

## Anti-Inflammatory Therapy with Canakinumab for the Prevention and Management of Diabetes

A Pre-Specified Secondary Endpoint from the Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)

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on behalf of the worldwide investigators and participants in the  
Canakinumab **Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)**

# IL-1 $\beta$ Inhibition and Type 2 Diabetes

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- Observational and experimental data support a pathologic role for subclinical inflammation in both insulin resistance and impaired insulin production and the development of type 2 diabetes
- Cellular and animal experiments suggest prolonged hyperglycemia and amyloid deposition in pancreatic islet cells lead to induction of the NLRP3 inflammasome and activation of IL-1 $\beta$  in pancreatic islet cells
- A randomized trial of anakinra, an IL-1 receptor antagonist, showed improvements in beta cell function and peripheral glucose sensitivity, as well as reductions in HbA1c, in a randomized trial in 70 patients with established type 2 diabetes (Larsen NEJM 2007)

# Aims

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- We tested the effects of canakinumab on major cardiovascular events in patients with and without diabetes at baseline
- We tested whether baseline concentrations of hsCRP and IL-6 associate with new onset diabetes in patients without diabetes at baseline
- We evaluated the effect of canakinumab on HbA1c in patients with and without established diabetes.
- In a protocol pre-specified secondary analysis, we tested whether canakinumab would reduce the risk of adjudicated cases of new onset type 2 diabetes among those with protocol-defined pre-diabetes at trial entry.

# Definitions Pre-Diabetes and New Onset Diabetes

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- Baseline pre-diabetes
  - HbA1c of 5.7 to <6.5% at screening or randomization OR
  - Fasting plasma glucose of 100 to 125 mg/dL (5.6-6.9 mmol/L) at screening or randomization
- New onset diabetes
  - HbA1c  $\geq$  6.5% on two occasions within 6 weeks of one another OR
  - Fasting plasma glucose  $\geq$ 126 mg/dL on two occasions within 6 weeks of one another OR
  - A combination of an elevated HbA1c or fasting plasma glucose within 6 weeks OR
  - A new prescription of an anti-diabetic medication
- Centrally adjudicated by endocrinologists who were blinded to study drug allocation.

# Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS)



**Stable CAD (post MI)  
Residual Inflammatory Risk  
(hsCRP  $\geq$  2 mg/L)**

**N = 10,061  
39 Countries  
April 2011 - June 2017  
1490 Primary Events**

**Randomized  
Canakinumab 50 mg  
SC q 3 months**

**Randomized  
Canakinumab 150 mg  
SC q 3 months**

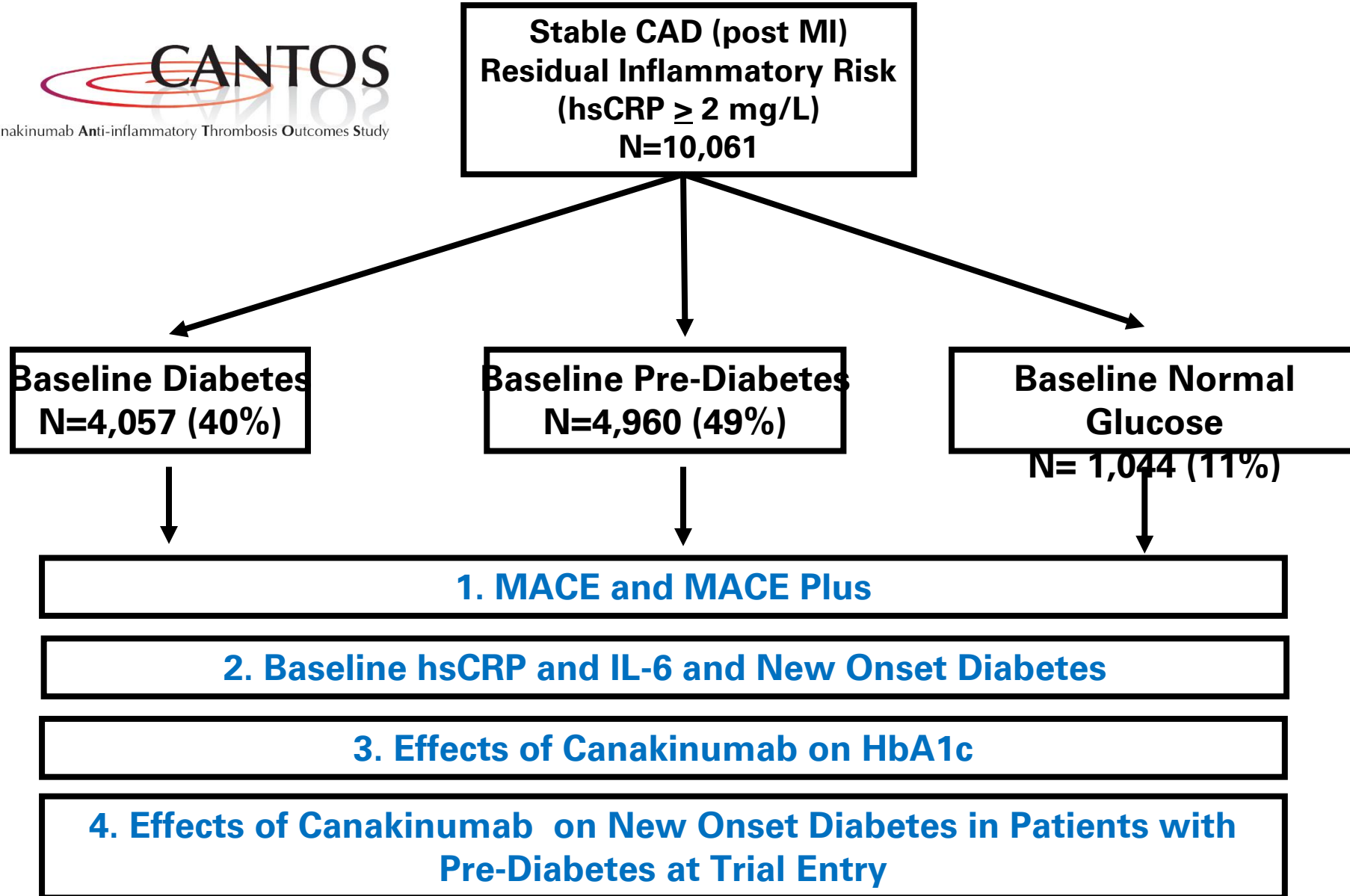
**Randomized  
Canakinumab 300 mg  
SC q 3 months**

**Randomized  
Placebo  
SC q 3 months**

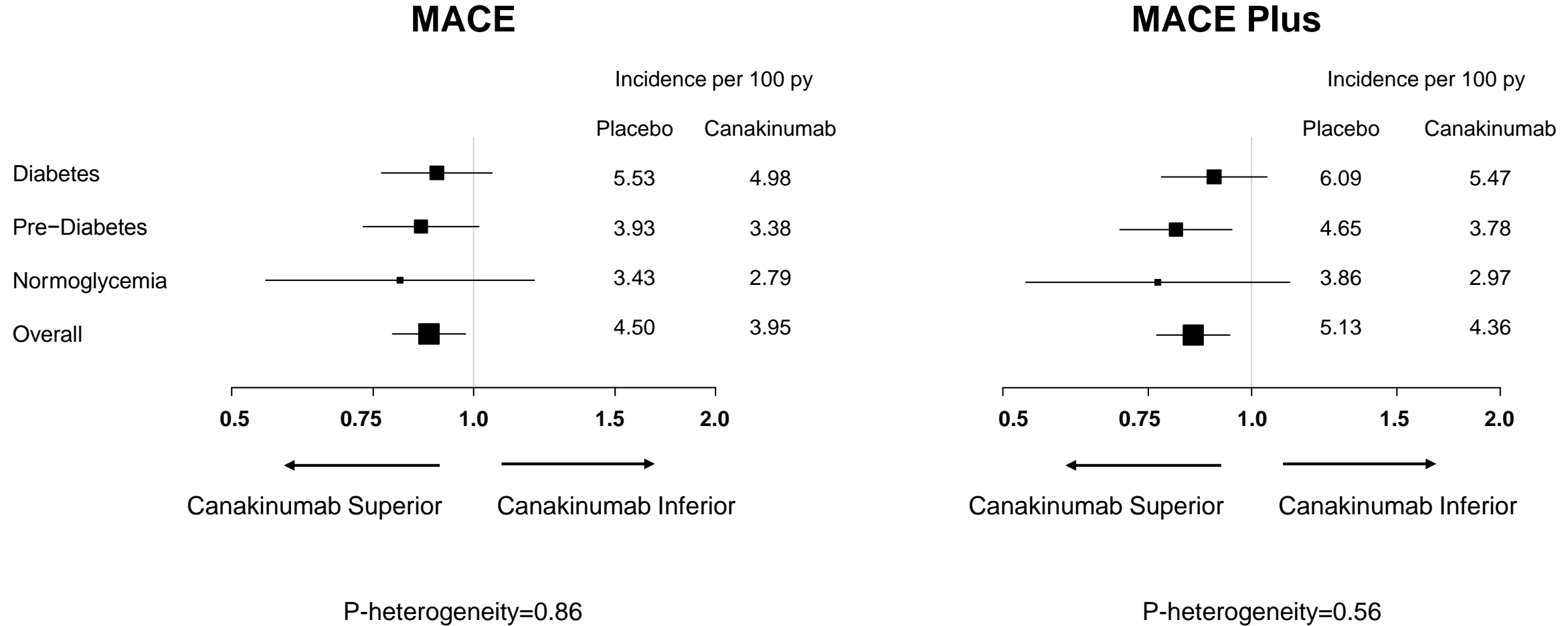
**Primary Cardiovascular Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)  
Secondary Cardiovascular Endpoint: MACE plus Unstable Angina Requiring Urgent Revascularization (MACE+)**

**Pre-Specified Secondary Endpoint: New Onset Diabetes among Patients with Protocol-Defined Pre-Diabetes at Trial Entry**

# New Onset Diabetes in CANTOS

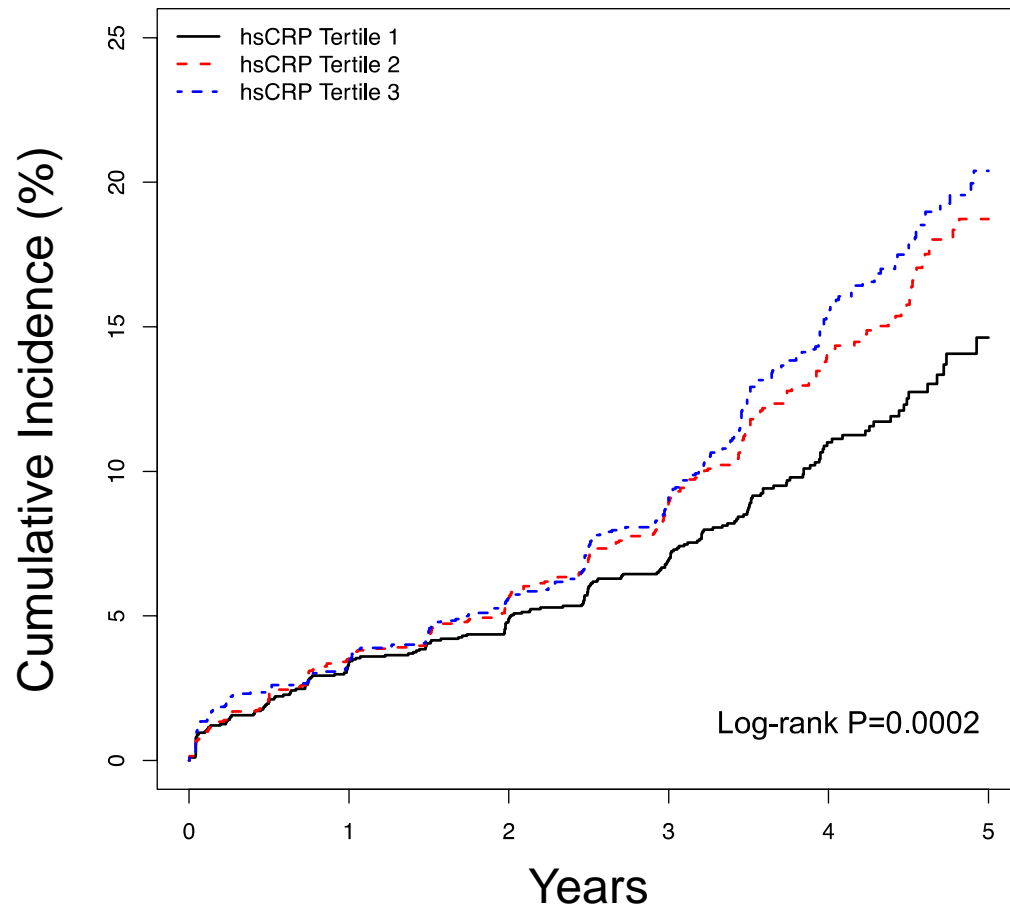


# Effects of Canakinumab on MACE and MACE Plus Among Those With and Without Diabetes at Study Entry

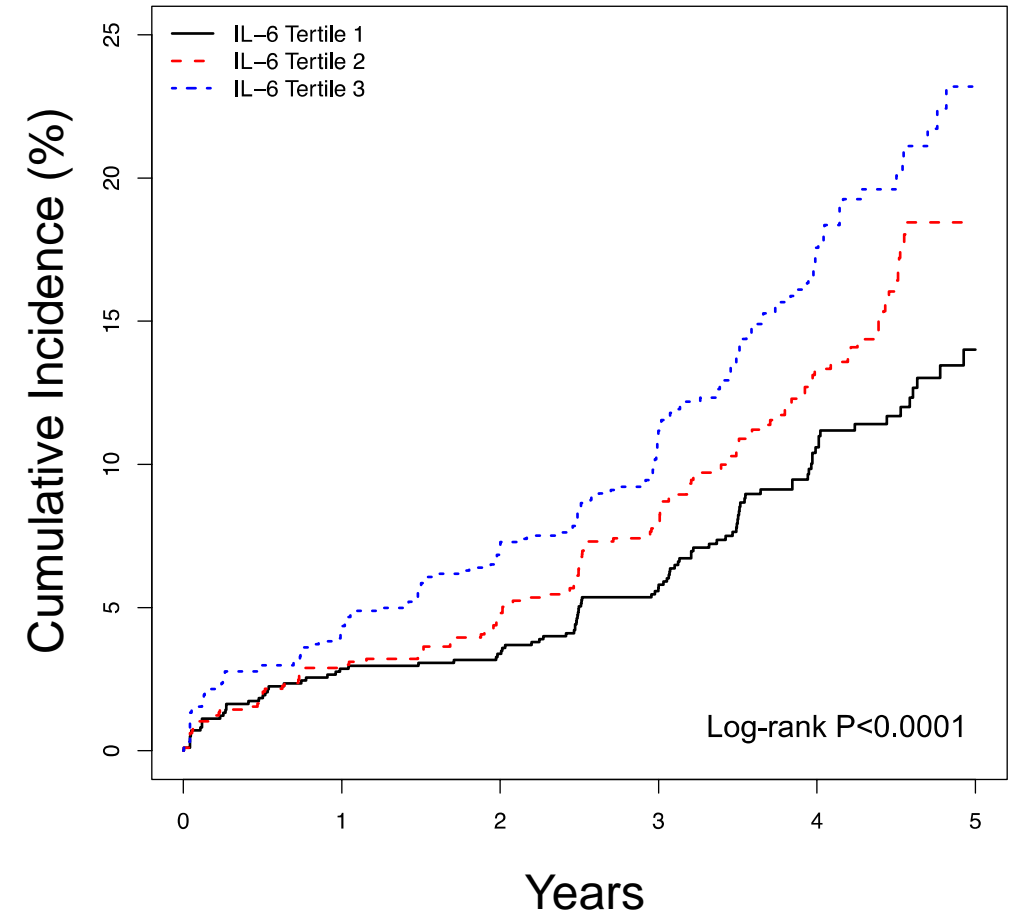


# Baseline hsCRP and IL-6 and Incident Diabetes in CANTOS

hsCRP and Incident Type 2 Diabetes



IL-6 and Incident Type 2 Diabetes



Both hsCRP and IL-6 remained statistically significant after multivariable adjustment. IL-6 remained significant after further adjustment for baseline HbA1c



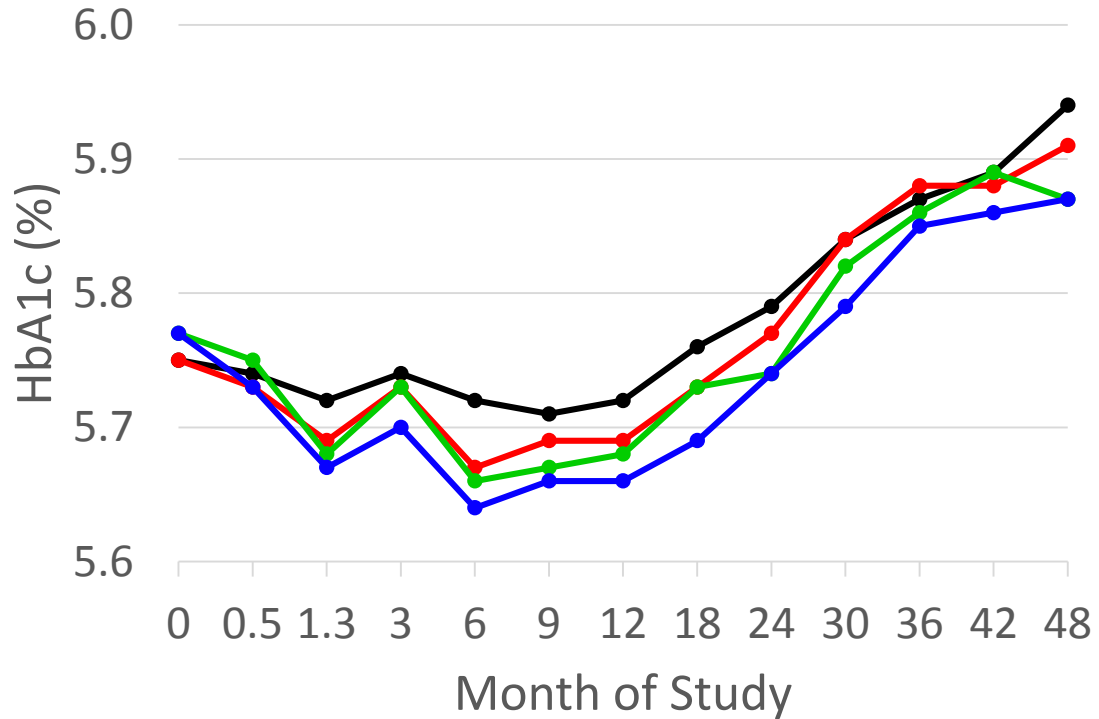
# Change in hsCRP and IL-6 after canakinumab in patients with pre-diabetes at baseline

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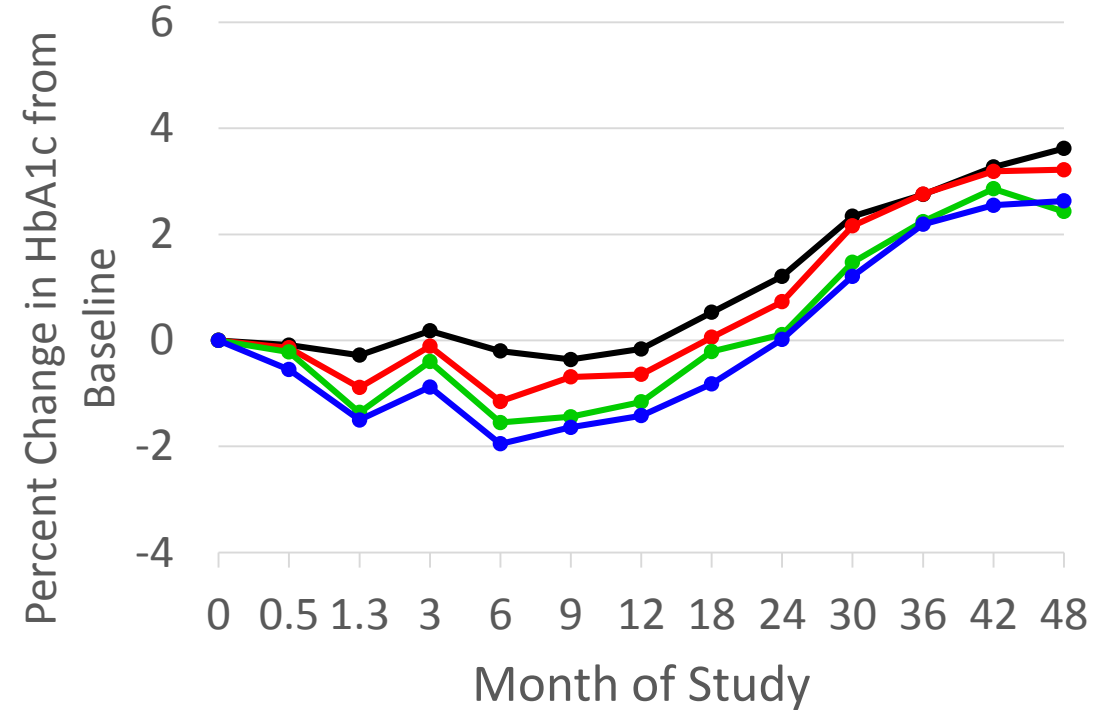
	Median Percent (IQR) Reduction Compared to Placebo	
Dose	hsCRP	IL-6
50 mg	-49.2 (-20.0, -67.2)	-25.7 (0.7, -46.6)
150 mg	-61.5 (-33.3, -75.8)	-37.4 (-9.1, -54.9)
300 mg	-67.1 (-43.2, -80.6)	-43.4 (-21.0, -60.0)

These reductions are similar to those observed in the CANTOS trial population as a whole

# HbA1c (%) and Percent Change in HbA1c from Baseline: Pre-diabetes

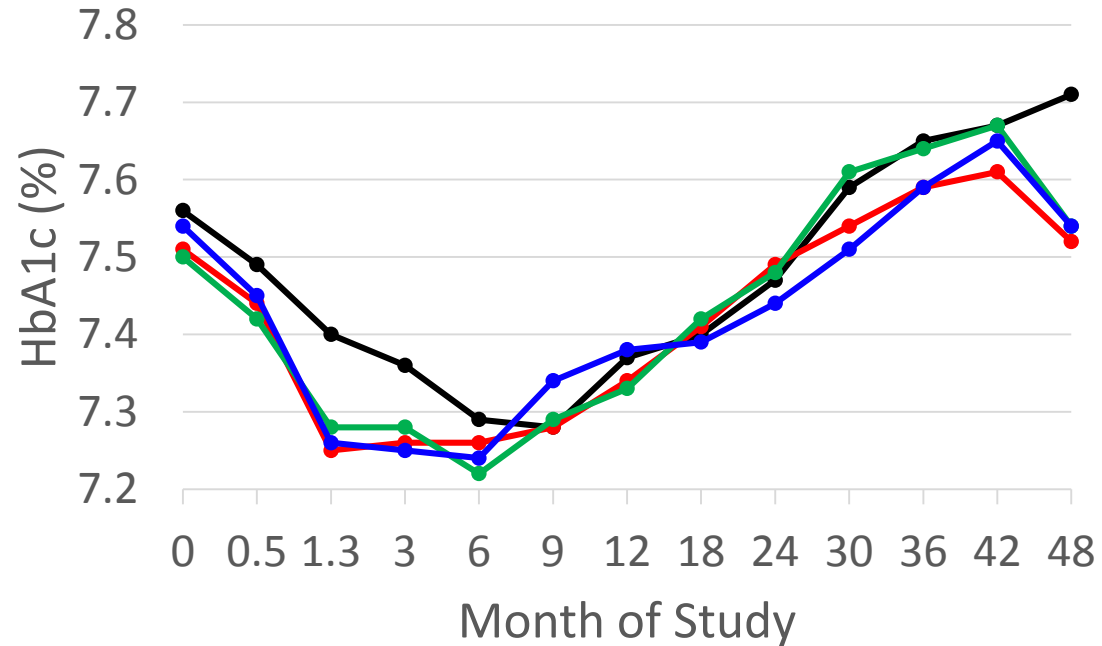


● Placebo ● 50mg ● 150mg ● 300mg

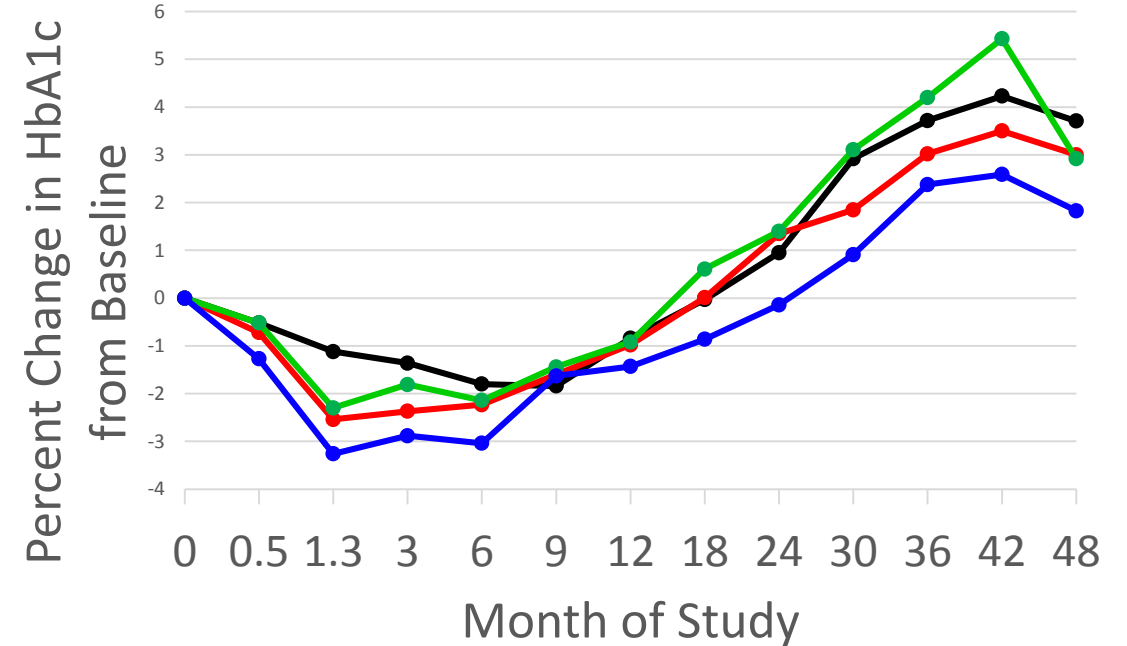


● Placebo ● 50mg ● 150mg ● 300mg  
P-value vs. placebo <0.0001 <0.0001 <0.0001

# HbA1c (%) and Percent Change in HbA1c from Baseline: Diabetes

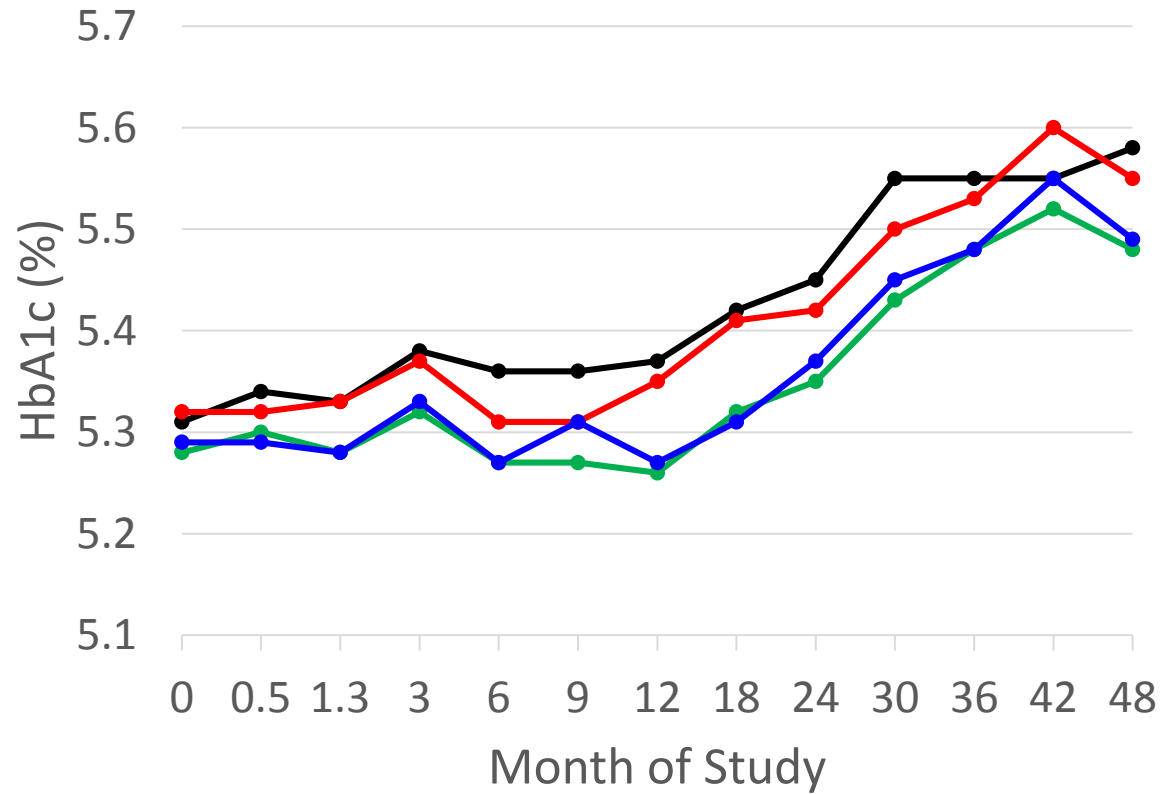


● Placebo ● 50mg ● 150mg ● 300mg

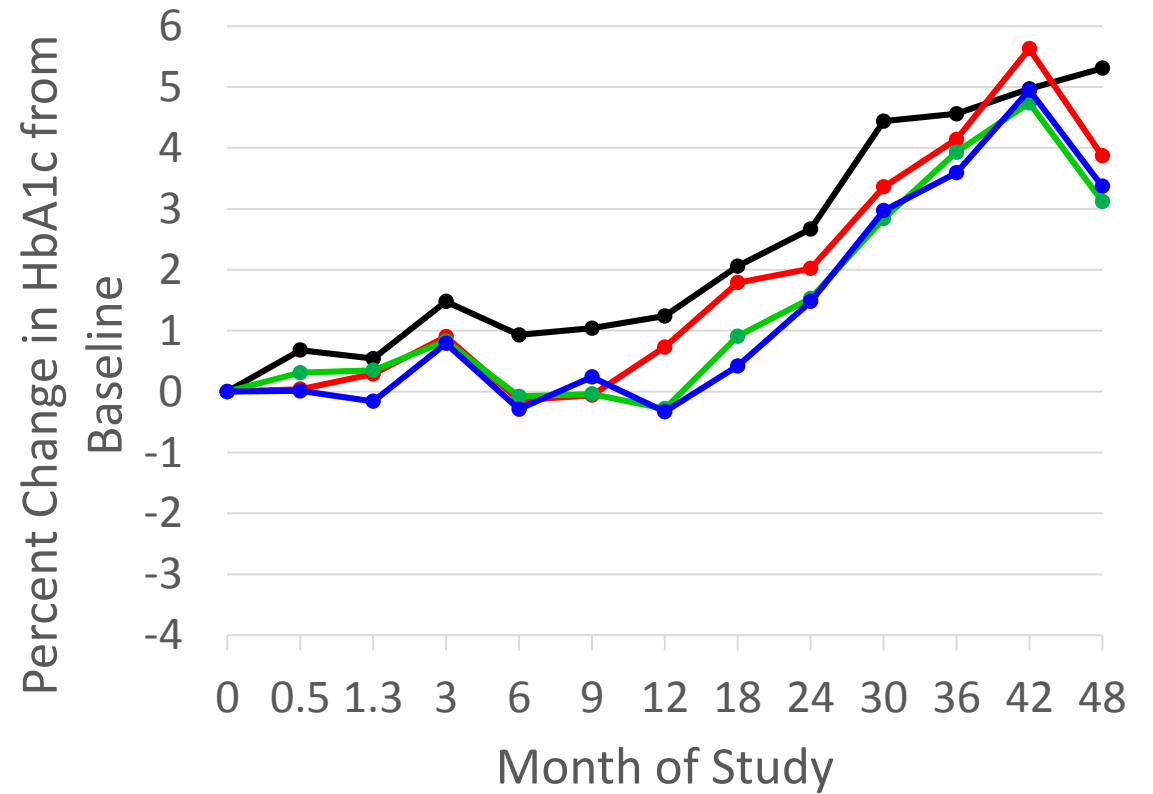


● Placebo ● 50mg ● 150mg ● 300mg  
P-value vs. placebo: 0.95, 0.92, 0.30

# HbA1c (%) and Percent Change in HbA1c from Baseline: Normal glucose



● Placebo ● 50mg ● 150mg ● 300mg

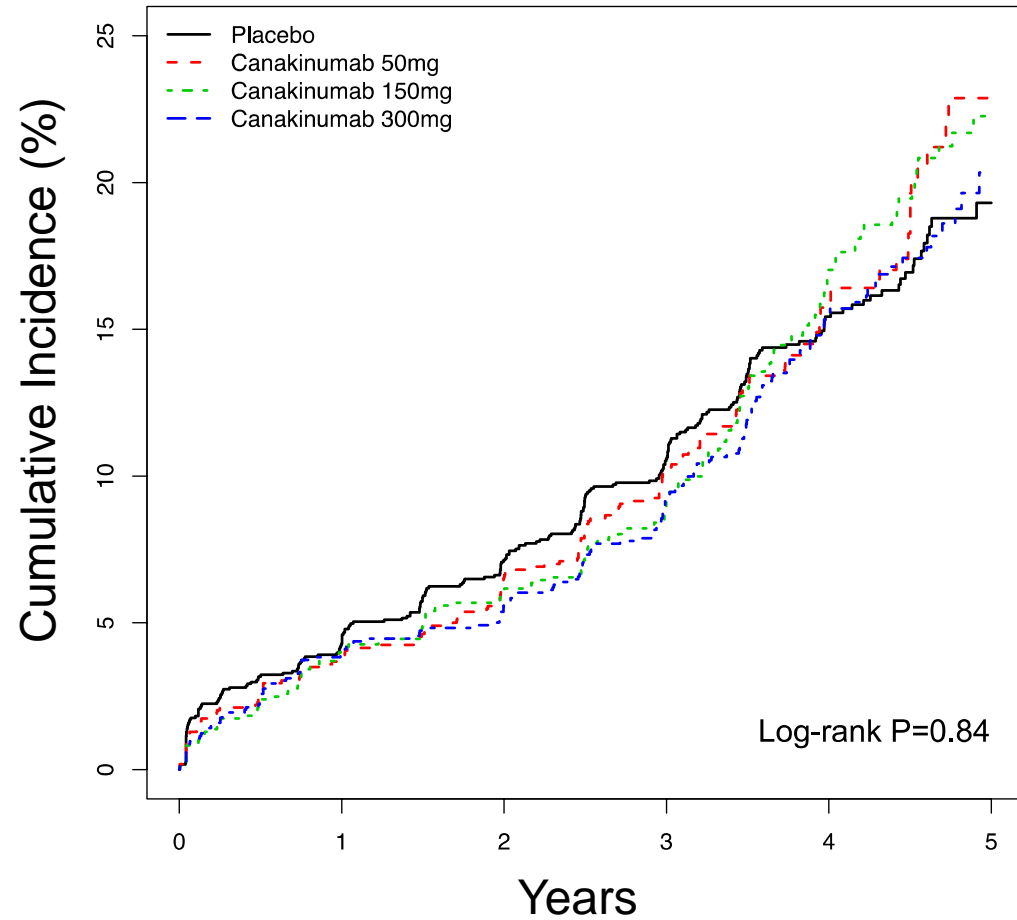


● Placebo ● 50mg ● 150mg ● 300mg

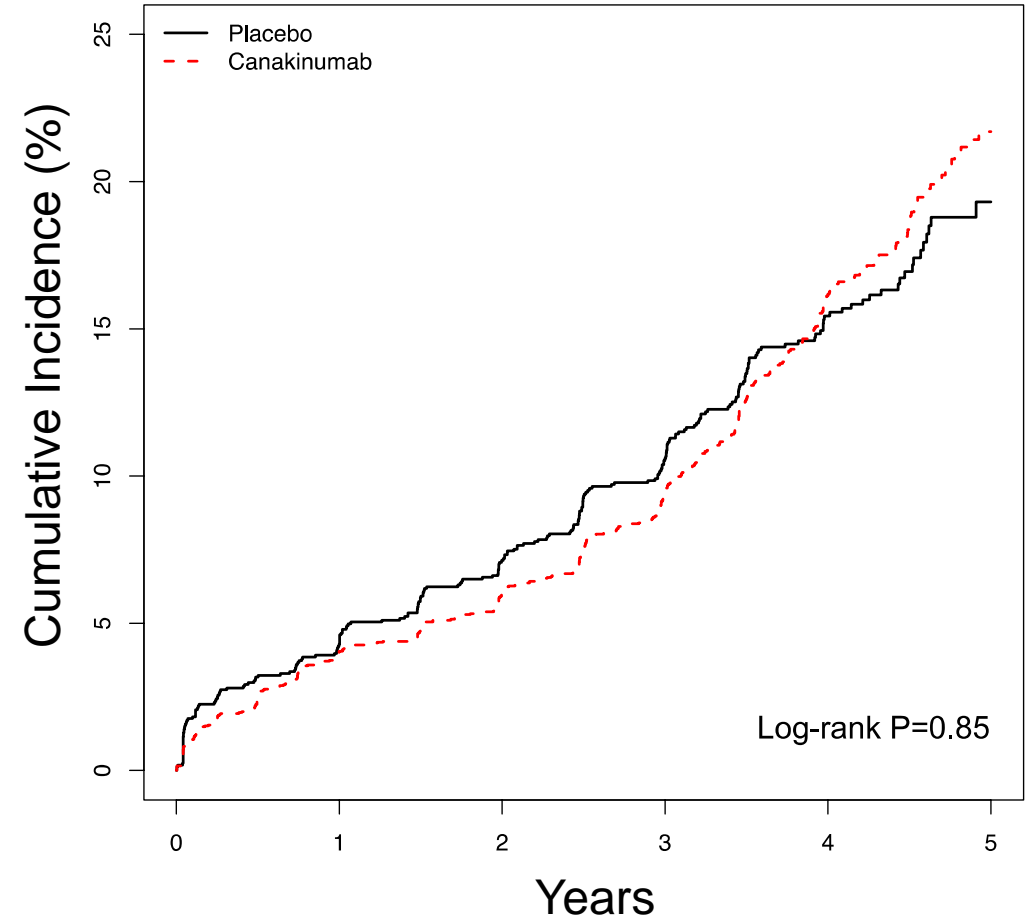
P-value vs. placebo      0.23      0.0002      0.0001

# Canakinumab and Incident Diabetes in Patients with Pre-Diabetes: CANTOS

Canakinumab and Incident Type 2 Diabetes



Canakinumab and Incident Type 2 Diabetes



## CANTOS: Incidence Rates and Effects of Canakinumab on New Onset Diabetes Among Those With Pre-Diabetes at Study Entry

		Canakinumab SC q 3 months			
	Placebo	50 mg	150 mg	300 mg	All Doses
<b>Adjudicated Diabetes</b>					
N Events/N at risk	246/1645	161/1089	171/1094	169/1132	501/3315
IR (per 100 person years)	4.20	4.24	4.35	4.12	4.23
HR (95% CI)	1.0	1.04 (0.85-1.27)	1.03 (0.85-1.26)	0.98 (0.80-1.19)	1.01 (0.87-1.18)
P	(referent)	0.70	0.75	0.80	0.86
<b>All Physician Reported Diabetes</b>					
N Events/N at risk	279/1645	186/1089	191/1094	190/1132	567/3315
IR (per 100 person years)	4.84	4.97	4.92	4.68	4.85
HR (95%CI)	1.0	1.06 (0.88-1.27)	1.02 (0.84-1.22)	0.97 (0.80-1.16)	1.01 (0.88-1.17)
P	(referent)	0.56	0.88	0.70	0.89

## Conclusions: CANTOS Diabetes

### The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

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- Interleukin-1 $\beta$  inhibition with canakinumab reduces major adverse cardiovascular event rates among high-risk atherosclerosis patients with diabetes and pre-diabetes, as well as among those with normoglycemia
- Our data confirm that baseline concentrations of the inflammatory biomarkers hsCRP and IL-6 predict the onset of type 2 diabetes in CANTOS

## Conclusions: CANTOS Diabetes

### The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

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- Interleukin-1 $\beta$  inhibition with canakinumab reduces HbA1c in patients with pre-diabetes for approximately 9-12 months, but effects were attenuated over time
- Canakinumab does not prevent the progression from pre-diabetes to diabetes among patients with prior myocardial infarction and hsCRP  $\geq 2$  mg/L



# Accepted Manuscript

Anti-Inflammatory Therapy with Canakinumab for the Prevention and Management of Diabetes

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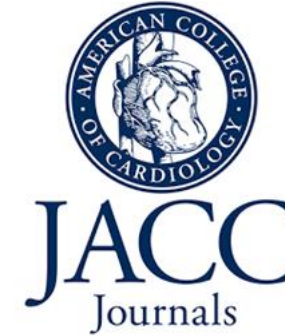
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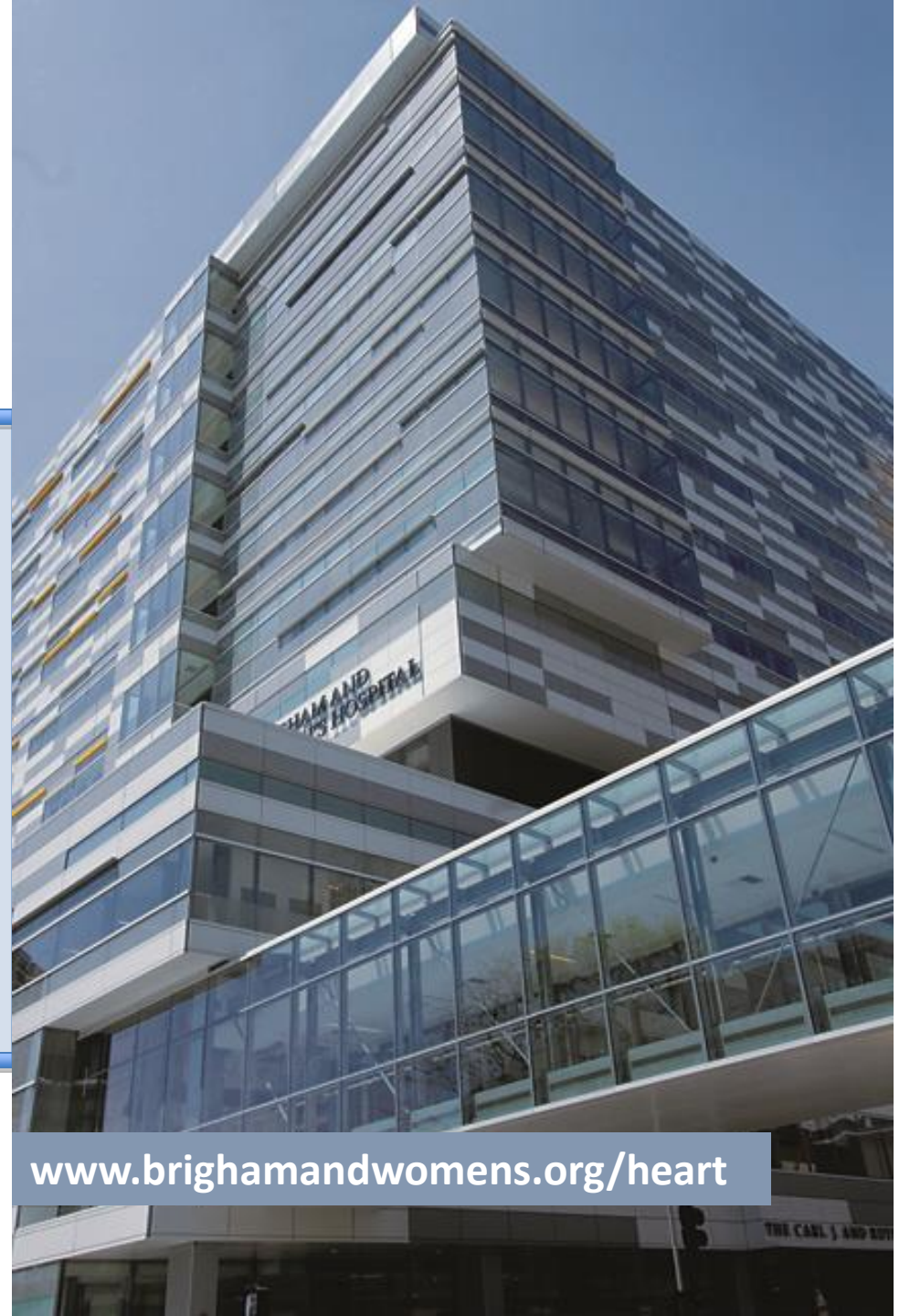
***Thank you!***

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