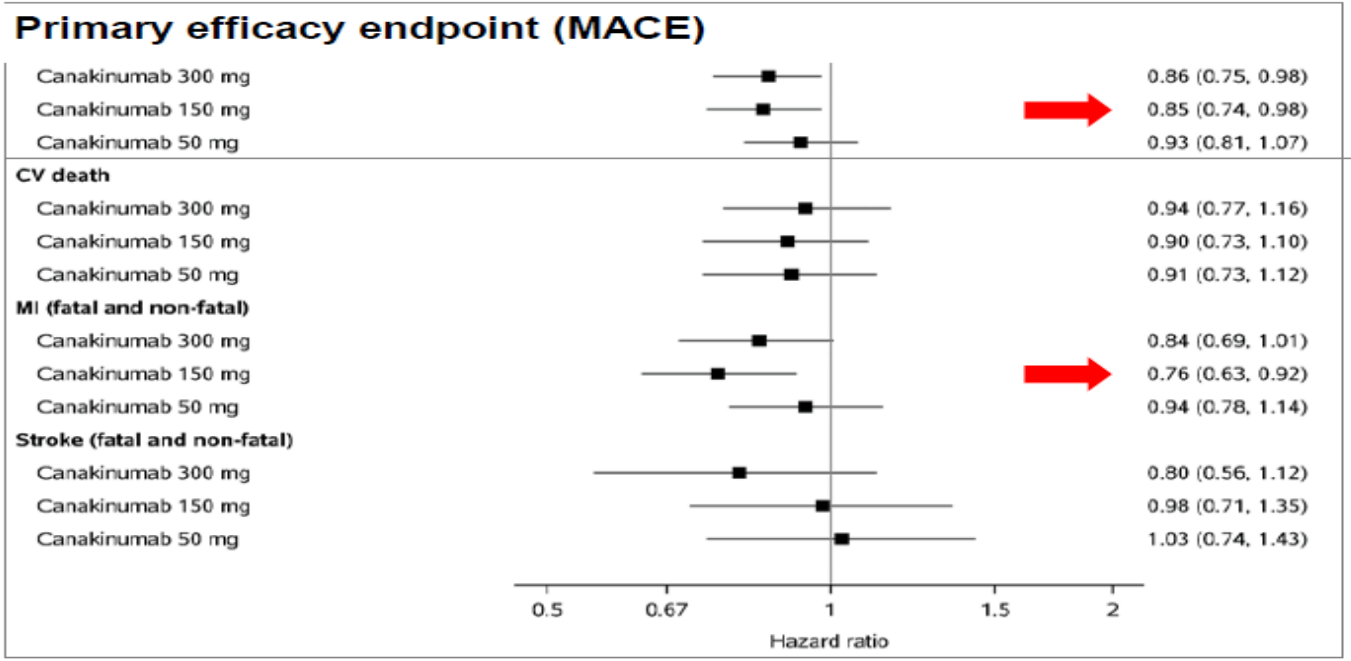
1. Deep Vein Thrombosis/Pulmonary Embolism 2. Chronic Heart Failure 3. Percutaneous Coronary Intervention/Coronary Artery Bypass Graft

Table 1. Characteristics of the Trial Participants.*

Characteristic	Placebo Group (N=3344)	Canakinumab			
		50-mg Group (N=2170)	150-mg Group (N=2284)	300-mg Group (N=2263)	All Doses (N=6717)
Age — yr	61.1±10.0	61.1±10.1	61.2±10.0	61.1±10.1	61.1±10.1
Female sex — no. (%)	865 (25.9)	541 (24.9)	575 (25.2)	606 (26.8)	1722 (25.6)
Current smoking — no. (%)	765 (22.9)	531 (24.5)	534 (23.4)	536 (23.7)	1601 (23.8)
Median body-mass index (IQR)	29.7 (26.6–33.8)	29.9 (26.6–33.9)	29.8 (26.5–33.7)	29.8 (26.5–33.8)	29.9 (26.6–33.8)
Hypertension — no. (%)	2644 (79.1)	1751 (80.7)	1814 (79.4)	1799 (79.5)	5364 (79.9)
Diabetes — no. (%)	1333 (39.9)	854 (39.4)	954 (41.8)	888 (39.2)	2696 (40.1)
Qualifying myocardial infarction — no. (%)					
STEMI	1807 (54.0)	1231 (56.7)	1231 (53.9)	1213 (53.6)	3675 (54.7)
Non-STEMI	1132 (33.9)	710 (32.7)	781 (34.2)	761 (33.6)	2252 (33.5)
Unknown type or missing data	405 (12.1)	229 (10.6)	272 (11.9)	289 (12.8)	790 (11.8)
History of PCI — no. (%)	2192 (65.6)	1454 (67.0)	1555 (68.1)†	1509 (66.7)	4518 (67.3)
History of CABG — no. (%)	469 (14.0)	302 (13.9)	324 (14.2)	316 (14.0)	942 (14.0)
History of congestive heart failure — no. (%)	721 (21.6)	451 (20.8)	478 (20.9)	523 (23.1)	1452 (21.6)
Lipid-lowering therapy — no./total no. (%)	3132/3344 (93.7)	2038/2169 (94.0)	2114/2280 (92.7)	2113/2259 (93.5)	6265/6708 (93.4)
Statin — no./total no. (%)	3045/3344 (91.1)	1990/2169 (91.7)	2065/2280 (90.6)	2057/2259 (91.1)	6112/6708 (91.1)
Renin–angiotensin inhibitor — no./total no. (%)	2665/3338 (79.8)	1718/2166 (79.3)	1817/2277 (79.8)	1792/2250 (79.6)	5327/6693 (79.6)
Anti-ischemia agent — no./total no. (%)‡	3080/3344 (92.1)	1974/2169 (91.0)	2079/2280 (91.2)	2058/2259 (91.1)	6111/6708 (91.1)
Antithrombotic agent or anticoagulant — no./total no. (%)	3188/3344 (95.3)	2059/2169 (94.9)	2157/2280 (94.6)	2149/2259 (95.1)	6365/6708 (94.9)
Median high-sensitivity CRP level (IQR) — mg/liter	4.10 (2.75–6.85)	4.25 (2.80–7.15)	4.25 (2.85–7.05)	4.15 (2.85–7.15)	4.20 (2.80–7.10)
Median interleukin-6 level (IQR) — ng/liter	2.61 (1.80–4.06)	2.53 (1.80–4.17)	2.56 (1.74–4.11)	2.59 (1.79–4.08)	2.56 (1.77–4.13)
Median total cholesterol level (IQR) — mg/dl	161 (137–190)	159 (136–189)	159 (136–188)	161 (137–189)	160 (136–189)
Median LDL cholesterol level (IQR) — mg/dl	82.8 (64.2–107.5)	81.2 (62.3–106.0)	82.4 (63.4–106.0)	83.5 (64.0–108.0)	82.0 (63.0–106.7)
Median HDL cholesterol level (IQR) — mg/dl	44.5 (37.1–52.6)	43.7 (37.0–52.2)	43.7 (36.3–52.0)†	44.0 (36.7–53.0)	43.7 (36.7–52.2)†
Median triglyceride level (IQR) — mg/dl	139 (100–194)	140 (102–198)	139 (101–196)	138 (103–194)	139 (102–196)
Median estimated GFR (IQR) — ml/min/1.73 m^2	79.0 (65.0–93.0)	79.0 (64.0–92.0)	79.0 (64.5–93.0)	78.0 (64.0–93.0)	78.5 (64.0–93.0)
Lost to follow-up — no. (%)	9 (0.3)	9 (0.4)	5 (0.2)	4 (0.2)	18 (0.3)

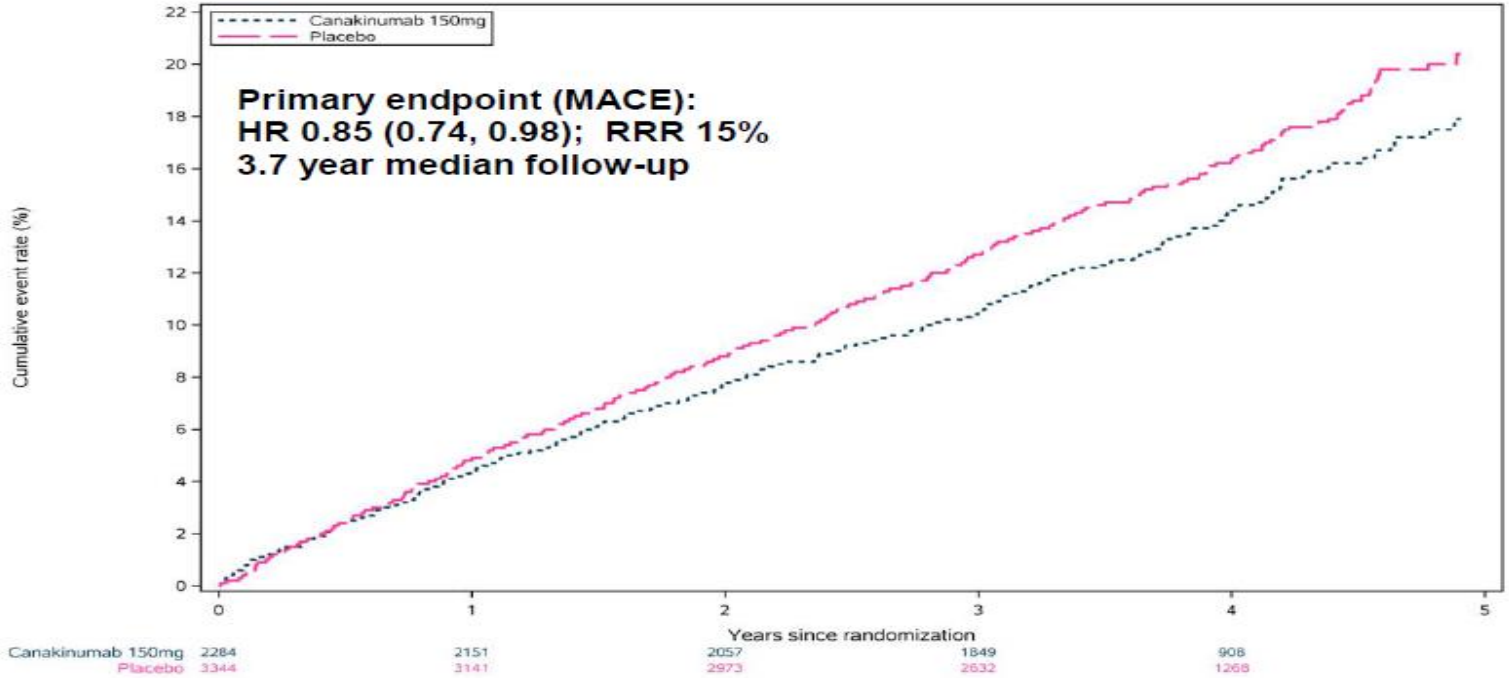
* Plus–minus values are means ±SD. There were no significant between-group differences at baseline, except as noted. The body-mass index is the weight in kilograms divided by the square of the height in meters. To convert the values for cholesterol to millimoles per liter, multiply by 0.02586. To convert the values for triglycerides to millimoles per liter, multiply by 0.01129. CABG denotes coronary-artery bypass grafting, CRP C-reactive protein, GFR glomerular filtration rate, HDL high-density lipoprotein, IQR interquartile range, LDL low-density lipoprotein, PCI percutaneous coronary intervention, and STEMI ST-segment elevation myocardial infarction.
† $P<0.05$ for the comparison of canakinumab with placebo.
‡ Anti-ischemia agents were defined as beta-blocking agents, nitrates, or calcium-channel–blocking agents.

Primary endpoint: Statistically significant 15% reduction of MACE driven by fatal/non-fatal MI



* Statistically significant 1-sided P-values≤ 0.0245 (adjusted according to the Multiple Testing Procedure and accounting for the 2 efficacy IAs)

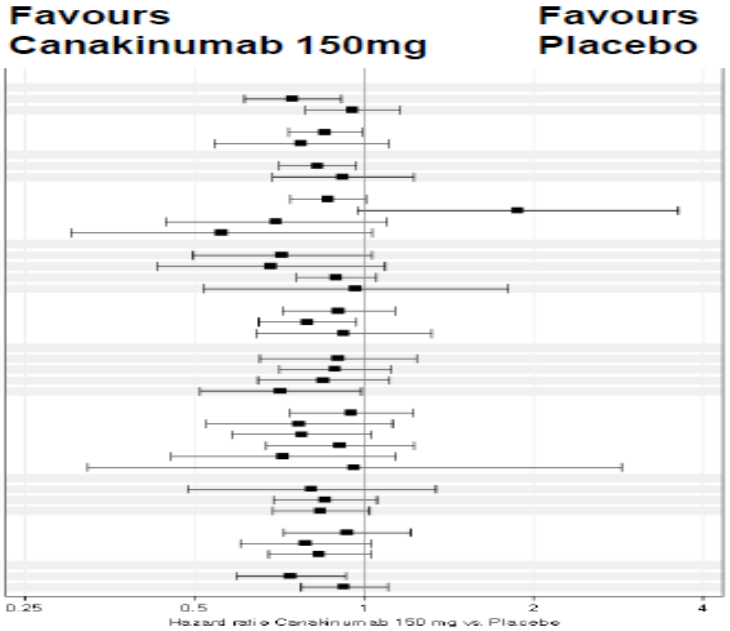
Benefit apparent within first year of treatment and sustained throughout trial duration



Consistent benefit across pre-specified baseline subgroups

Primary endpoint; Canakinumab 150 mg (1/2)

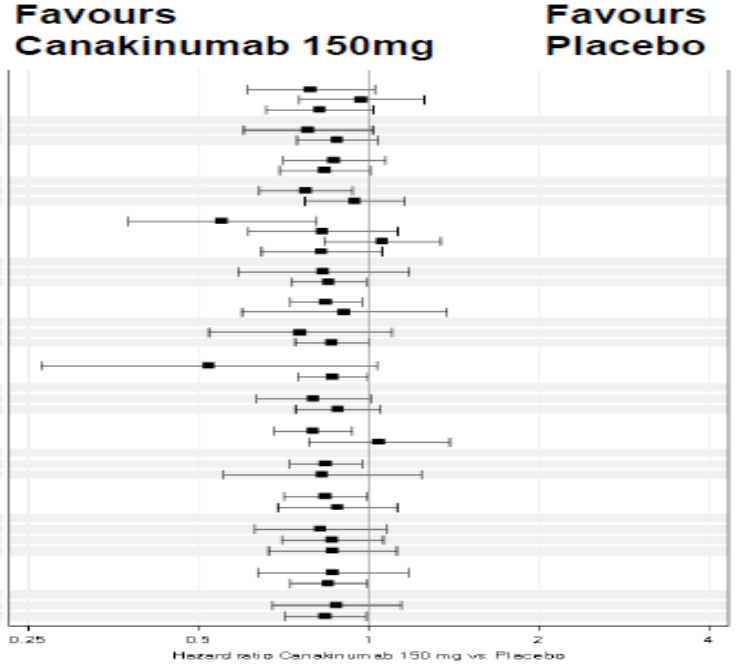
Subgroup	n / N (n/100py) Canakinumab 150 mg (N=2284)	Placebo (N=3344)
Age group 1		
< 65 years	148 / 1428 (2.79)	284 / 2089 (3.71)
>= 65 years	172 / 856 (5.75)	251 / 1255 (5.94)
Age group 2		
< 75 years	271 / 2066 (3.59)	456 / 3045 (4.17)
>= 75 years	49 / 219 (6.64)	79 / 299 (8.40)
Sex		
Male	248 / 1709 (3.97)	414 / 2479 (4.75)
Female	74 / 575 (3.53)	121 / 865 (3.83)
Race		
Caucasian	259 / 1808 (3.98)	424 / 2652 (4.55)
Black	18 / 67 (8.27)	18 / 106 (4.37)
Asian	29 / 278 (2.64)	55 / 388 (3.72)
Other	14 / 129 (3.09)	37 / 195 (5.55)
Ethnicity		
Hispanic/Latino	43 / 357 (3.43)	86 / 523 (4.75)
Asian	27 / 262 (2.60)	59 / 371 (3.79)
Other	232 / 1586 (4.05)	374 / 2356 (4.49)
Unknown	18 / 79 (6.63)	22 / 94 (6.79)
Type of qualifying MI		
Non-STEMI	121 / 761 (4.34)	191 / 1132 (4.77)
STEMI	150 / 1231 (3.30)	287 / 1807 (4.12)
Unknown	49 / 270 (5.15)	77 / 404 (5.56)
BMI		
< 25 kg/m²	61 / 356 (4.79)	95 / 522 (5.22)
>= 25 to < 30 kg/m²	117 / 814 (3.99)	194 / 1220 (4.47)
>= 30 to < 35 kg/m²	86 / 651 (3.65)	140 / 926 (4.27)
>= 35 kg/m²	54 / 459 (3.16)	106 / 673 (4.37)
Geographic region		
North America	106 / 587 (4.73)	145 / 756 (4.90)
Latin America	40 / 316 (3.65)	79 / 483 (4.75)
Western Europe	74 / 556 (3.74)	134 / 810 (4.81)
Central Europe	66 / 520 (3.69)	117 / 895 (4.09)
Asia	28 / 264 (2.69)	53 / 376 (3.69)
Others	6 / 41 (4.14)	7 / 44 (4.31)
Baseline glycemic status		
Normoglycemic	23 / 229 (2.78)	43 / 357 (3.43)
Prediabetic	126 / 1094 (3.39)	234 / 1645 (3.93)
Diabetic	161 / 961 (4.68)	256 / 1342 (5.53)
Baseline smoking status		
Never	97 / 689 (3.86)	141 / 960 (4.09)
Current smoker	85 / 534 (4.50)	150 / 755 (5.63)
Former smoker	139 / 1091 (3.55)	244 / 1619 (4.23)
Baseline hsCRP level		
<= 4 mg/L	116 / 1076 (2.93)	229 / 1635 (3.92)
> 4 mg/L	204 / 1205 (4.72)	306 / 1706 (5.08)



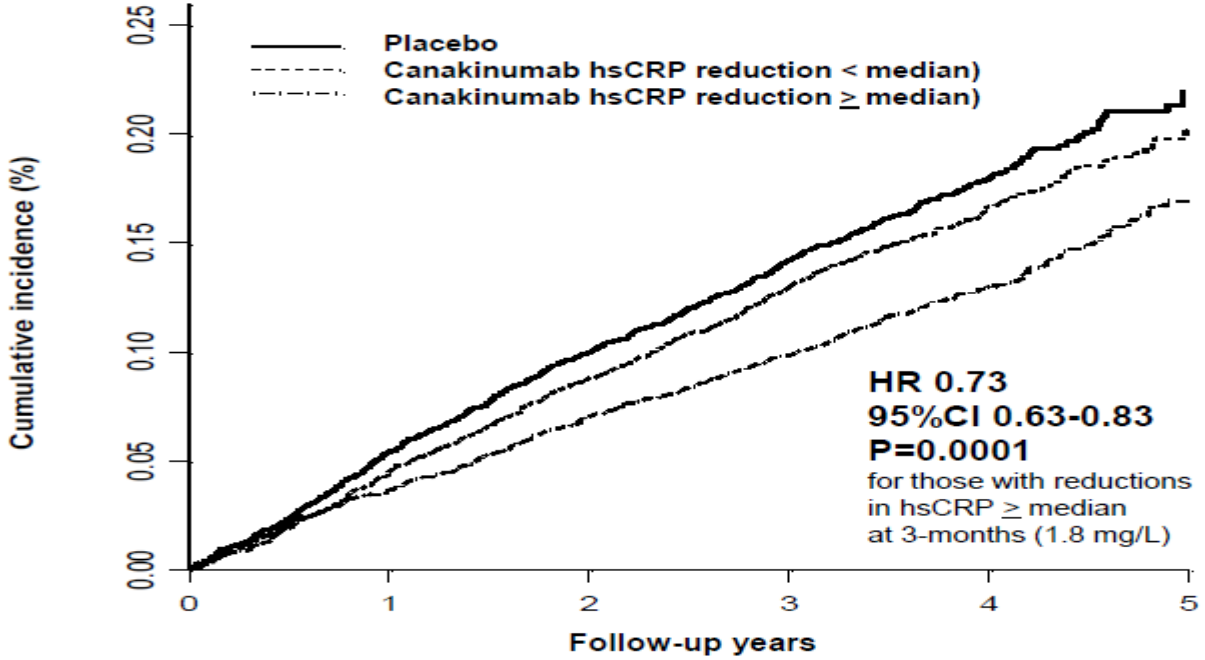
Consistent benefit across pre-specified baseline subgroups

Primary endpoint; Canakinumab 150 mg (2/2)

Subgroup	n / N (n/100py) Canakinumab 150 mg (N=2284)	Placebo (N=3344)
Baseline LDL-C tertiles		
<= 1.81 mmol/L	81 / 773 (3.24)	152 / 1038 (4.05)
> 1.81 to <= 2.51 mmol/L	89 / 754 (3.56)	148 / 1113 (3.62)
> 2.51 mmol/L	128 / 740 (4.79)	226 / 1108 (5.79)
Baseline LDL-C level		
< 1.8 mmol/L	87 / 758 (3.16)	151 / 1075 (4.00)
>= 1.8 mmol/L	229 / 1509 (4.18)	376 / 2236 (4.71)
Baseline SBP level		
< 130 mmHg	145 / 1136 (3.47)	229 / 1602 (3.93)
>= 130 mmHg	175 / 1148 (4.26)	308 / 1742 (5.06)
Baseline DBP level		
< 80 mmHg	167 / 1241 (3.71)	300 / 1777 (4.73)
>= 80 mmHg	153 / 1043 (4.04)	235 / 1567 (4.24)
Baseline statin dose level		
No Dose	37 / 282 (3.60)	69 / 400 (6.50)
Low Dose	67 / 511 (3.50)	108 / 707 (4.21)
Medium Dose	116 / 768 (4.25)	163 / 1147 (3.97)
High Dose	100 / 723 (2.82)	174 / 1090 (4.57)
Aspirin usage		
No	51 / 271 (5.49)	85 / 398 (8.59)
Yes	288 / 2807 (3.85)	449 / 2953 (4.25)
Medical history of gout		
No	283 / 2109 (3.70)	480 / 3094 (4.36)
Yes	37 / 175 (5.87)	55 / 250 (6.41)
Hypertension		
No	42 / 470 (2.43)	82 / 700 (3.17)
Yes	279 / 1814 (4.24)	453 / 2644 (4.97)
Dyslipidemia		
No	12 / 78 (4.49)	28 / 93 (8.61)
Yes	308 / 2206 (3.84)	509 / 3251 (4.40)
Prior PCI		
No	108 / 728 (4.10)	206 / 1152 (5.08)
Yes	212 / 1555 (3.75)	329 / 2192 (4.21)
Prior CABG		
No	239 / 1959 (3.33)	426 / 2875 (4.14)
Yes	81 / 324 (7.25)	109 / 469 (6.81)
Prior stroke or TIA		
No	278 / 2098 (3.65)	479 / 3115 (4.30)
Yes	41 / 198 (8.36)	56 / 229 (7.59)
History of heart failure		
No	216 / 1806 (3.23)	360 / 2623 (3.79)
Yes	104 / 478 (6.53)	175 / 721 (7.33)
eGFR MDRD		
< 60 mL/min/SA	83 / 409 (6.02)	148 / 626 (7.28)
>= 60 to < 90 mL/min/SA	147 / 1205 (3.33)	234 / 1707 (3.92)
>= 90 mL/min/SA	90 / 670 (3.61)	153 / 1010 (4.12)
Time since index event		
< 6 months	87 / 538 (3.50)	107 / 756 (4.00)
>= 6 months	253 / 1740 (3.98)	428 / 2586 (4.66)
Time since index event		
< 12 months	90 / 753 (3.35)	149 / 1104 (3.78)
>= 12 months	230 / 1525 (4.12)	386 / 2238 (4.87)



Pre-specified sub-group analysis of patients achieving hsCRP of 1.8 mg/L after 1st dose at month 3 show 27% RRR for MACE*



HR	(95%CI)	P
1.0	(referent)	(referent)
0.95	(0.84-1.08)	0.47
0.73	(0.63-0.83)	0.0001

* Values for 3 point MACE (primary endpoint) or 4 point MACE (MACE + urgent revascularization) similar – graph above for MACE + urgent revascularisation

Key secondary endpoint met at 150 mg dose

36% RRR for urgent revascularization component

17% RRR in composite of MACE + hospitalization for unstable angina requiring unplanned revascularization

	Treatment	N	n (n/100py)	Hazard ratio vs. Placebo (95% CI)	Adjusted P-value
MACE or unstable angina requiring unplanned revascularization	Canakinumab 300 mg	2263	348 (4.25)	0.82 (0.72, 0.94)	0.0648
	Canakinumab 150 mg	**2284**	**352 (4.29)**	**0.83 (0.73, 0.95)**	**0.0241***
	Canakinumab 50 mg	2170	344 (4.56)	0.90 (0.79, 1.03)	0.1895
	Placebo	3344	601 (5.13)		

36% RRR for hospitalization for unstable angina requiring unplanned revascularization

	Treatment	N	n (n/100py)	Hazard ratio vs. Placebo (95% CI)
Unstable angina requiring unplanned revascularization	Canakinumab 300 mg	2263	34 (0.40)	0.58 (0.39, 0.86)
	Canakinumab 150 mg	**2284**	**38 (0.44)**	**0.64 (0.44, 0.94)**
	Canakinumab 50 mg	2170	38 (0.48)	0.71 (0.48, 1.05)
	Placebo	3344	85 (0.69)	

* Statistically significant 1-sided P-values≤ 0.0245 (adjusted according to the Multiple Testing Procedure and accounting for the 2 efficacy IAs)

Preliminary NNT[1] for both, overall population and hsCRP responders, compares favorably to recent benchmarks

Endpoint MACE (MI, Stroke, CV death)	CANTOS 150mg[2] All patients	CANTOS 150mg hsCRP responders (<1.5 mg/L)	FOURIER[3]
2 years	78	50	74
3.7 years	46	30	N/A

** lung cancer incidence and mortality benefit with 300 mg confirmed for both groups*

1. NNT: Number needed to treat to prevent one MACE event
2. Calculated using Hazard Ratio approach
3. N Engl J Med 2017; 376:1713-1722

Adverse event and tolerability profile

Generally comparable to placebo

	Can. 300 mg N=2263 n (%)	Can. 150 mg N=2285 n (%)	Can. 50 mg N=2170 n (%)	Placebo N=3348 n (%)
Subjects with at least one AE	1987 (87.8)	1970 (86.2)	1872 (86.3)	2914 (87.0)
Subjects with at least one SAE	836 (36.9)	812 (35.5)	741 (34.1)	1203 (35.9)
AEs suspected to be related to study drug	355 (15.7)	350 (15.3)	267 (12.3)	474 (14.2)
Subjects who permanently discontinued study drug due to AEs	175 (7.7)	164 (7.2)	142 (6.5)	244 (7.3)
Discontinued due to SAEs	135 (6.0)	130 (5.7)	117 (5.4)	197 (5.9)
Discontinued due to non-serious AEs	40 (1.8)	34 (1.5)	25 (1.2)	47 (1.4)
AEs leading to study treatment interruption	268 (11.8)	270 (11.8)	228 (10.5)	399 (11.9)

Select safety topics of interest[1]

Adverse Event (%)	Placebo (N=3347)	Canakinumab SC q 3 months 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

1. Based on known or potential risks of canakinumab

Summary of CANTOS cardiovascular results

CANTOS study demonstrated ACZ885 is the first anti-inflammatory therapy to demonstrate reduced risk of major cardiovascular events, particularly in sub-group of hsCRP responders

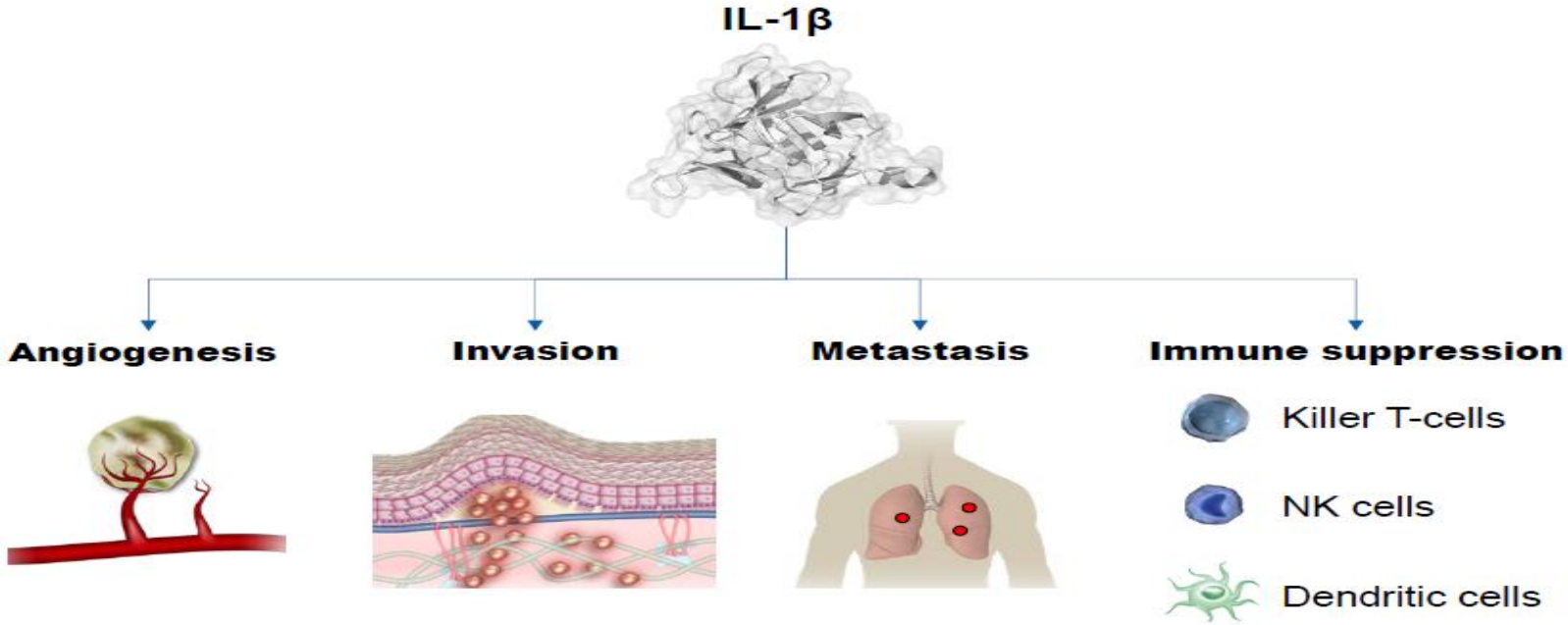
- 15% relative risk reduction (RRR) in MACE (p=0.0241,150mg)
- Effect driven by 24% RRR of fatal or non-fatal heart attack; a 10% RRR of cardiovascular death and neutral effect on risk of stroke
- Subgroup of patients achieving a reduction of hsCRP below 1.8 mg/L after 1st dose (at 3 months) show 27% RRR for MACE, with NNT of 50 at year 2 and 30 at 3.7 years

The 150-mg dose, but not the other doses, met the pre-specified multiplicity-adjusted threshold for statistical significance for the primary end point and the secondary end point

CANTOS study well-conducted with impact on biomarkers without impact on lipids

- Baseline demographics for age, sex, time since prior MI, smoking status, type 2 diabetes, and dyslipidemia **comparable across groups**
- **Patients well managed** at baseline for LDL-C and blood pressure:
  - Over 90% on lipid lowering agents, anti-thrombotics, and anti-ischemics
  - Over 80% on beta blockers and RAAS blockers
- Dose dependent **reductions in hsCRP and IL-6**
- **No meaningful changes in LDL-C, HDL-C, and Triglycerides**

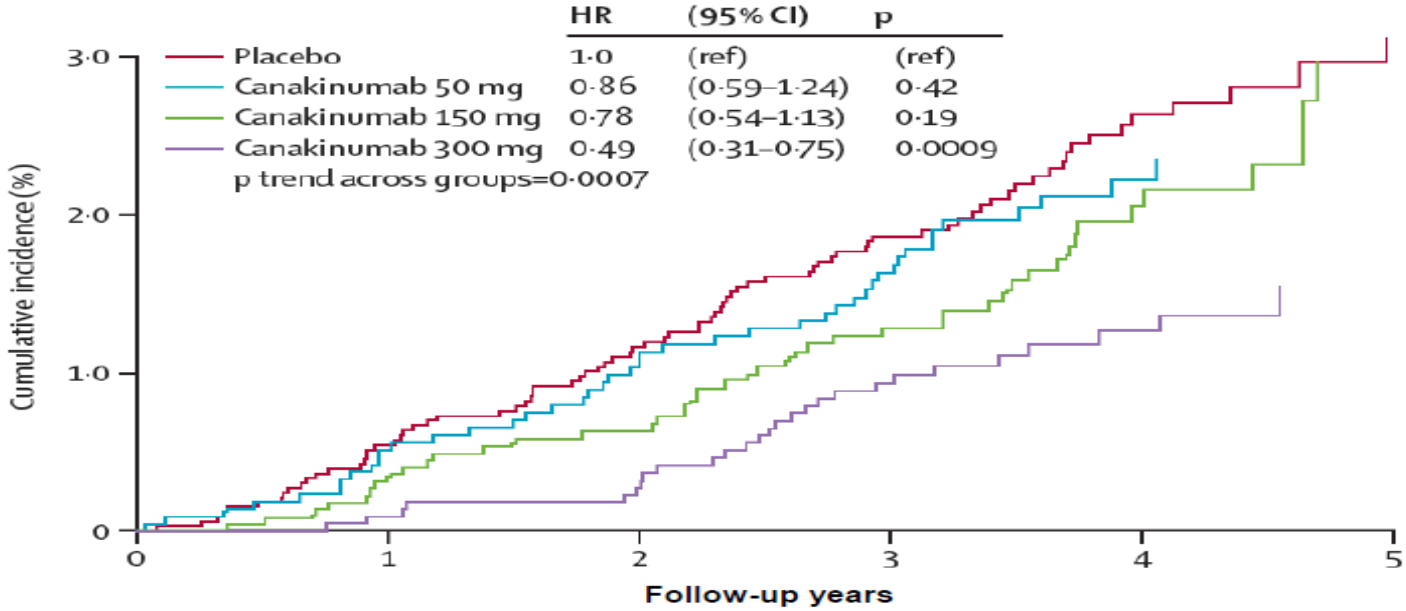
IL-1β promotes cancer progression*



* Dinarello CA. Why not treat human cancer with interleukin1 blockade? *Cancer Metastasis Rev* 2010; 29: 317–29.
* Lewis AM. Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment *J Transl Med*. 2006; 4: 48

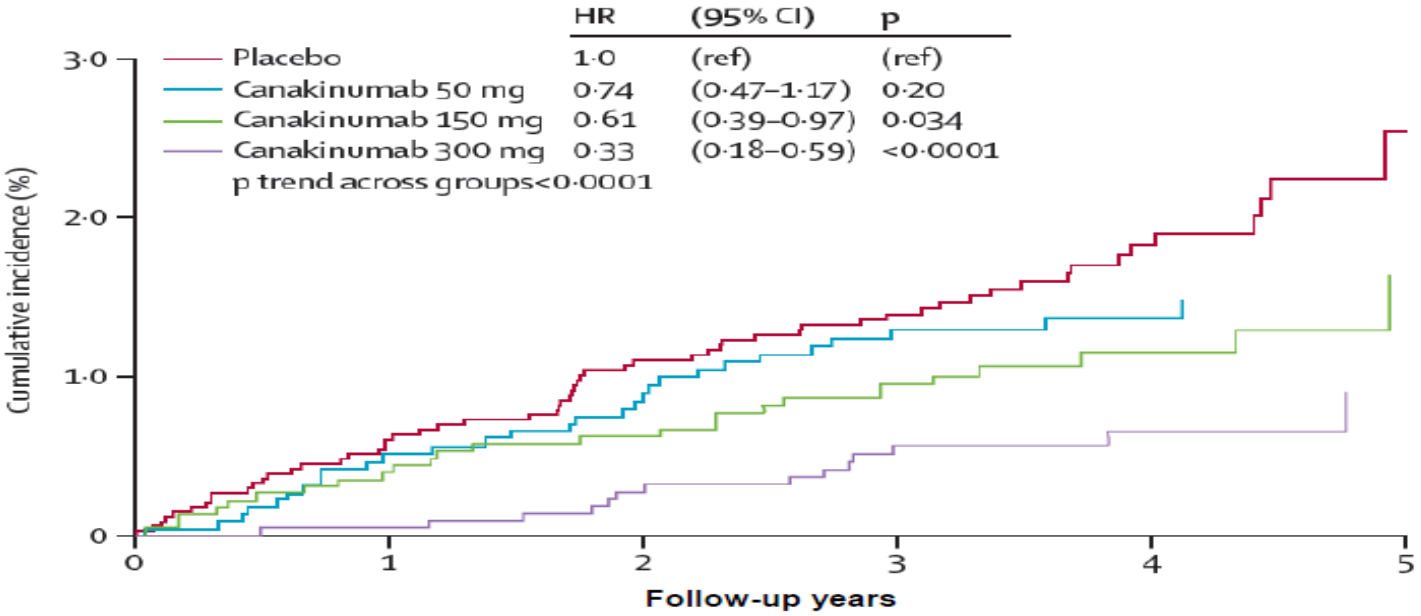
Dose dependent risk reduction with canakinumab in all fatal cancer incidence of 51% (300mg)

Cumulative incidence all fatal cancers



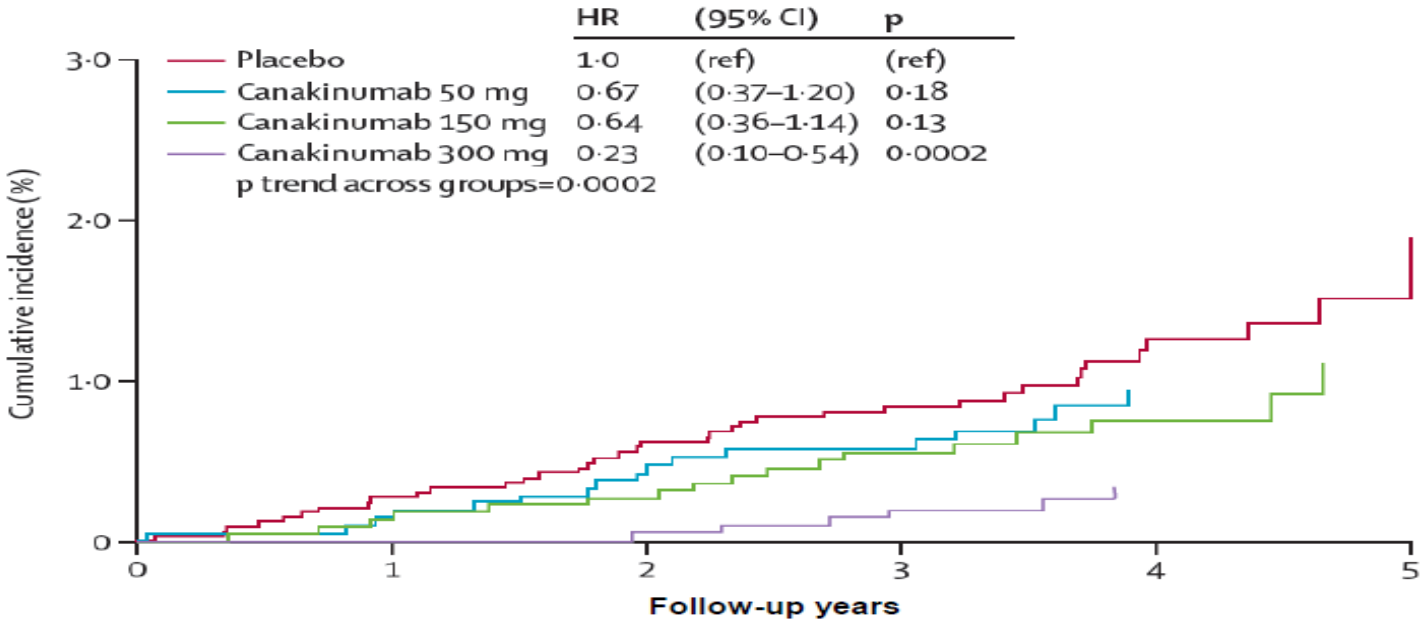
Dose dependent risk reduction with canakinumab in lung cancer incidence of 67% (300 mg)

Cumulative incidence lung cancer



Dose dependent risk reduction with canakinumab in lung cancer mortality incidence of 77% (300mg)

Cumulative incidence lung cancer mortality



Summary of CANTOS lung cancer results

Clinical Outcome	Canakinumab Dose (SC q 3 months) Placebo (N=3344)	50mg (N=2170)	150mg (N=2284)	300mg (N=2263)	All doses (N=6717)	P-value for trend across doses
Any Cancer (all)						
Incident rate, (N)	1.88 (231)	1.85 (144)	1.69 (143)	1.72 (144)	1.75 (431)	0.31
Hazard ratio	1.00	0.99	0.90	0.91	0.93	
95 % CI	(referent)	0.80-1.22	0.73-1.11	0.74-1.12	0.79-1.09	
P	(referent)	0.91	0.31	0.38	0.38	
Any Cancer (fatal)						
Incidence rate, (N)	0.64 (81)	0.55 (44)	0.50 (44)	0.31 (27)	0.45 (115)	0.0007
Hazard ratio	**1.00**	**0.86**	**0.78**	**0.49**	**0.71**	
95% CI	(referent)	0.59-1.24	0.54-1.13	0.31-0.75	0.53-0.94	
P	(referent)	0.42	0.19	0.0009	0.016	
Lung Cancer (all)						
Incidence rate, (N)	0.49 (61)	0.35 (28)	0.30 (26)	0.16 (14)	0.27 (68)	<0.0001
Hazard ratio	**1.00**	**0.74**	**0.61**	**0.33**	**0.55**	
95% CI	(referent)	0.47-1.17	0.39-0.97	0.18-0.59	0.39-0.78	
P	(referent)	0.20	0.034	<0.0001	0.0007	
Lung Cancer (fatal)						
Incidence rate, (N)	0.30 (38)	0.20 (16)	0.19 (17)	0.07 (6)	0.15 (39)	0.0002
Hazard ratio	**1.00**	**0.67**	**0.64**	**0.23**	**0.51**	
95% CI	(referent)	0.37-1.20	0.36-1.14	0.10-0.54	0.33-0.80	
P	(referent)	0.18	0.13	0.0002	0.0026	

Trend of up to 37% risk reduction for fatal – non-lung – cancers also observed

Clinical Outcome	Canakinumab Dose (SC q 3 months)					P-value for trend across doses
	Placebo (N=3344)	50mg (N=2170)	150mg (N=2284)	300mg (N=2263)	All doses (N=6717)	
Non-Lung Cancer (all)						
Incident rate, (N)	1.46 (179)	1.55 (121)	1.44 (122)	1.60 (134)	1.53 (377)	0.54
Hazard ratio	1.00	1.08	0.99	1.10	1.05	
95 % CI	(referent)	0.85-1.36	0.78-1.24	0.88-1.37	0.88-1.26	
P	(referent)	0.54	0.91	0.42	0.58	
Non-Lung Cancer (fatal)						
Incidence rate, (N)	0.39 (49)	0.38 (30)	0.34 (30)	0.24 (21)	0.32 (81)	0.06
Hazard ratio	**1.00**	**0.96**	**0.88**	**0.63**	**0.82**	
95% CI	(referent)	0.61-1.51	0.56-1.39	0.38-1.04	0.58-1.17	
P	(referent)	0.86	0.60	0.07	0.28	

Summary of CANTOS Oncology findings

Anti-inflammatory therapy with ACZ885 targeting the IL-1β innate immunity pathway may markedly impact early/undetected lung cancers and lung cancer mortality

- In pre-clinical models for over a decade, IL-1β inhibition demonstrated to reduce cancer invasiveness, metastasis, and angiogenesis.
- Incident cancers and cancer deaths were prospective, blinded safety analyses in the CANTOS study, adjudicated by an independent Oncology monitoring committee, as agreed with FDA in 2010
- Dose dependent **51% RRR in total cancer mortality** (p=0.0009, 300mg); **77% RRR in lung cancer mortality** (p=0.0002, 300mg);
  67% RRR in incident lung cancers (p=0.00008, 300mg)
- **37% RRR trend** in cancer mortality excluding lung cance

Summary of CANTOS findings in CV risk reduction[1] and cancer therapy[2]

CANTOS study demonstrated ACZ885 is the first anti-inflammatory therapy to demonstrate reduced risk of major cardiovascular events, particularly in sub-group hsCRP[3] responders

- 15% relative risk reduction (RRR) in MACE[4] (p=0.0241[5],150mg)
- Effect driven by 24% RRR of fatal or non-fatal heart attack
- Subgroup of patients achieving a reduction of hsCRP below 1.8 mg/L after 1st dose (at 3 months) show 27% RRR for MACE, with NNT[6] of 50 at year 2 and 30 at 3.7 years

Anti-inflammatory therapy with ACZ885 targeting the IL-1β innate immunity pathway may markedly impact early/undetected lung cancers and lung cancer mortality

- It has been hypothesized that inhibition of IL-1β might reduce cancer invasiveness, metastasis, and angiogenesis
- Incident cancers and cancer deaths was prospective, blinded safety analysis adjudicated by an independent Oncology monitoring committee as agreed with FDA in 2010
- Dose dependent 51% RRR in total cancer mortality (p=0.0009, 300mg); 77% RRR in lung cancer mortality (p=0.0002, 300mg); 67% RRR in incident lung cancers (p=0.00008, 300mg)
- 37% RRR trend in cancer mortality, excluding lung cancer

1. Ridker P. et al., Anti-Inflammatory Therapy with Canakinumab for Atherosclerotic Disease, NEJM 2017 2. Ridker P. et al, Effects of Interleukin-1 β Inhibition with Canakinumab on Incident Lung Cancer: Results from a Randomized Clinical Trial, LANCET 2017 3. High sensitivity C-reactive protein 4. CV death, non-fatal MI, or non-fatal stroke 5. adjusted for multiplicity; All other p-values are unadjusted 6. NNT: Number needed to treat to prevent one MACE event

CONCLUSION FROM CANTOS TRIAL :

- Anti-inflammatory therapy targeting the interleukin-1β innate immunity pathway with canakinumab at a dose of 150 mg every 3 months led to a significantly lower rate of recurrent cardiovascular events than placebo, independent of lipid-level lowering.

Take home message

- The positive results of CANTOS study certainly open new doors to the prevention and treatment of cardiovascular disease.

- If we can identify those patients who have low LDL level with high CRP level, it would be a new way of treating people who would otherwise follow a fatal path.

- The results of the study inevitably raise the question whether reducing inflammation by improving diet and lifestyle will provide similar results as treatment with an expensive drug with potential side effects.

THANK YOU