

**AHA Scientific Sessions
November 13, 2017**

Discussion of CANTOS

**"Relationship of CRP Reduction to Cardiovascular Event
Reduction Following Treatment with Canakinumab"**

**Ira Tabas, M.D., Ph.D.
Richard J. Stock Professor of Medicine,
Cell Biology, and Physiology
iat1@columbia.edu**

Atherosclerotic Cardiovascular Disease (CVD)

circulating
apoB-lipoproteins
(LDL, remnant lipoproteins)



Subendothelial apoB-lipoproteins

Atherosclerotic Cardiovascular Disease (CVD)

circulating
apoB-lipoproteins
(LDL, remnant lipoproteins)



Subendothelial apoB-lipoproteins

Disturbed blood flow

Genetic factors

Systemic risk factors
(smoking, diabetes, etc.)

Age/clonal hematopoiesis



Inflammation

Defective resolution of inflammation

Atherosclerotic Cardiovascular Disease (CVD)

circulating
apoB-lipoproteins
(LDL, remnant lipoproteins)



Subendothelial apoB-lipoproteins

Disturbed blood flow

Genetic factors

Systemic risk factors
(smoking, diabetes, etc.)

Age/clonal hematopoiesis



Inflammation

Defective resolution of inflammation



Atherosclerosis



CVD

Proven Therapeutic Approach

~~circulating
apoB-lipoproteins
(LDL, remnant lipoproteins)~~

↓ **Subendothelial apoB-lipoproteins**

Disturbed blood flow

Genetic factors

**Systemic risk factors
(smoking, diabetes, etc.)**

Age/clonal hematopoiesis

↓ **Inflammation**

↓ **Defective resolution of inflammation**

↓ **Atherosclerosis**

↓ **CVD**

Highly Intensive LDL Lowering in Highest Risk Patients

~~circulating apoB-lipoproteins (LDL remnant lipoproteins)~~

↓↓ **Subendothelial apoB-lipoproteins**

Disturbed blood flow

Genetic factors

**Systemic risk factors
(smoking, diabetes, etc.)**

Age/clonal hematopoiesis

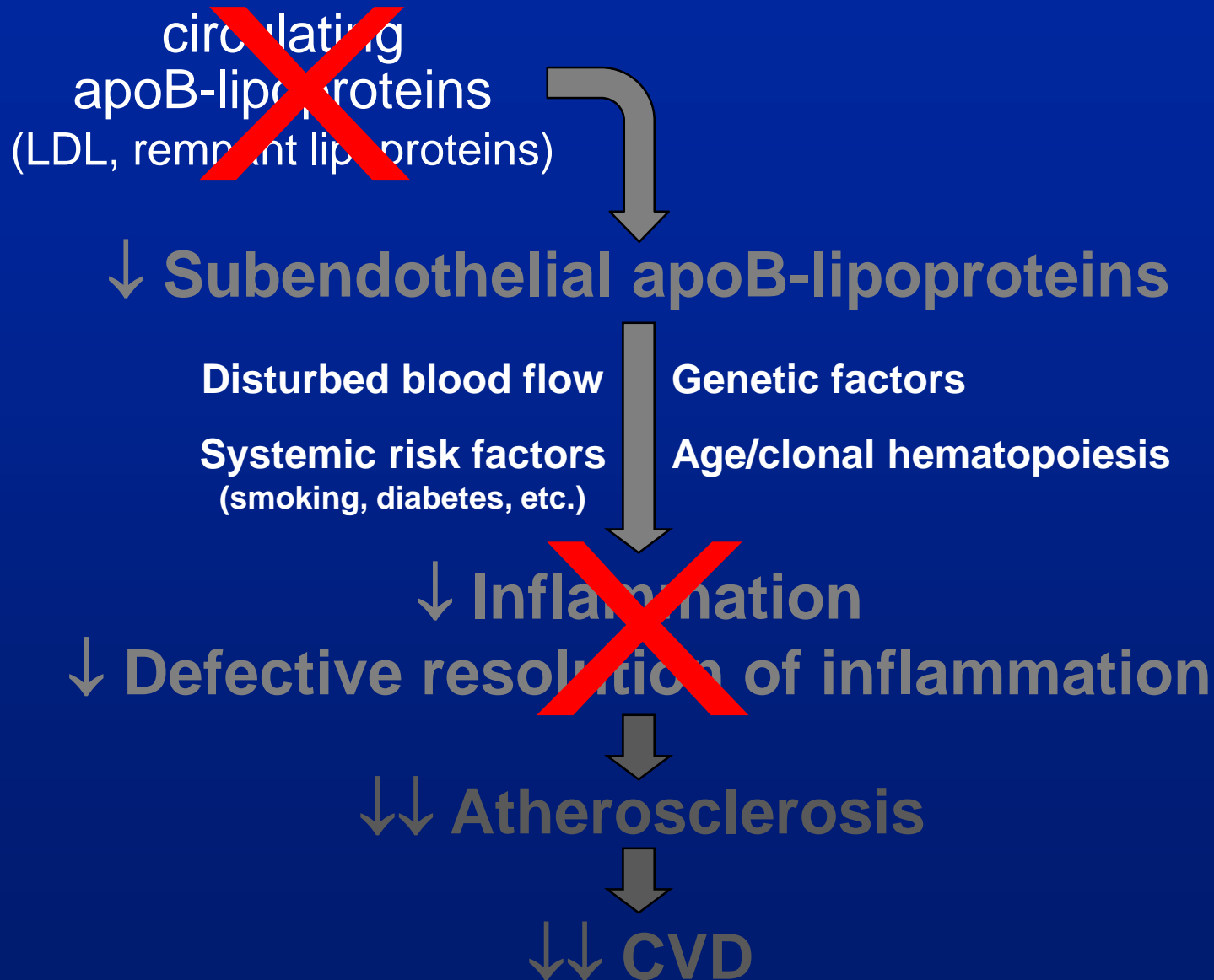
↓↓ **Inflammation**

↓↓ **Defective resolution of inflammation**

↓↓ **Atherosclerosis**

↓↓ **CVD**

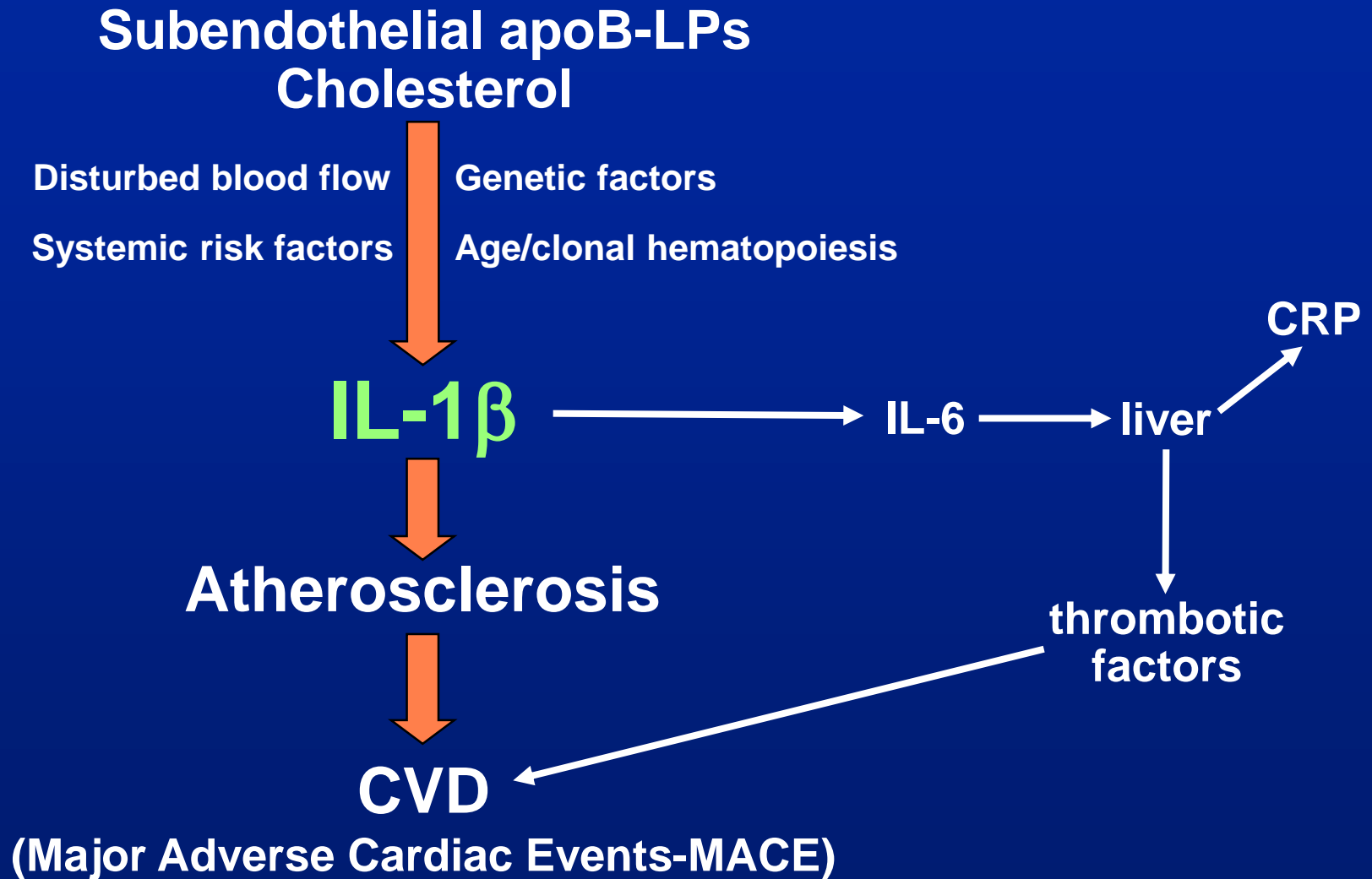
Unproven Therapeutic Hypothesis



Key Issues About Targeting Inflammation

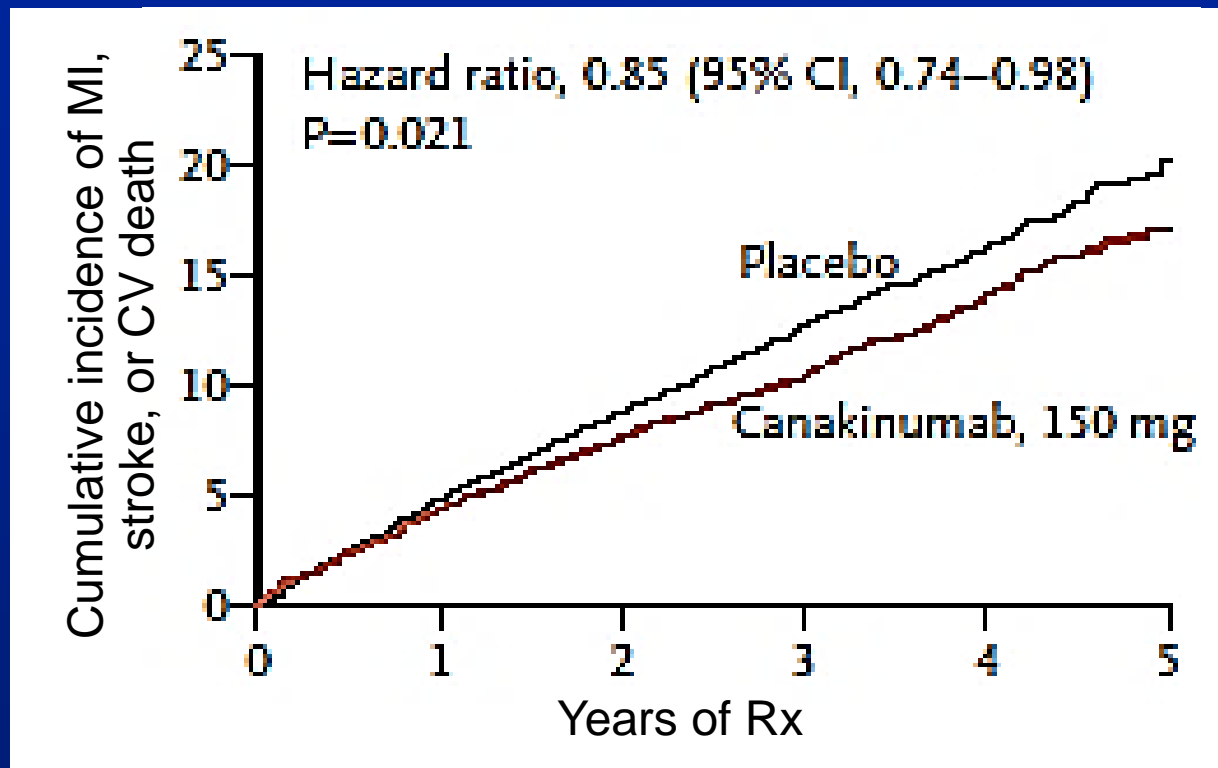
- Is there a *dominant* inflammatory factor?
- Will *compensatory* responses to anti-inflammation therapy prevent efficacy?
- Will compromise of *host defense* cause unacceptable adverse events?

The Premise of CANTOS



CANTOS

Anti-IL-1 β Therapy of High-Risk Subjects



CANTOS

A Landmark Study

- Conceptual advance: inflammation, importance of IL-1 β in atherosclerotic CVD
- Future promise of targeting inflammation to combat CVD

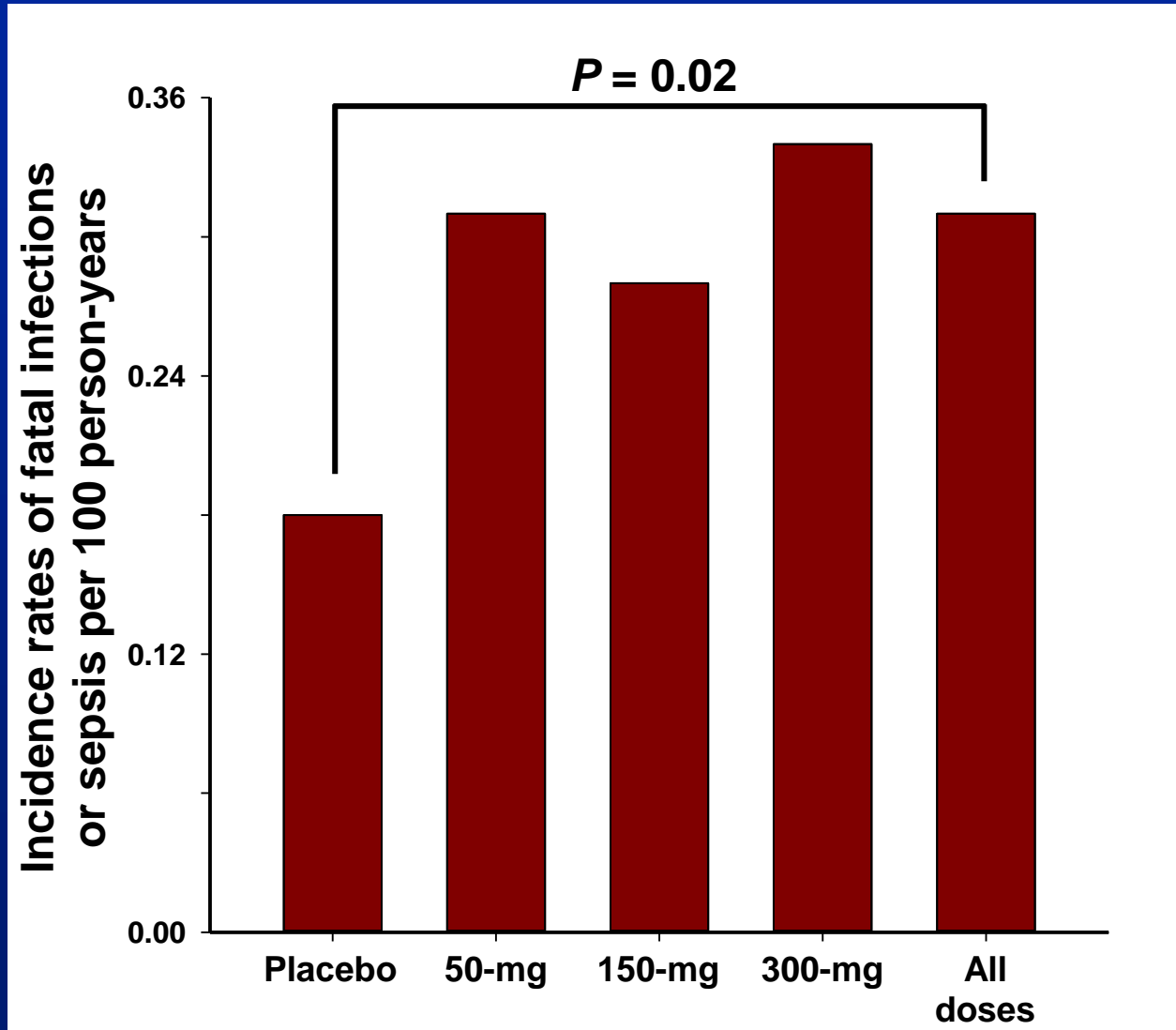
CANTOS

Issues Arising From the Original Analysis

- Dose effect
- Host defense
- ? Similar benefit by lowering LDL further ?
- Cardiovascular mortality
- Is benefit related to level of inflammation suppression

Host Defense

Fatal Infections or Sepsis



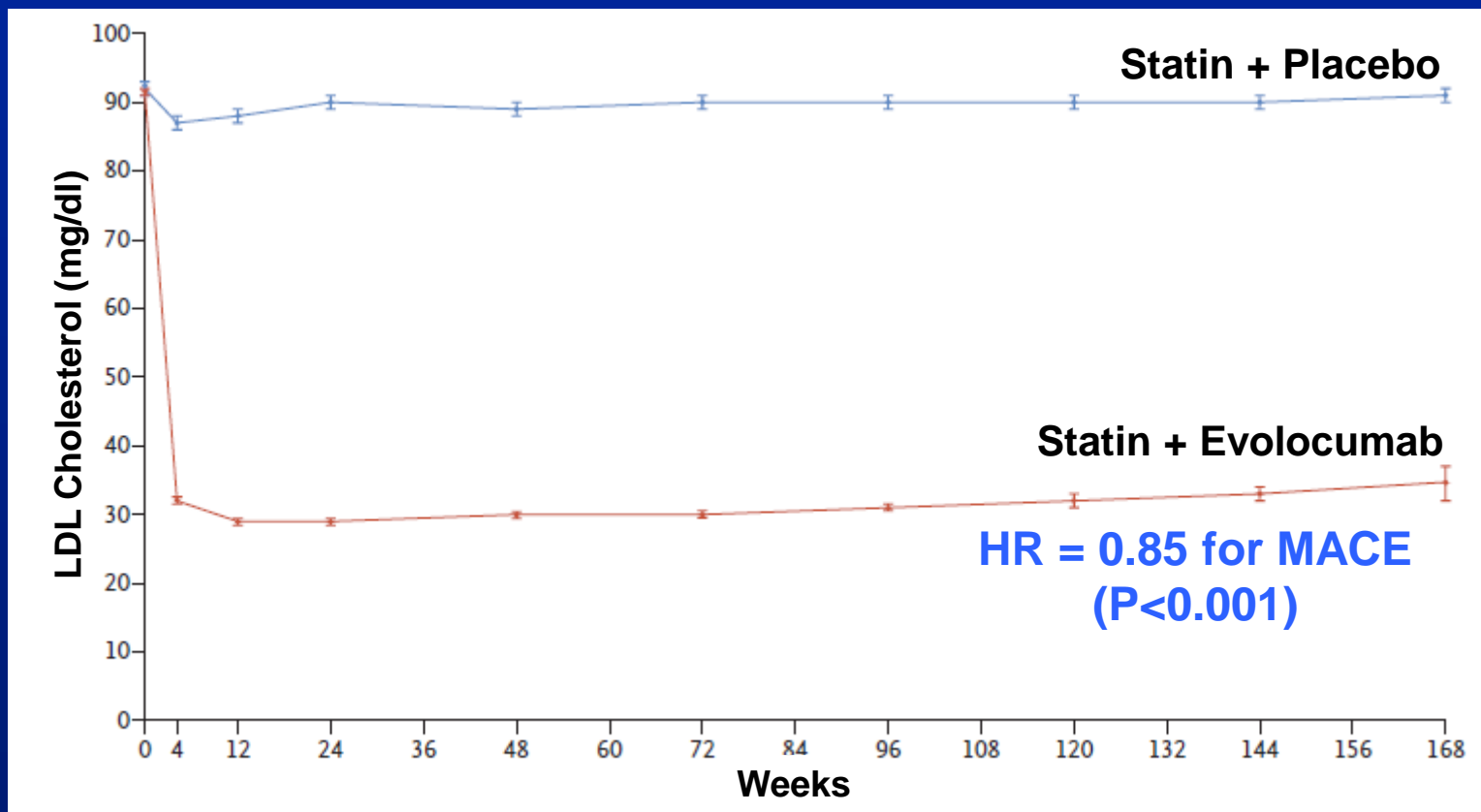
CANTOS

Issues Arising From the Original Analysis

- Dose effect
- Host defense
- ? Similar benefit by lowering LDL further ?
- Cardiovascular mortality
- Is benefit related to level of inflammation suppression

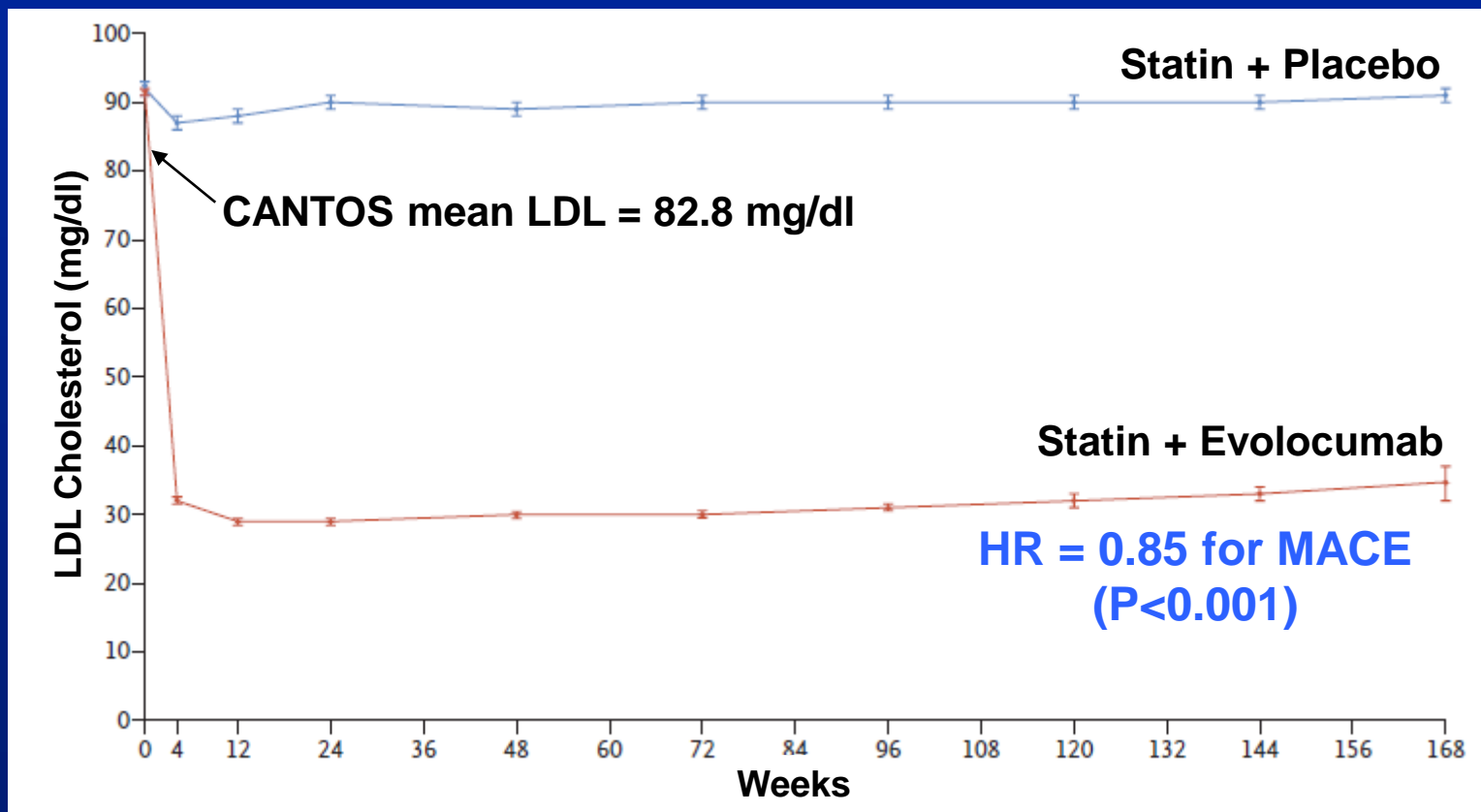
? Room to Move in Lowering LDL ?

FOURIER



? Room to Move in Lowering LDL ?

FOURIER



CANTOS

Issues Arising From the Original Analysis

- Dose effect
- Host defense
- ? Similar benefit by lowering LDL further ?
- Cardiovascular mortality
- Is benefit related to level of inflammation suppression

CANTOS: CRP-Response Subgroup Analysis

Implications

- Strengthens biological premise
- Addresses issues of concern from original analysis
 - Greater MACE effect in responders with all 3 doses
 - Reduced CV and all-cause mortality in responders
- Fatal infections were similar among responders and non-responders
 - Potential for higher benefit:risk ratio in responders
 - ? Mechanism ?
- Hypothesis-generating for future prospective studies using a targeted approach

CANTOS: CRP-Response Subgroup Analysis

Implications

- Strengthens biological premise
- Addresses issues of concern from original analysis
 - Greater MACE effect in responders with all 3 doses
 - Reduced CV and all-cause mortality in responders
- Fatal infections were similar among responders and non-responders
 - Potential for higher benefit:risk ratio in responders
 - ? Mechanism ?
- Hypothesis-generating for future prospective studies using a targeted approach

CANTOS: CRP-Response Subgroup Analysis

Implications

- Strengthens biological premise
- Addresses issues of concern from original analysis
 - Greater MACE effect in responders with all 3 doses
 - Reduced CV and all-cause mortality in responders
- Fatal infections were similar among responders and non-responders
 - Potential for higher benefit:risk ratio in responders
 - ? Mechanism ?
- Hypothesis-generating for future prospective studies using a targeted approach

CANTOS: CRP-Response Subgroup Analysis

Implications

- Strengthens biological premise
- Addresses issues of concern from original analysis
 - Greater MACE effect in responders with all 3 doses
 - Reduced CV and all-cause mortality in responders
- Fatal infections were similar among responders and non-responders
 - Potential for higher benefit:risk ratio in responders
 - ? Mechanism ?
- Hypothesis-generating for future prospective studies using a targeted approach

Where do we go from here?

- Further prospective testing of anti-inflammatory Rx
 - Optimize efficacy and minimize adverse effects via targeted approach and infectious disease monitoring
 - Optimize route of delivery and lower cost, *e.g.*, oral inflammasome inhibitors
 - ? Use in primary prevention in select subjects
 - Integration with intense LDL lowering
- Integration with drugs for diabetes that show a CV-protective effect (SGLT2 inhibitors, liraglutide)
- Drugs that enhance resolution of inflammation

Where do we go from here?

- Further prospective testing of anti-inflammatory Rx
 - Optimize efficacy and minimize adverse effects via targeted approach and infectious disease monitoring
 - Optimize route of delivery and lower cost, e.g., oral inflammasome inhibitors
 - ? Use in primary prevention in select subjects
 - Integration with intense LDL lowering
- Integration with drugs for diabetes that show a CV-protective effect (SGLT2 inhibitors, liraglutide)
- Drugs that enhance resolution of inflammation

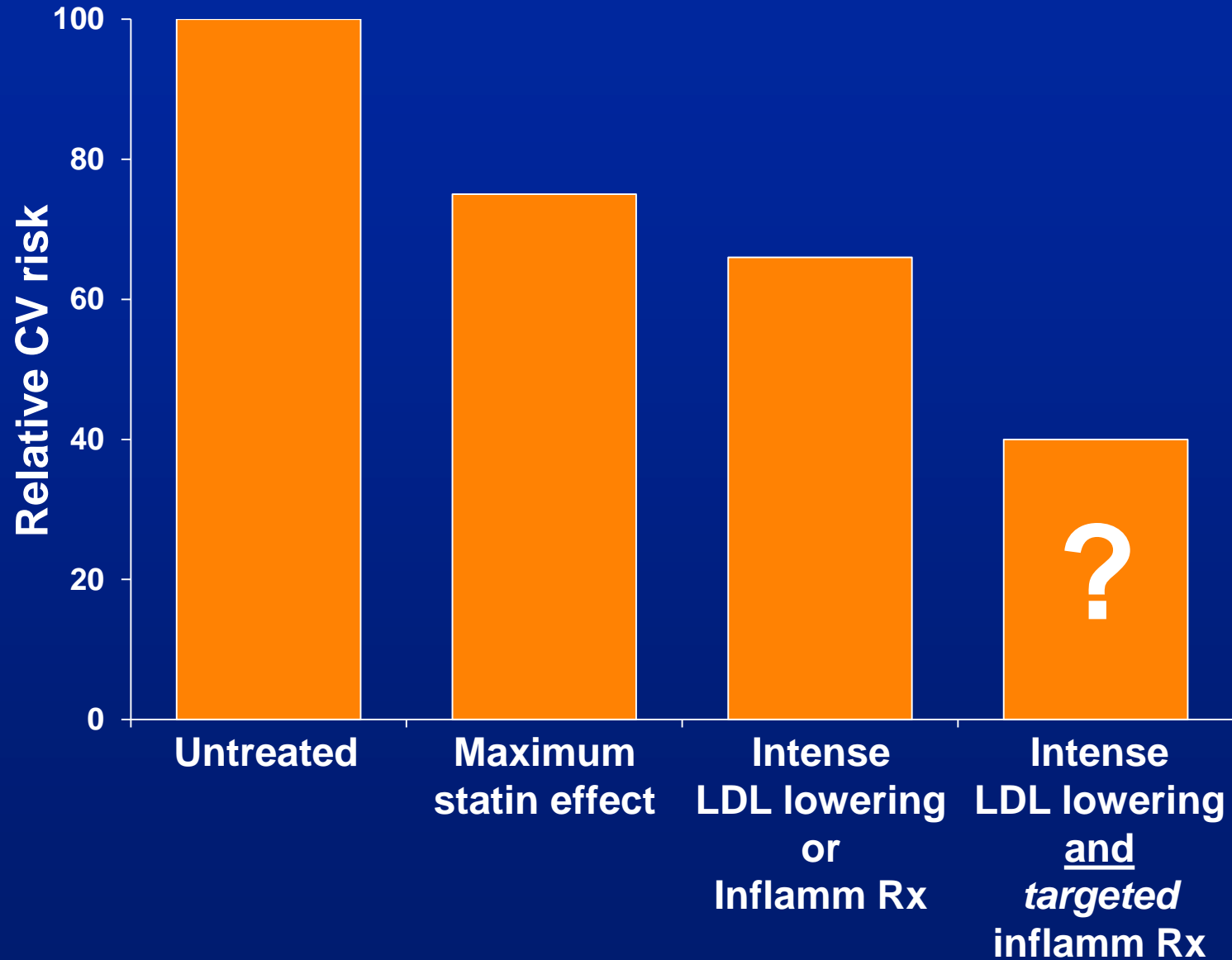
Where do we go from here?

- Further prospective testing of anti-inflammatory Rx
 - Optimize efficacy and minimize adverse effects via targeted approach and infectious disease monitoring
 - Optimize route of delivery and lower cost, e.g., oral inflammasome inhibitors
 - ? Use in primary prevention in select subjects
 - Integration with intense LDL lowering
- Integration with drugs for diabetes that show a CV-protective effect (SGLT2 inhibitors, liraglutide)
- Drugs that enhance resolution of inflammation

Where do we go from here?

- Further prospective testing of anti-inflammatory Rx
 - Optimize efficacy and minimize adverse effects via targeted approach and infectious disease monitoring
 - Optimize route of delivery and lower cost, e.g., oral inflammasome inhibitors
 - ? Use in primary prevention in select subjects
 - Integration with intense LDL lowering
- Integration with drugs for diabetes that show a CV-protective effect (SGLT2 inhibitors, liraglutide)
- Drugs that enhance resolution of inflammation

Treatment of High-Risk Patients



Where do we go from here?

- Further prospective testing of anti-inflammatory Rx
 - Optimize efficacy and minimize adverse effects via targeted approach and infectious disease monitoring
 - Optimize route of delivery and lower cost, *e.g.*, oral inflammasome inhibitors
 - ? Use in primary prevention in select subjects
 - Integration with intense LDL lowering
- Integration with drugs for diabetes that show a CV-protective effect (SGLT2 inhibitors, liraglutide)
- Drugs that enhance resolution of inflammation

Where do we go from here?

- Further prospective testing of anti-inflammatory Rx
 - Optimize efficacy and minimize adverse effects, via targeted approach and infectious disease monitoring
 - Optimize route of delivery and lower cost, e.g., oral inflammasome inhibitors
 - ? Use in primary prevention in select subjects
 - Integration with intense LDL lowering
- Integration with drugs for diabetes that show a CV-protective effect (SGLT2 inhibitors, liraglutide)
- Drugs that enhance resolution of inflammation

Nature's Way of Resolving Inflammation May Spare Host Defense

Inflammatory response

Cytokines
(e.g., IL-1 β , TNF α)



Kill pathogens
... but at the expense of
collateral tissue damage

Nature's Way of Resolving Inflammation May Spare Host Defense

Inflammatory response

Cytokines
(e.g., IL-1 β , TNF α)



Kill pathogens
... but at the expense of
collateral tissue damage

**Lipid and protein
resolution mediators**
(e.g., resolvins, IL-10)



- Dampen inflammation
- Repair tissue damage
- **Clear residual pathogens**



Therapeutic Potential of Resolving Mediator Therapy for CVD in the Post-CANTOS Era

- **Advanced human atheroma have impaired resolution and are deficient in resolution mediators**

Therapeutic Potential of Resolving Mediator Therapy in the Post-CANTOS Era

- **Advanced human atheroma have impaired resolution and are deficient in resolution mediators**
- **Resolution mediator therapy blocks plaque progression in animal models of advanced atherosclerosis**

The Outlook for Testing Inflammation-Targeting Strategies

Pre-CANTOS



The Outlook for Testing Inflammation-Targeting Strategies

Pre-CANTOS



Post-CANTOS

