# Anti-Inflammatory Therapy with Canakinumab for Atherosclerotic Disease

CANTOS

Canakinumab Anti-inflammatory Thrombosis Outcomes Study

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on behalf of the worldwide investigators and participants in the

**C**anakinumab **An**ti-Inflammatory **T**hrombosis **O**utcomes **S**tudy (CANTOS)

# Low Grade Systemic Inflammation *Precedes* By Many Years the Onset of Vascular Events

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INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN

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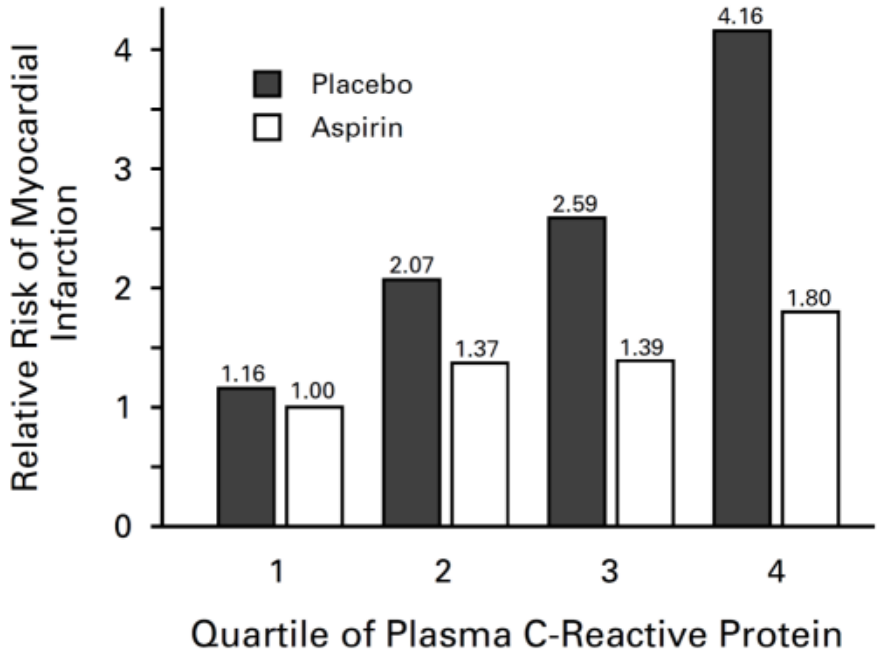


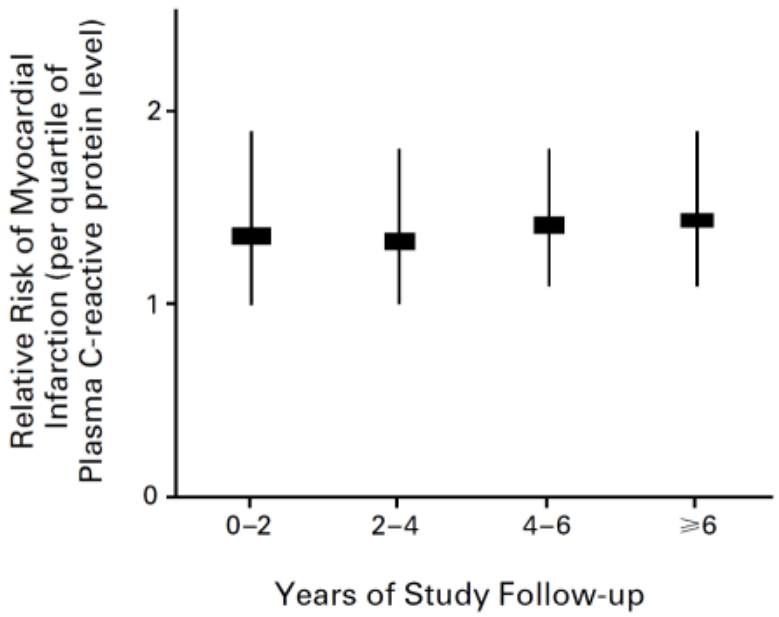


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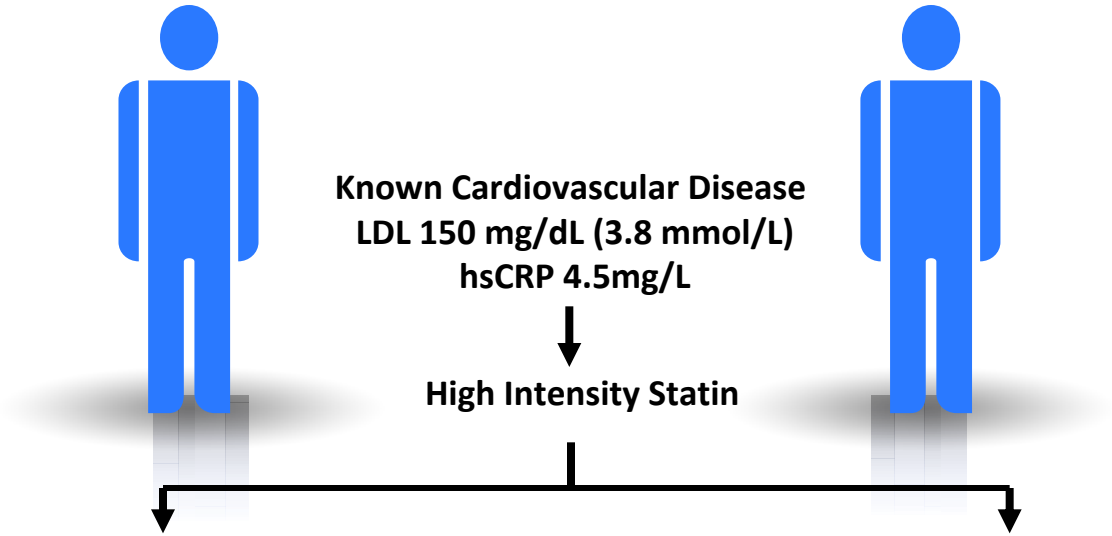
# Clinical Impact of Inflammation on Atherosclerosis

- **Plasma levels of inflammatory biomarkers including hsCRP and IL-6 robustly predict first and recurrent cardiovascular events, independent of lipid levels.**
- **Statins are both lipid lowering and anti-inflammatory, and the greatest benefits of statin therapy accrue to those who not only lower LDLC, but who also lower hsCRP.**
- **In primary prevention, the JUPITER trial demonstrated that those with elevated hsCRP but low levels of LDLC markedly benefit from statin therapy.**
- **In secondary prevention, clinicians now distinguish between those with "residual cholesterol risk" and those with "residual inflammatory risk"**

Ridker PM. JACC 2016;67:712-23

# Residual Inflammatory Risk:
# Addressing the Obverse Side of the Atherosclerosis Prevention Coin

*Ridker PM. Eur Heart J 2016;37:1720-22*




## "Residual Cholesterol Risk"

**LDL 110 mg/dL (2.8 mmol/L)**
**hsCRP 1.8 mg/L**

↓

**Additional**
**LDL Reduction**

**IMPROVE-IT : Ezetimibe 6% RRR**
**FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR**

## "Residual Inflammatory Risk"

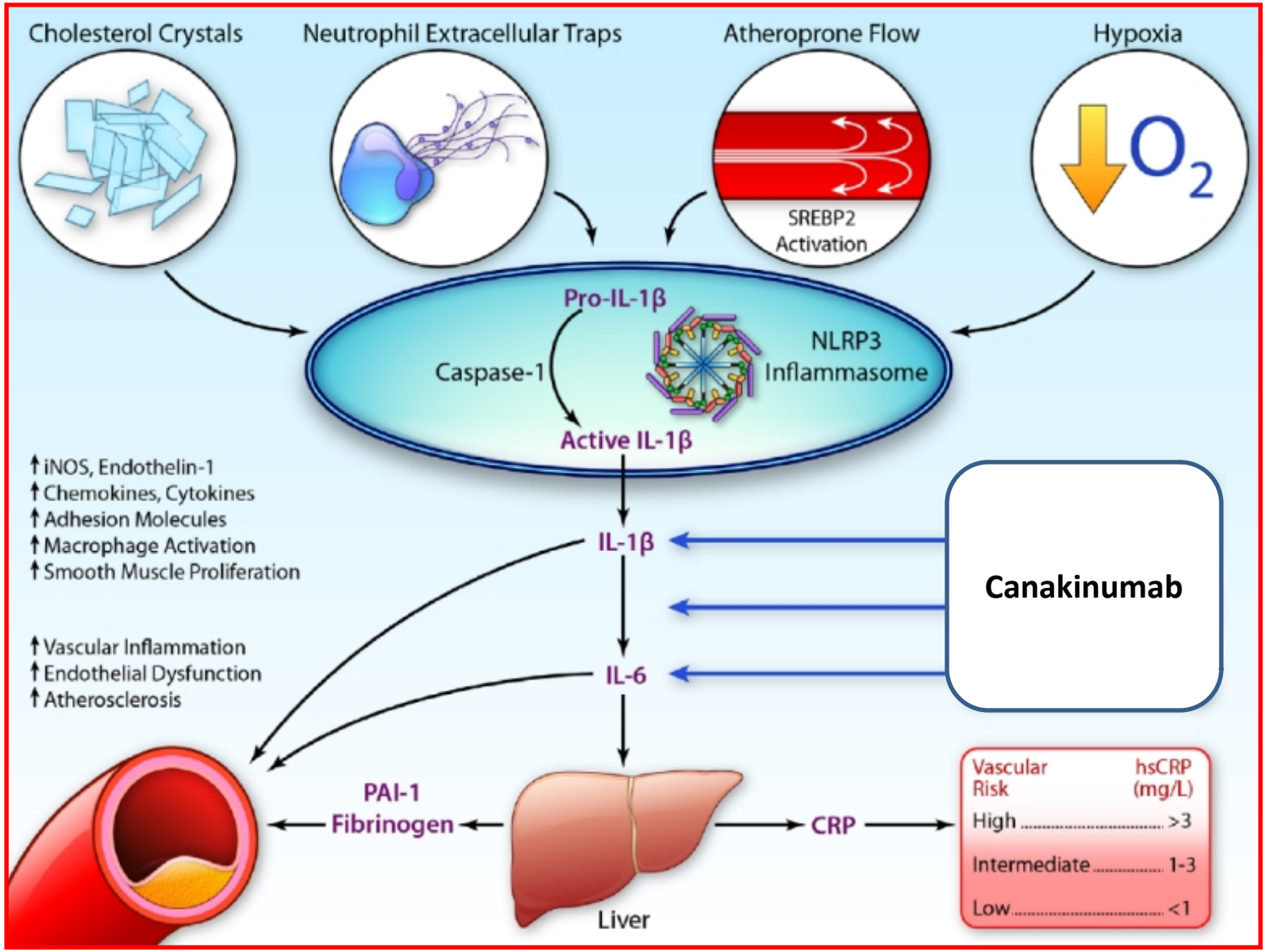
**LDL 70 mg/dL (1.8 mmol/L)**
**hsCRP 3.8 mg/L**

↓

**Additional**
**Inflammation Reduction**

**No Prior Proof of Concept**

# From CRP to IL-6 to IL-1: Moving Upstream to Identify Novel Targets for Atheroprotection




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

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# Canakinumab (Novartis)

- **high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)**
- **designed to bind to human IL-1β and functionally neutralize the bioactivity of this pro-inflammatory cytokine**
- **long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months**

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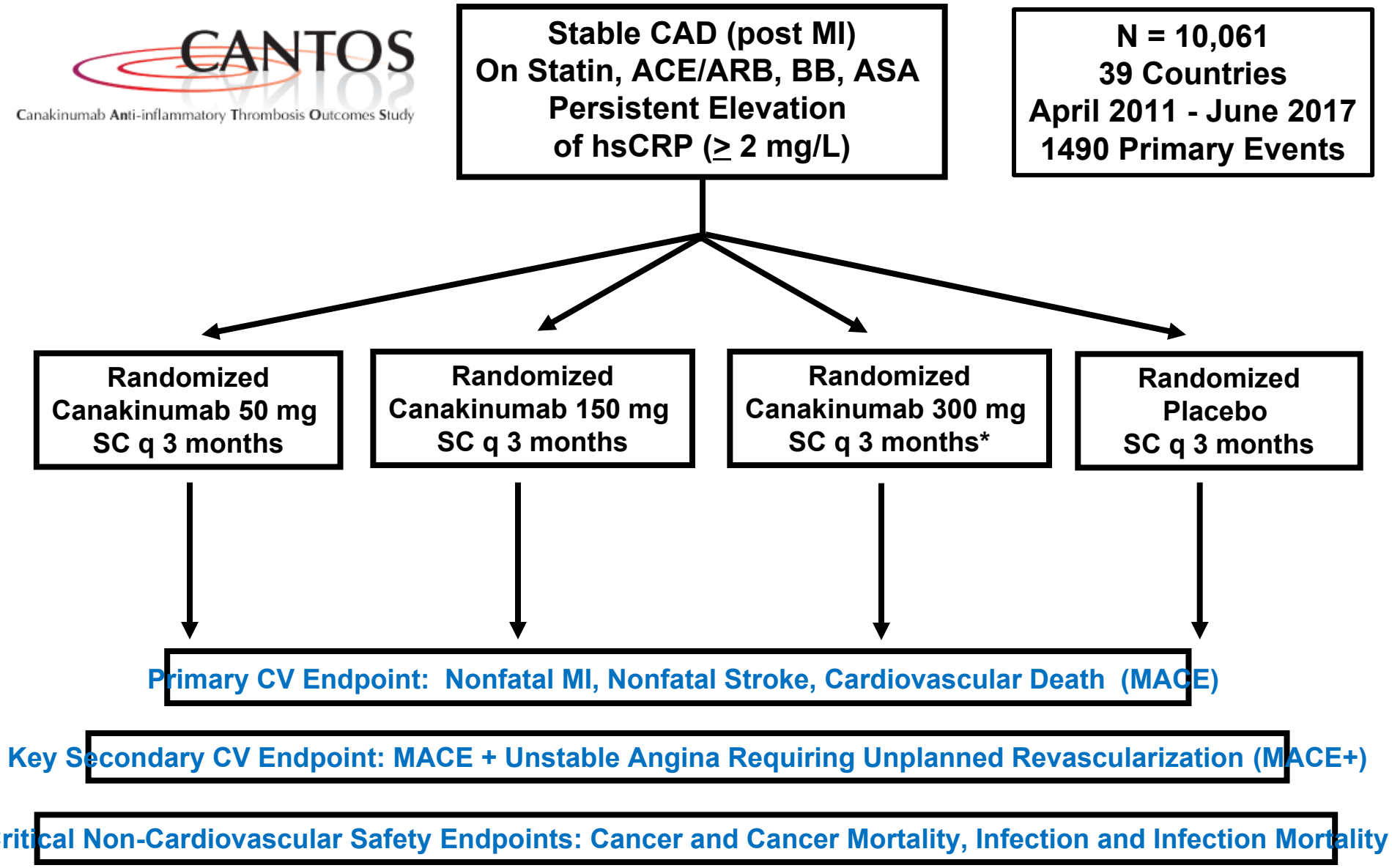
# Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

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# Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

**39 countries**
**> 1000 investigators**


**17482 Screened**

**7377 Excluded Prior to Entering Randomization Process**
- 146 refused consent
- 71 child-bearing potential
- 44 age out of range
- 251 no documented MI
- 3390 hsCRP < 2 mg/L
- 728 exclusionary concomitant disease
- 1873 tuberculosis risk factors
- 104 infectious disease
- 76 immunocompromised state
- 27 life threatening condition
- 574 withdrew consent
- 137 site closure
- 81 physician decision
- 49 unable to contact
- 7 adverse event
- 11 died
- 139 other reasons

**10105 Entered Into Randomization Process**

**44 Failed Randomization Process**
- 41 Invalid randomization
- 3 major GCP violations

**10061 Successfully Randomized**

**3344 placebo**
18.1% discontinued study drug
3335 known final vital status
9 unknown final vital status

**2170 canakinumab 50mg**
16.7% discontinued study drug
2161 known final vital status
9 unknown final vital status

**2284 canakinumab 150mg**
19.2% discontinued study drug
2279 known final vital status
5 unknown final vital status

**2263 canakinumab 300mg**
20.1% discontinued study drug
2259 known final vital status
4 unknown final vital status

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# CANTOS - Baseline Clinical Characteristics

| | | Canakinumab SC q 3 months | | |
|---|---|---|---|---|
| Characteristic | 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 |

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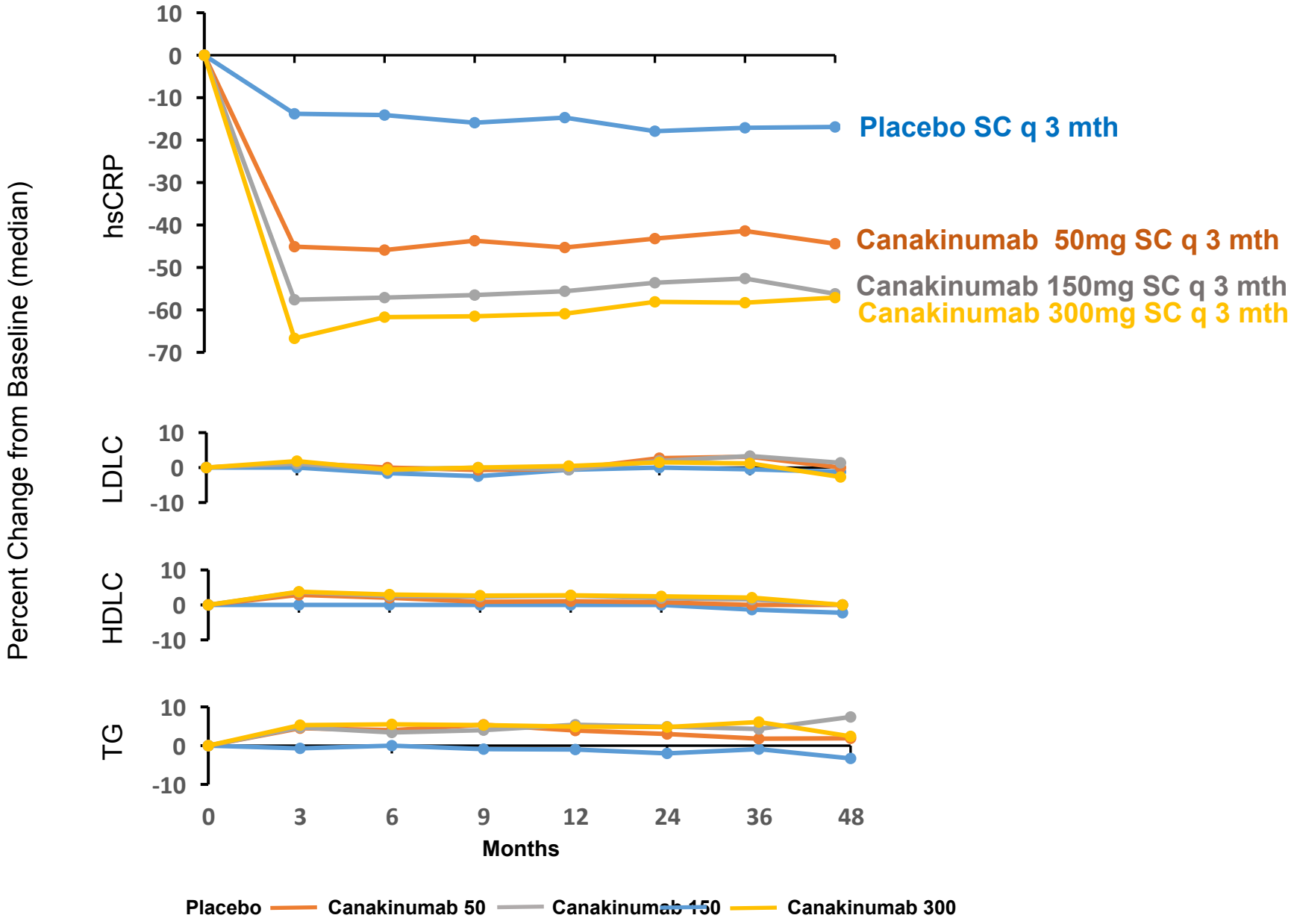
# CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)

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# CANTOS: Primary Clinical Outcome Effects on MACE and MACE +

| | | Canakinumab SC q 3 months | | | |
|---|---|---|---|---|---|
| | Placebo (N=3347) | 50 mg (N=2170) | 150 mg (N=2284) | 300 mg (N=2263) | P-trend |
| **Primary Endpoint** | | | | | |
| IR (per 100 person years) | 4.5 | 4.1 | 3.9 | 3.9 | 0.020 |
| HR | 1.0 | 0.93 | 0.85 | 0.86 | |
| 95%CI | (referent) | 0.80-1.07 | 0.74-0.98 | 0.75-0.99 | |
| P | (referent) | 0.30 | 0.021* | 0.031 | |
| **Secondary Endpoint** | | | | | |
| IR (per 100 person years) | 5.1 | 4.6 | 4.3 | 4.3 | 0.003 |
| HR | 1.00 | 0.90 | 0.83 | 0.83 | |
| 95%CI | (referent) | 0.78-1.03 | 0.73-0.95 | 0.72-0.94 | |
| P | (referent) | 0.11 | 0.005* | 0.004 | |

*Statistically significant, adjusted for multiplicity, in accordance with the pre-specified closed-testing procedures

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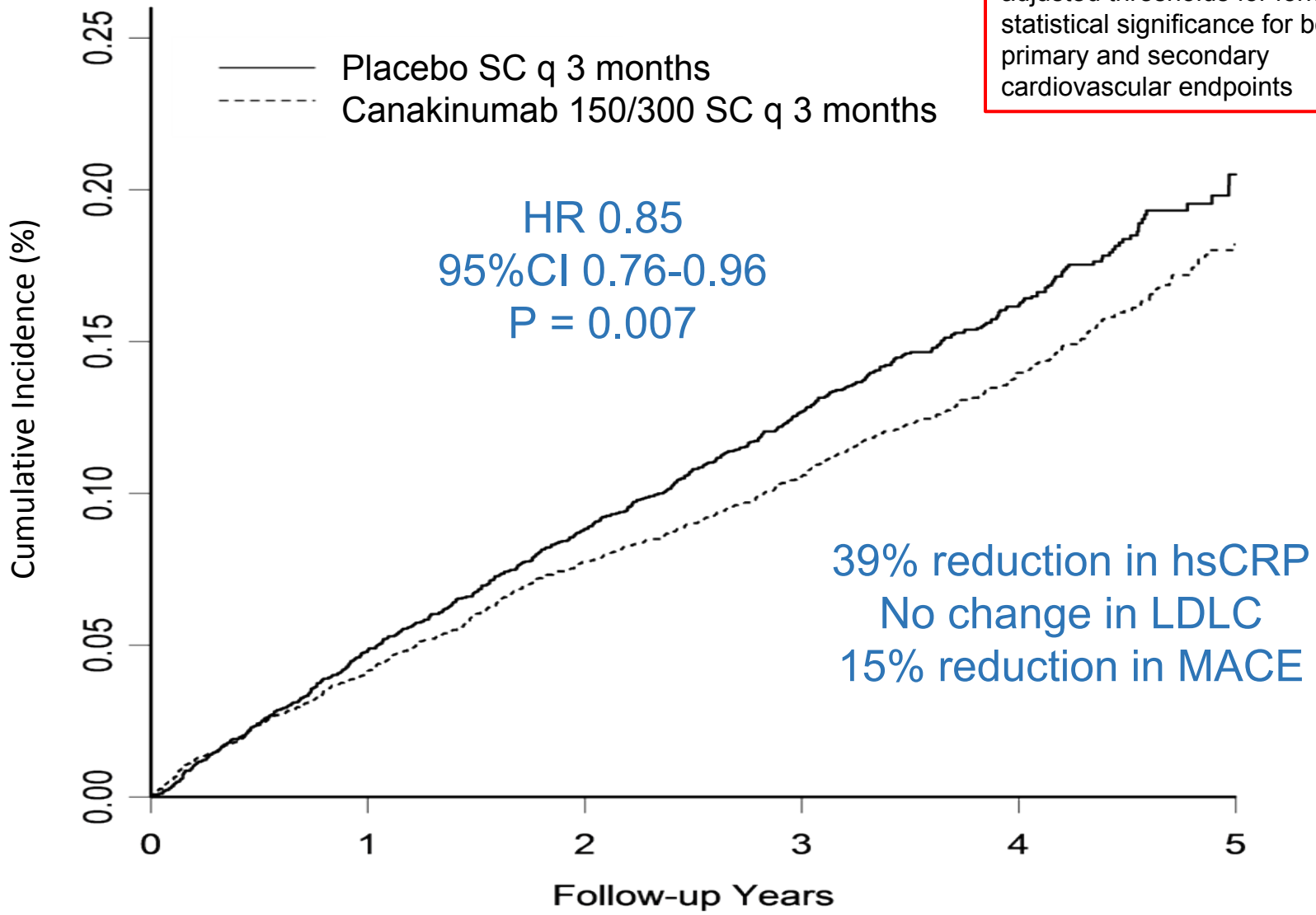
# CANTOS: Primary Cardiovascular Endpoint (MACE)

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

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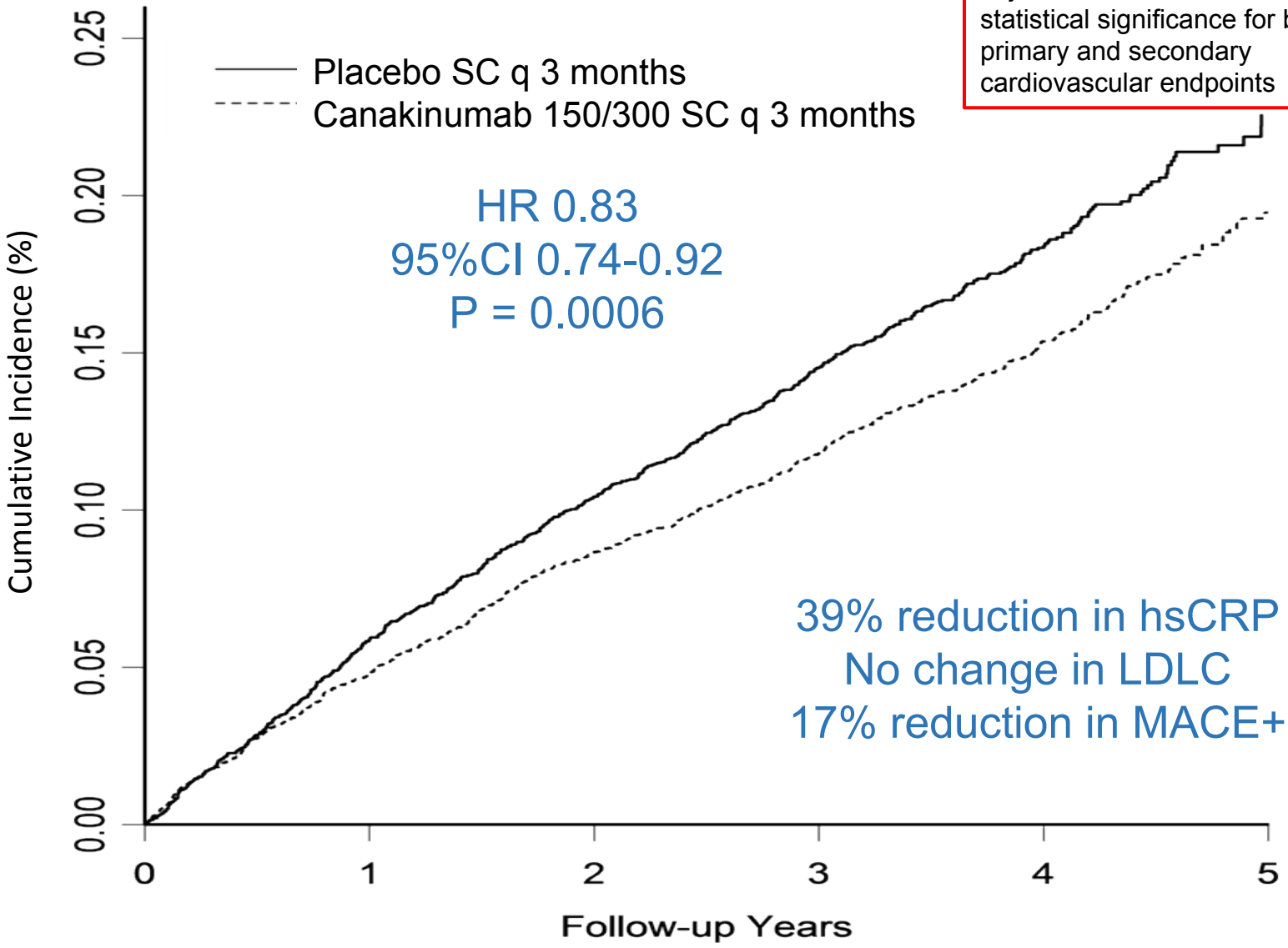
# CANTOS: Key Secondary Cardiovascular Endpoint (MACE+)

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

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# CANTOS: Consistency of HRs Across All Cardiovascular Endpoints

| | | Canakinumab SC q 3 months | | | |
|---|---|---|---|---|---|
| Endpoint | Placebo (N=3347) | 50 mg (N=2170) | 150 mg (N=2284) | 300 mg (N=2263) | P-trend |
| 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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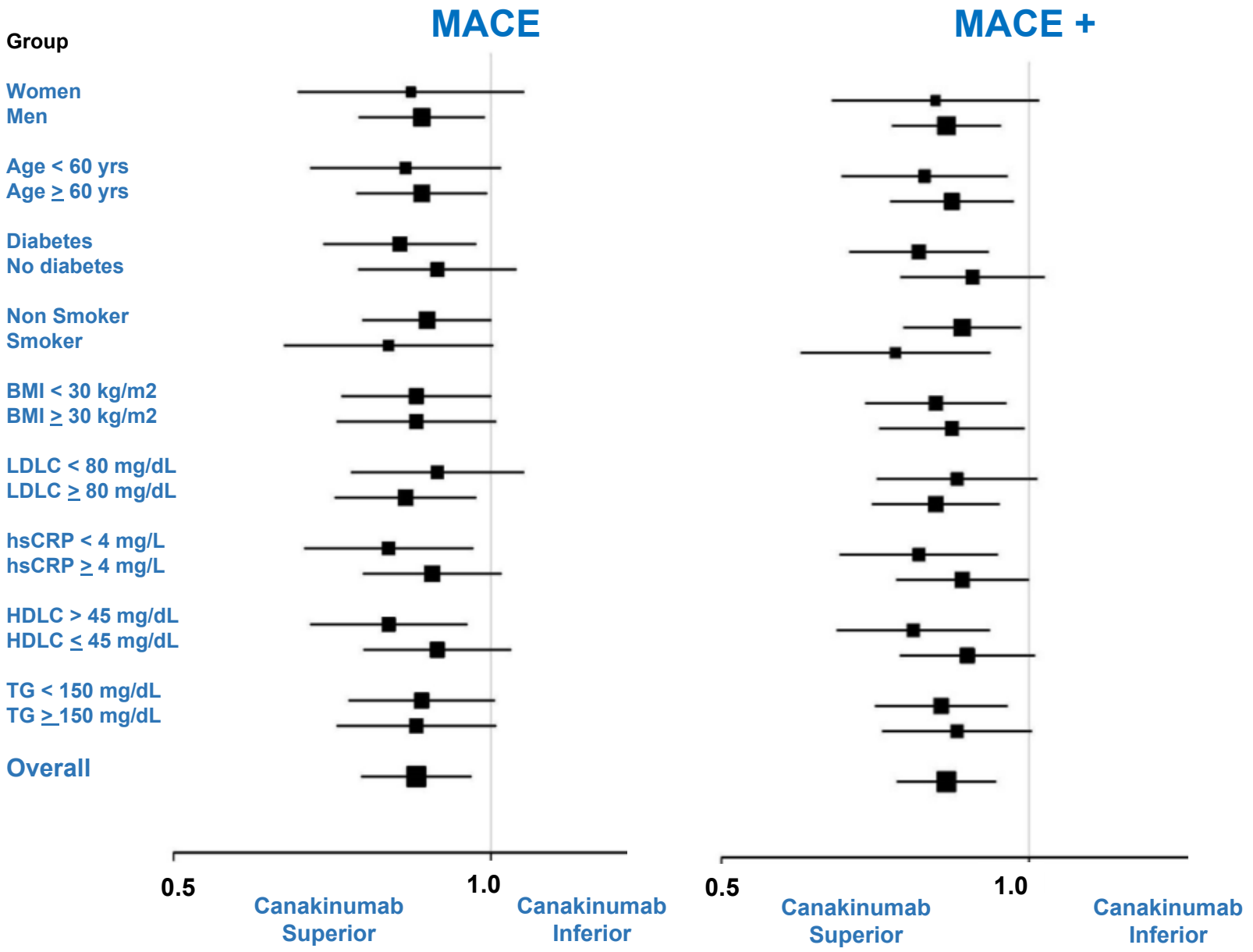
# CANTOS: Consistency of Effect Across All Patient Groups

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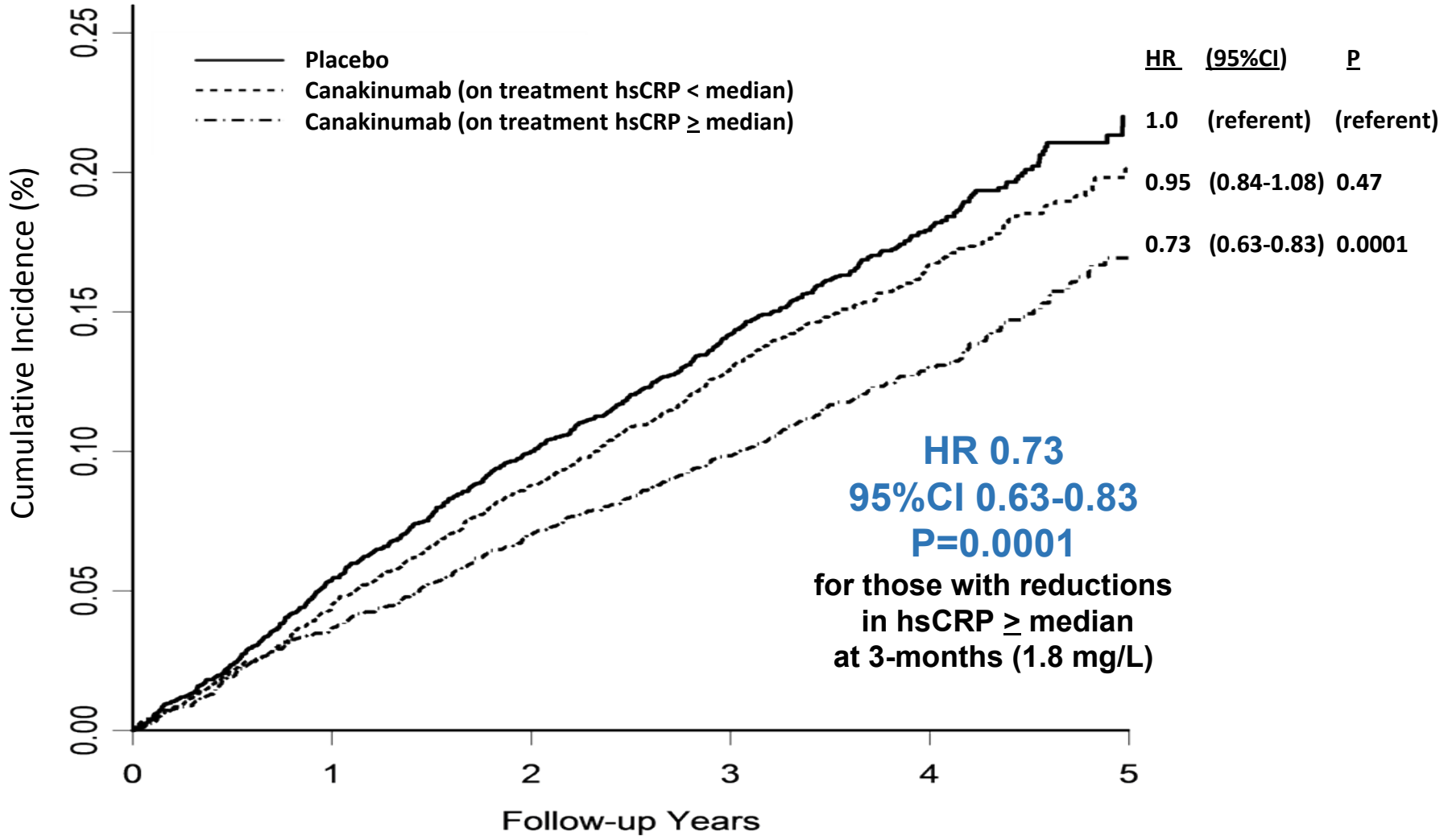
# CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)

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# 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

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# Conclusions:

## The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

1. CANTOS was designed to directly test the inflammatory hypothesis of atherothrombosis.

2. As shown in these data, inhibition of IL-1β with SC canakinumab given once every three months among patients with a prior myocardial infarction substantially lowered the inflammatory biomarkers hsCRP and IL-6 while having no beneficial impact on atherogenic lipids.

3. Concordantly, while the 50 mg dose of canakinumab did not have cardiovascular efficacy compared to placebo during an average follow-up period of 3.7 years, hazard reductions of 15% for the primary endpoint of MACE (P=0.007) and 17% for the secondary endpoint of MACE+ (P=0.006) were observed for the combined 150mg and 300mg doses groups. The 150mg group met all pre-specified multiplicity adjusted thresholds for statistical significance for both the primary and secondary cardiovascular outcomes.

# Conclusions:

## The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

4. In exploratory analyses, relative hazard reductions of 27% (P<0.001) were observed among those with the lowest levels of on-treatment hsCRP measured at 3 months. Thus, “lower is better” appears to be true for inflammation as well as LDLC .

5. Given mild neutropenia and an increase in risk of fatal infection, patients being considered for treatment with canakinumab will require monitoring for early signs and symptoms of infection in a manner similar to that currently done for individuals taking other biologic anti-inflammatory agents.

6. Placebo event rates in CANTOS were high, approaching 25% at five years. These data thus affirm that statin-treated patients with “**residual inflammatory risk**” as assessed by baseline hsCRP ≥2 mg/L have future event rates as high, if not higher, than statin-treated patients with “**residual cholesterol risk**”. These two patient groups differ substantially and require different personalized approaches to treatment.

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# Conclusions:

## The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

7. Inflammation is also a determinant of invasiveness, progression, and metastasis for certain cancers. In exploratory analyses within CANTOS, those allocated to canakinumab had large dose-dependent relative risk reductions in deaths due to cancer (P=0.0007), incident lung cancers (P<0.0001), and fatal lung cancer (P=0.0002) such that those in the canakinumab 300mg group had a 50 percent reduction in cancer fatality (P=0.0009). Replication of these data is required.

8. In conclusion, these randomized placebo-controlled trial data demonstrate that targeting the IL-1β to IL-6 pathway of innate immunity with canakinumab reduces cardiovascular event rates and potentially reduces rates of incident lung cancer and lung cancer mortality. These data provide proof that inflammation inhibition, in the absence of lipid lowering, can improve atherothrombotic outcomes and potentially alter the progression of some fatal cancers.