

TOURMALINE

INVESTOR DAY

December 10, 2024

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Agenda

Carrying pacibekitug momentum into 2025

Sandeep Kulkarni, MD
Co-Founder & CEO

Addressing residual inflammatory risk in CV diseases

Marc P. Bonaca, MD, MPH
*University of Colorado
CPC Clinical Research*

Pioneering the next frontier in CV with IL-6 inhibition

Emil deGoma, MD
SVP, Medical Research

Pacibekitug's practice-changing potential in CV

Gerhard Hagn
SVP, Head of Commercial & BD

Confirming pacibekitug's best-in-disease opportunity in TED

Gerhard Hagn
SVP, Head of Commercial & BD

Q&A

From company creation to two high-value, distinct opportunities in less than three years



2022



2023



2024

Company

- ✓ Pacibekitug licensed from Pfizer in May 2022
- ✓ Go-public transaction in October 2023
- ✓ Follow-on equity offering in January 2024
- ✓ 70+ person company built with significant experience in developing and commercializing mAb
- ✓ \$426M in total financing proceeds raised to date; cash and investments of \$314M as of 9/30/24

Pacibekitug

- ✓ 2 IND applications cleared
- ✓ GMP clinical material produced
- ✓ World-class Cardiovascular Scientific Advisory Board advising Tourmaline
- ✓ Phase 2 TRANQUILITY trial in cardiovascular inflammation ongoing; topline data expected in Q2 2025
- ✓ Pivotal Phase 2b spiriTED trial in thyroid eye disease ongoing; topline data expected in H2 2025

We plan to deliver two potentially transformational readouts in 2025

Q2 2025

TRANQUILITY



- Pending success, program will be Phase 3-ready in ASCVD (as previously aligned with FDA)
- Potentially transformative value for millions of CV patients may translate into multi-billion-dollar peak revenue opportunity

H2 2025

spirITED



- TED represents an independent shot on goal
- Pending success, pacibekitug has best-in-disease and blockbuster potential

TRANQUILITY over-enrolled with 143 patients in just 7 months



- Underscores enthusiasm to address **IL-6-driven cardiovascular inflammation**
- Goal is to show **rapid and robust hs-CRP reduction** through **quarterly** SC injections

Tourmaline Bio Highlights Cardiovascular Inflammation Focus and Announces Key Clinical and Strategic Updates at Investor Day

December 10, 2024 8:30 ET | Source: [Tourmaline Bio, Inc.](#)

– Phase 2 TRANQUILITY trial surpasses enrollment target, with 143 total patients enrolled; topline data expected in second quarter of 2025 –

– Deepak L. Bhatt, MD, MPH, MBA and Dipender Gill, MD, PhD join Cardiovascular Scientific Advisory Board –

– Company nominates abdominal aortic aneurysm as second cardiovascular indication for pacibekitug, expanding development for inflammation-driven cardiovascular disease –

Pacibekitug: a long-acting anti-IL-6 monoclonal antibody with best-in-class potential



Attributes observed to date

Long-acting with terminal half-life of ~7 weeks¹

>90% pathway inhibition after single 10mg dose²

Fully human with ADAs in only 0.5% of patients³

High affinity to IL-6⁴

Existing data from approximately **450 study participants**¹







Potential value to patients

- **Dosing quarterly**⁵ (CV) or **every 8 weeks**⁶ (TED)
- **Rapid and robust impact** across diseases
- Durable benefit **without need to increase dose**
- Volume of ≤ 1 ml for **SC injection**^{5,6}
- Generally **well-tolerated safety profile** observed to date

¹Across six clinical trials in healthy volunteers and RA, SLE, and CD patients. ²Data on file; single intravenous 10mg dose in Ph1 MAD study in RA patients; as measured by C-reactive protein (CRP), a pharmacodynamic marker of IL-6 signaling. ³Generated from Medarex transgenic mouse platform; across approximately 450 subjects dosed with pacibekitug, only 2 subjects generated anti-drug antibodies (ADAs) following treatment. ⁴Data on file. ⁵To be evaluated in CV Phase 2 trial. ⁶To be evaluated in TED Phase 2 trial. Every 8-week dosing was achieved in prior Phase 2 trials. CD: Crohn's Disease. CV: cardiovascular. SC: subcutaneous. RA: rheumatoid arthritis. SLE: systemic lupus erythematosus. TED: thyroid eye disease.

Our expanding clinical development plan for pacibekitug

Disease focus	Indication	Preclinical	Phase 1	Phase 2	Phase 3	Expected key milestones
Cardiovascular inflammation	Atherosclerotic cardiovascular disease (ASCVD)				<p>TRANQUILITY Phase 2 topline data expected in Q2 2025</p>	
		<p><i>Phase 3 planning in process</i></p> 				
	Abdominal aortic aneurysm (AAA)	<p><i>Phase 2 PoC planning in process</i></p> 			Phase 2 PoC trial initiation expected after TRANQUILITY topline data	
Autoimmune disease	Thyroid eye disease (TED)				<p>spirITED Phase 2b topline data expected in H2 2025</p> <p>Phase 3 initiation dependent upon spirITED results</p>	

Our world-class Cardiovascular Scientific Advisory Board



Deepak L. Bhatt, MD, MPH, MBA
SAB Chair
Mount Sinai Fuster Heart Hospital



Joshua A. Beckman, MD, MSc
University of Texas Southwestern



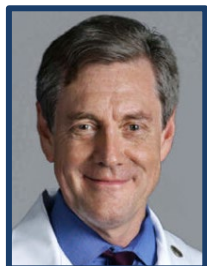
Marc P. Bonaca, MD, MPH
University of Colorado
CPC Clinical Research



Robin Choudhury, MA, DM
University of Oxford



Dipender Gill, MD, PhD
Sequoia Genetics



Douglas L. Mann, MD
Washington University
School of Medicine



James Min, MD
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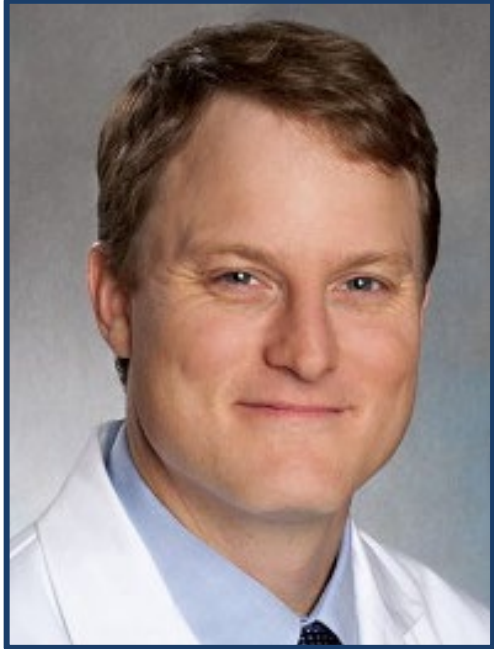
Pradeep Natarajan, MD, MMSC
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Harvard Medical School



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Wake Forest University



Michael Szarek, PhD
University of Colorado
CPC Clinical Research



Marc P. Bonaca, MD, MPH

Executive Director, CPC Clinical Research

Director of Vascular Research

Professor, Division of Cardiology

William R. Hiatt Endowed Chair in Cardiovascular Research



School of Medicine

UNIVERSITY OF COLORADO
ANSCHUTZ MEDICAL CAMPUS

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SVP, Head of Commercial & BD

Q&A



Addressing Residual Inflammatory Risk in CV Diseases

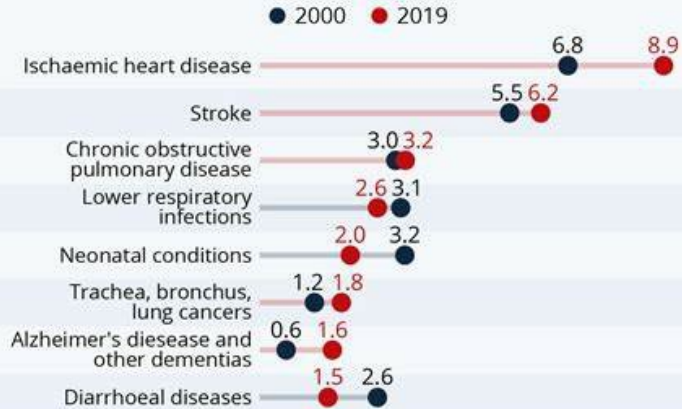
Marc P. Bonaca MD MPH
Director of Vascular Research

William R. Hiatt Endowed Chair in Cardiovascular Research
Professor of Medicine
University of Colorado School of Medicine

Atherosclerosis is a Systemic Disease

The World's Leading Causes Of Death

Total number of people who died from the following conditions (in millions)

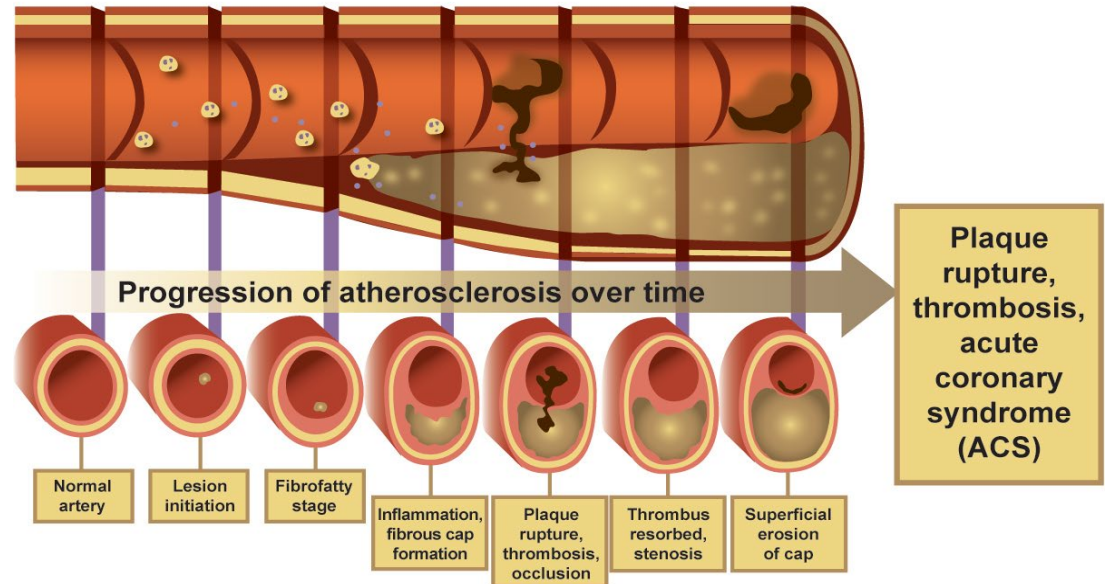


Source: World Health Organization



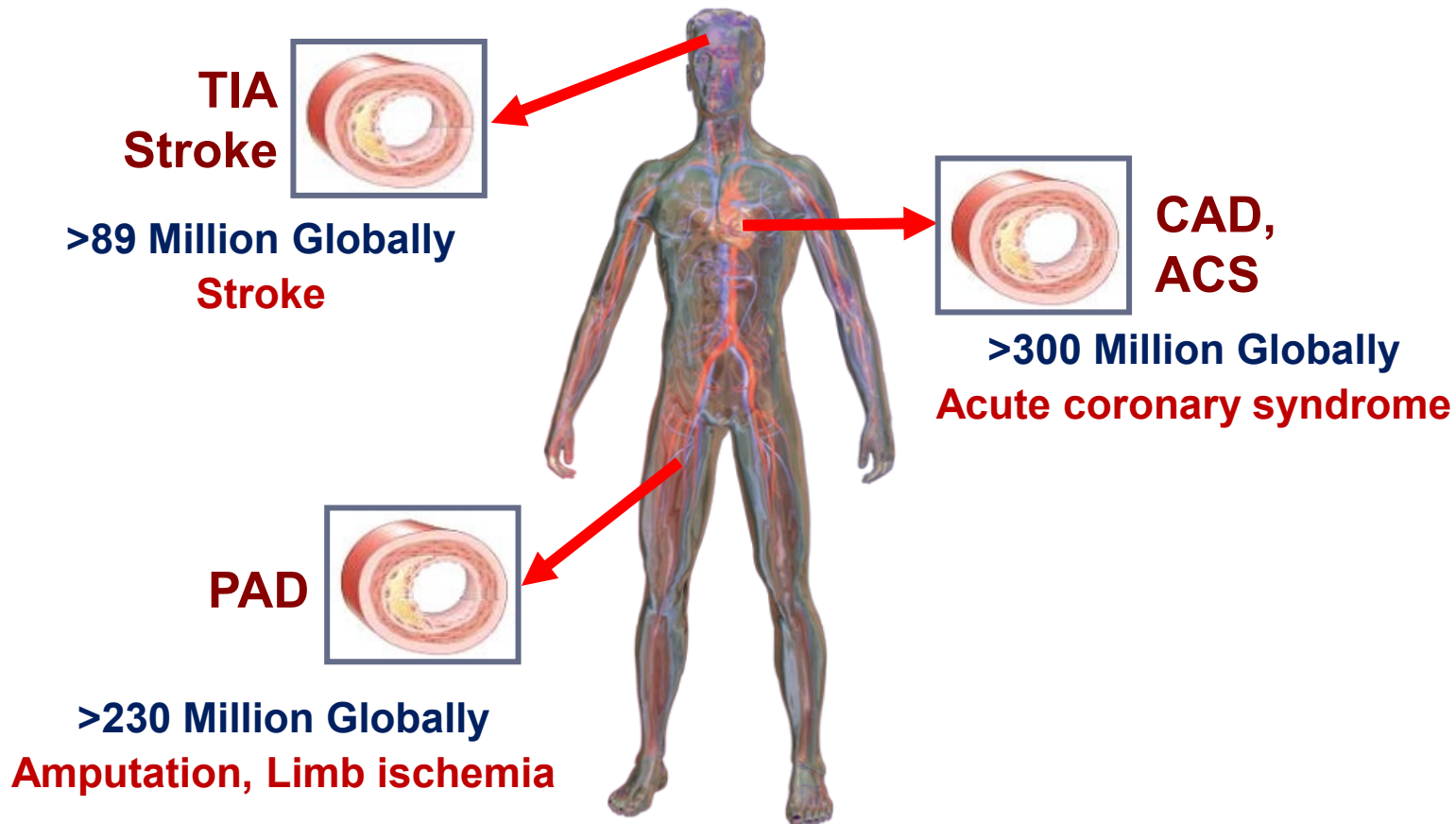
statista

Atherosclerotic Vascular Diseases Coronary, Cerebrovascular, Lower Extremity



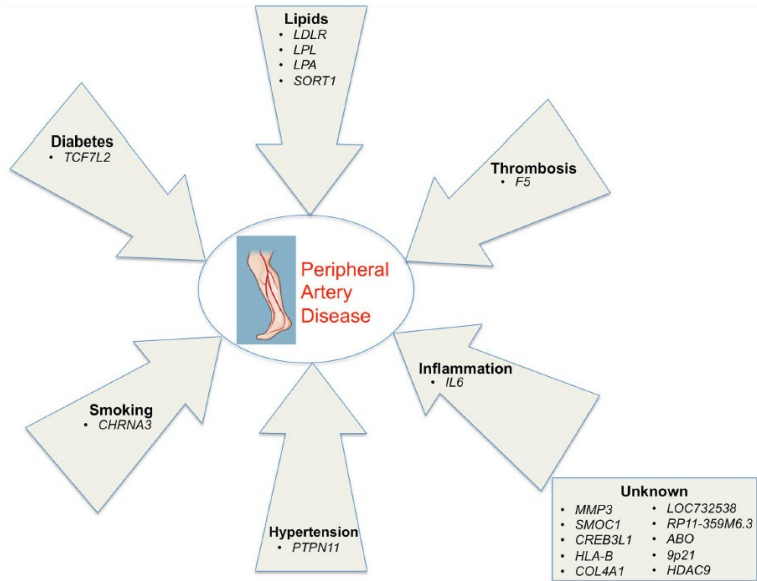
Atherosclerosis is a Systemic Disease

> 500 million worldwide suffer from cardiovascular disease with ~20 million dying in 2021

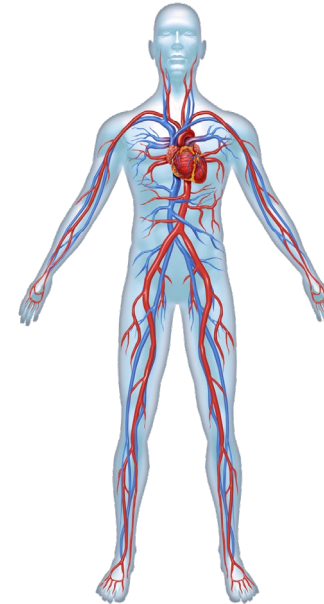


American Heart Association. *Heart Disease and Stroke Statistics – 2021 Update*. Song et al. *Lancet Glob Health* 2019; Lindstrom et al. *JACC* 2022. Coronado et al. *Global Responses to Prevent, Manage, and Control Cardiovascular Diseases*. ACS: acute coronary syndrome. CAD: coronary artery disease. PAD: peripheral artery disease. TIA: transient ischemic attack.

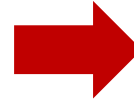
Multiple Drivers of Risk



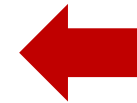
Lifestyle
(exercise, diet)



Lipid Risk
(LDL & Lp(a))



Thrombosis Risk



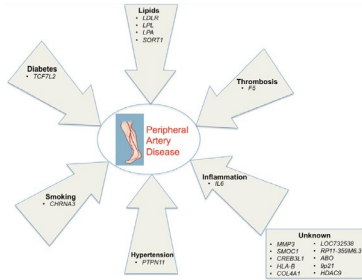
Diabetes Risk
(micro and macrovascular)



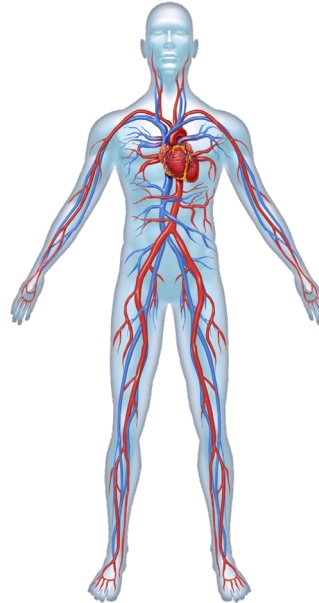
Inflammatory Risk



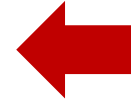
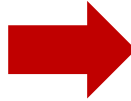
Current Treatment Landscape



Lifestyle
(exercise, diet, environment)



Lipid Risk
Statins
PCSK9i



Thrombosis
Antiplatelet monotherapy
DAPT
Rivaroxaban

Diabetes Risk (micro and macrovascular)
GLP1a / SGLTi
Glycemic targets per GL



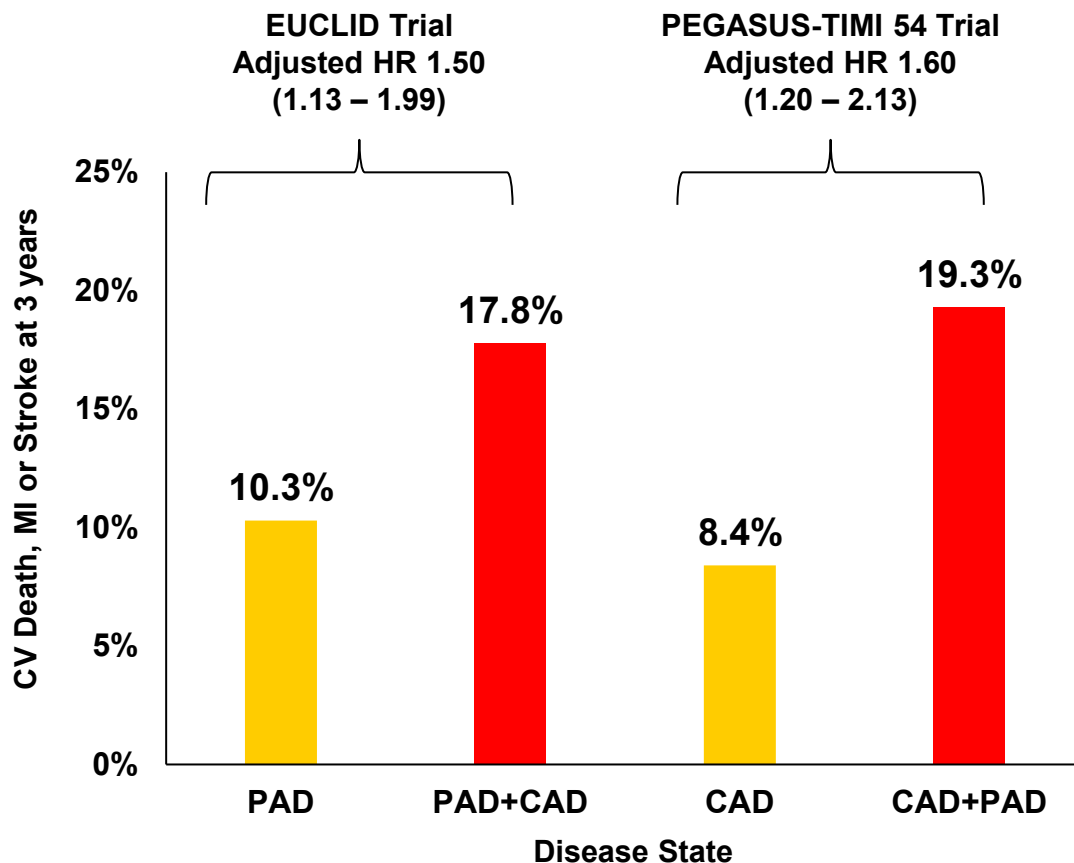
Inflammatory Risk
?

DAPT: dual antiplatelet therapy. GL: glycemic load. GLP1a: glucagon-like peptide-1 agonist. PCSK9i: proprotein convertase subtilisin/kexin type 9 inhibitor. SGLTi: sodium-glucose cotransporter inhibitor

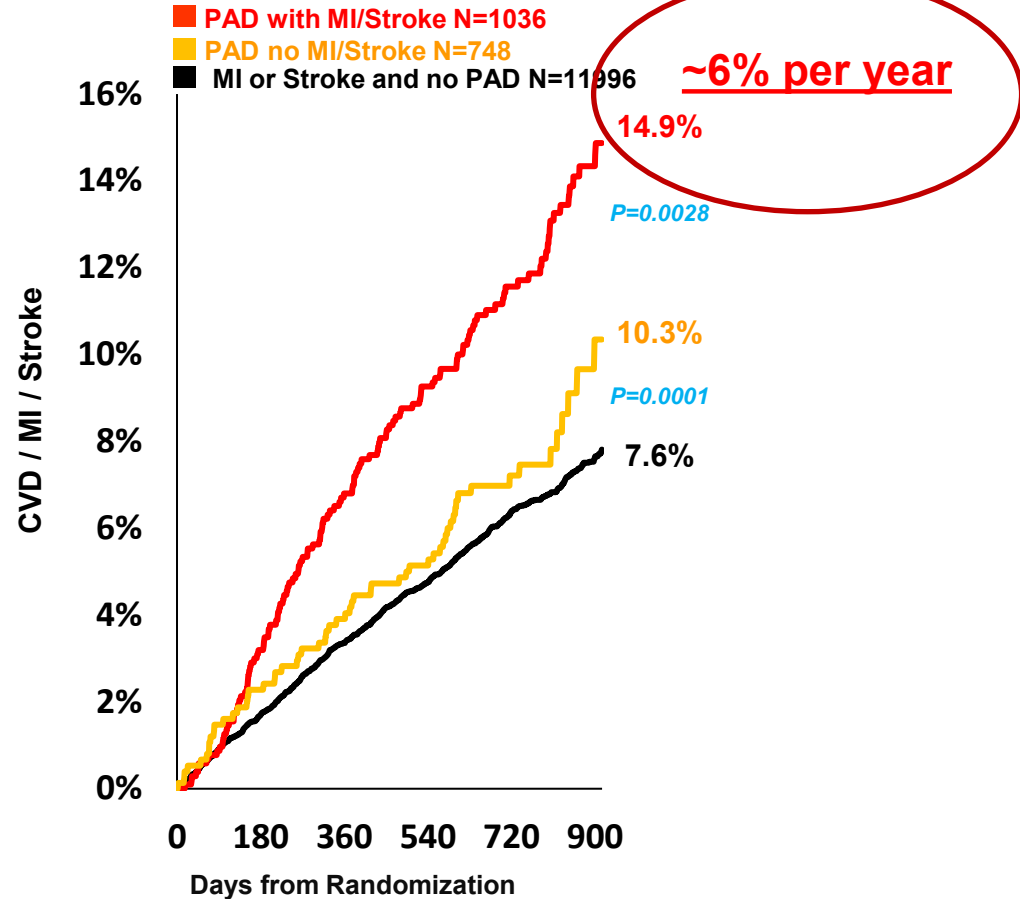
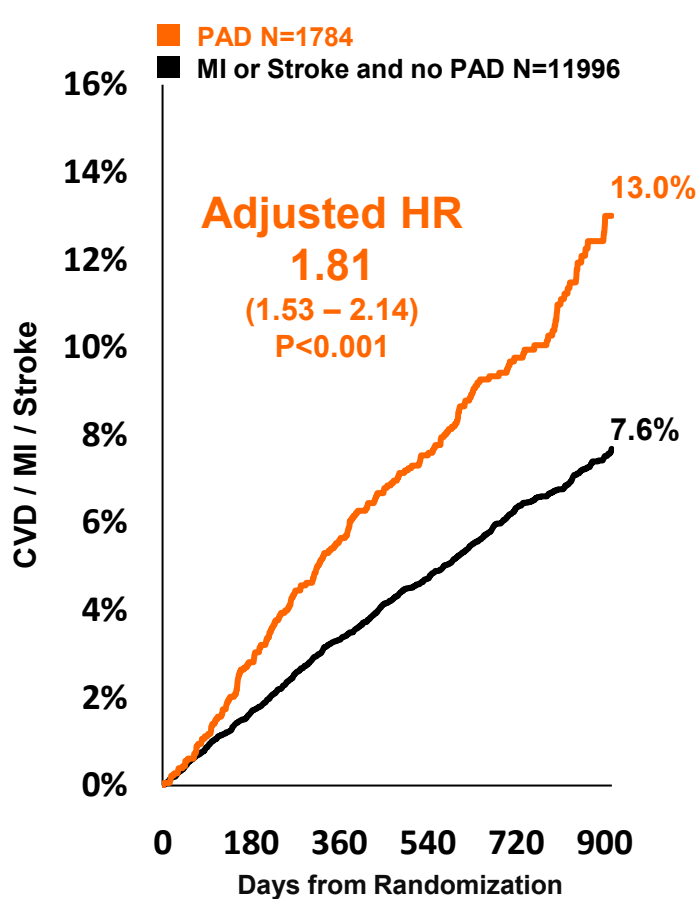
Populations at the Highest Risk

Metastatic Atherosclerosis

Polyvascular Disease in PAD is Associated with Increased MACE Risk



PAD, Polyvascular Disease and Risk of MACE

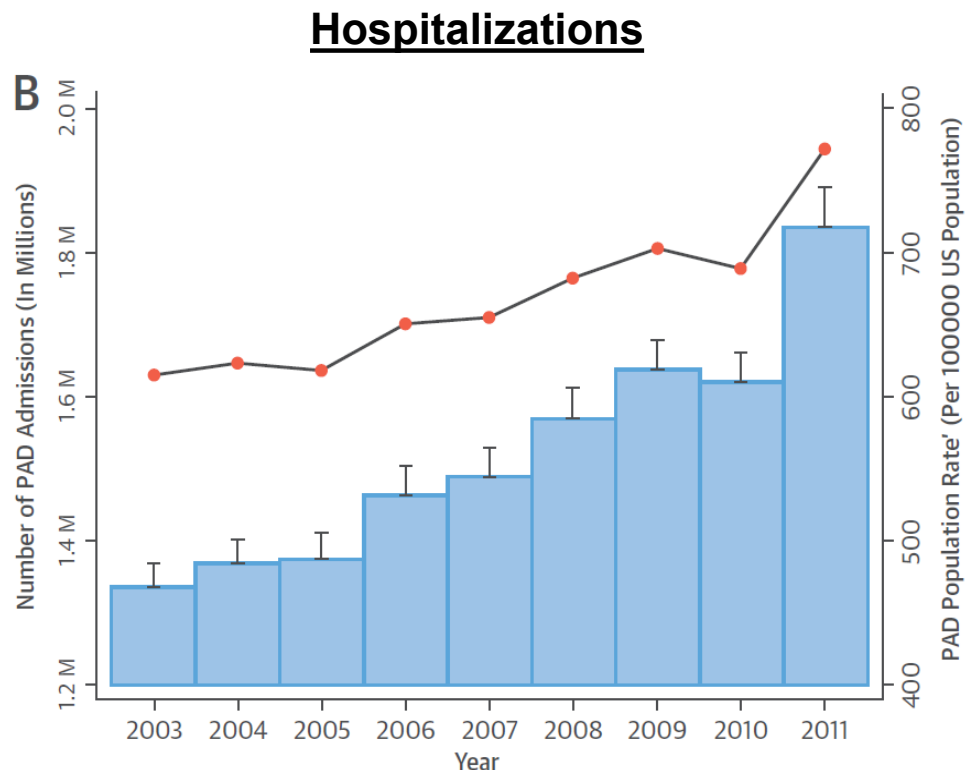
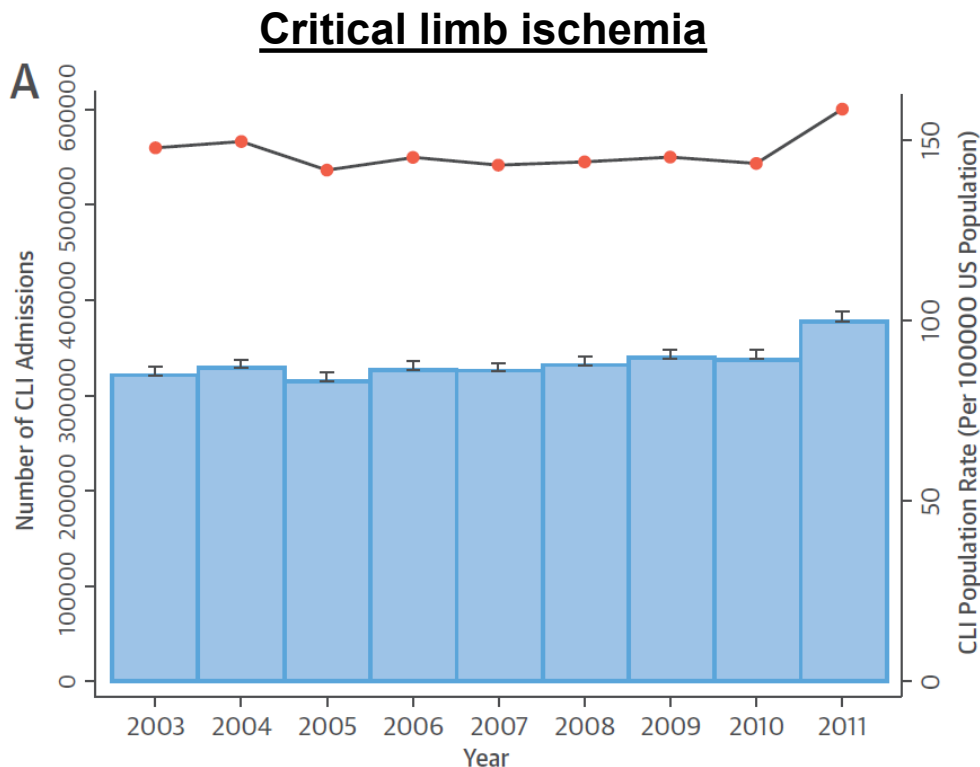


Bonaca et al. Circulation 2018. adjusted age, sex, race, BMI, diabetes, hypertension, smoking, eGFR, CHF, prior MI, CABG/PCI, and history of stroke or TIA. MACE: major adverse cardiovascular events. PAD: peripheral artery disease.

Populations at the Highest Risk

Peripheral Artery Disease

Increasing Rates of Critical Limb Ischemia and Hospitalizations

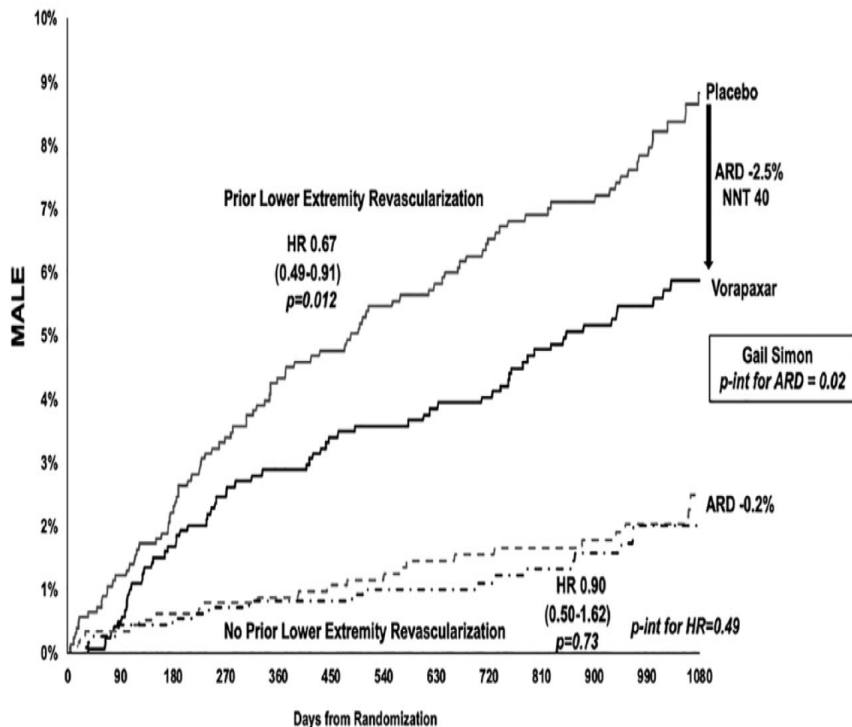


Estimated to be ~500,000 Peripheral Revascularizations in the US each Year

Chronic Patients with Prior Revascularization at Higher Risk of ALI

MALE Event Rate ~3% per year in stable with prior revascularization¹

Risk of MALE ~4 fold higher after adjustment for other baseline differences



TRA2P-TIMI 50 PAD²

Characteristic	Adjusted HR for ALI
Prior Peripheral Revascularization	HR 3.60 (2.10 – 6.18) P<0.001
ABI ≤ 0.5	HR 2.86 (1.81 – 4.51)
ABI ≥ 1.3	HR 2.71 (1.09 – 6.72)
Current Smoking	HR 2.17 (1.01 – 4.67) P=0.046

PEGASUS-TIMI 54 PAD³

Prior revascularization
Adjusted HR for ALI 3.76
(2.26 – 6.25)
p<0.001

EUCLID⁴

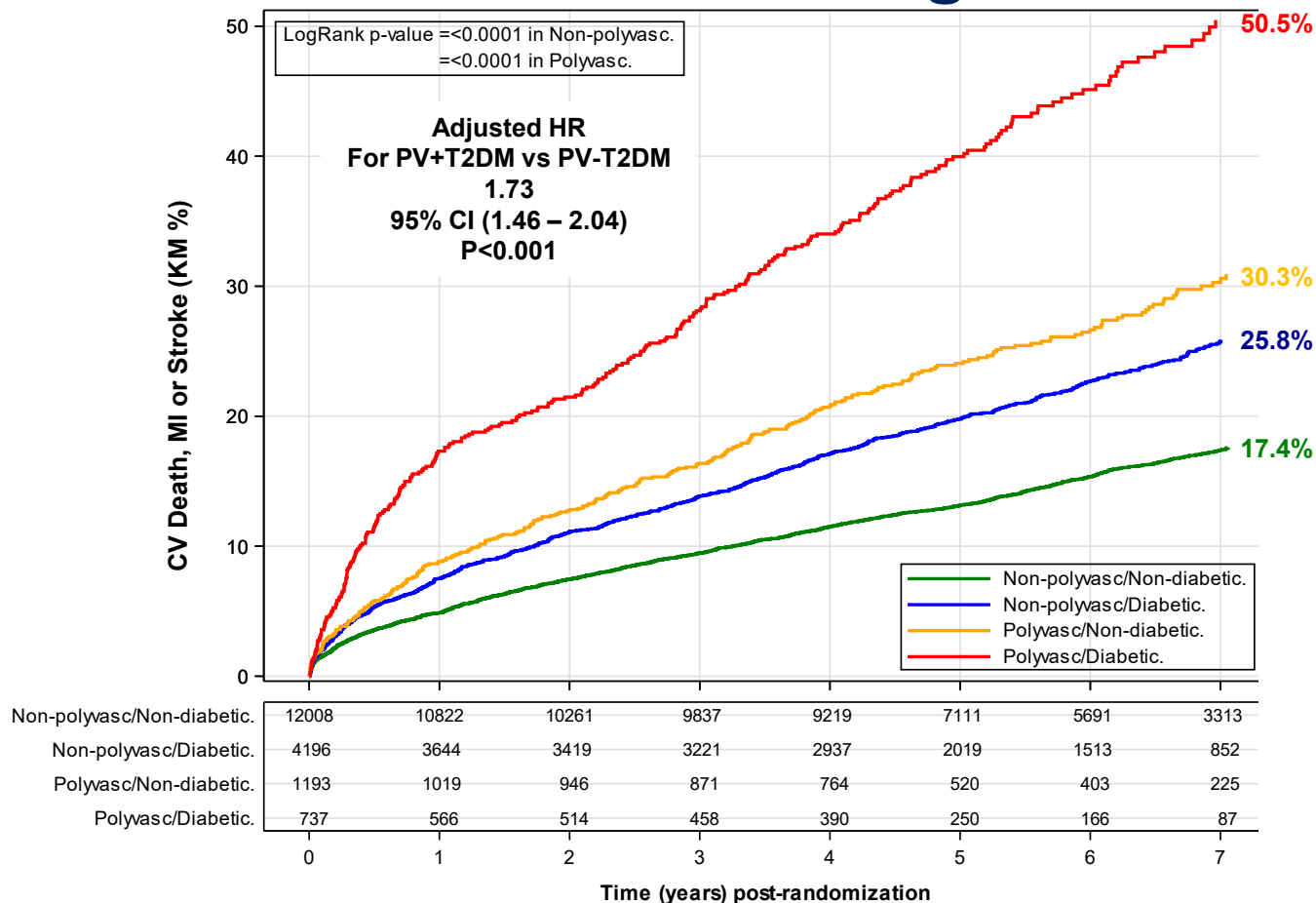
Prior revascularization
Adjusted HR for ALI 4.23
(2.86 – 6.25)
p<0.001

¹Qamar Vasc Med 2019. ²Bonaca et al. Circulation 2016. ³Bonaca et al. JACC 2016. ⁴Jones et al., Circulation 2016. ABI: ankle brachial index. ALI: acute limb ischemia. ARD: absolute risk difference. HR: hazard ratio. MALE: major adverse limb event. NNT: number needed to treat. PAD: peripheral artery disease

Populations at the Highest Risk

Acute Coronary Syndrome & Diabetes

PAD and Diabetes in ACS – A Malignant Combination



Bonaca et al. Lancet Diabetes & Endocrinology 2018. ACS: acute coronary syndrome. CV: cardiovascular. HR: hazard ratio. MI: myocardial infarction. PAD: peripheral artery disease. PV: polyvascular

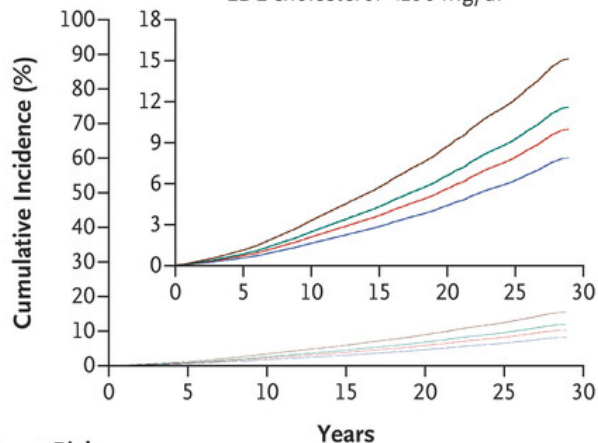
Summary

- **Patients with ASCVD are at high risk for severe events including heart attack, stroke, and limb outcomes; some are at very high risk**
 - **Polyvascular Disease**
 - **PAD particularly after revascularization**
 - **CAD with high-risk features (e.g. T2DM, recent ACS)**
- **Despite novel therapies to address diabetes risk, thrombotic risk, and lipid risk, significant residual risk remains – particularly in the highest risk patients**
- **Inflammation remains the core risk driver without a proven therapy**
 - **Target**
 - **Toxicity**
 - **Matching treatment to the population**

Inflammation – An Independent Risk Factor

A High-Sensitivity CRP and LDL Cholesterol

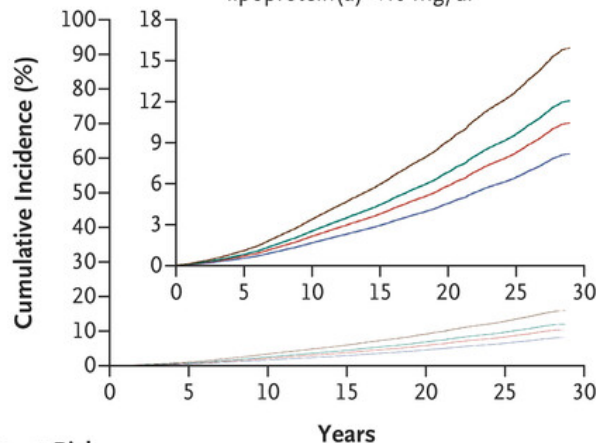
- High-sensitivity CRP ≥ 2 mg/liter and LDL cholesterol ≥ 130 mg/dl
- High-sensitivity CRP ≥ 2 mg/liter and LDL cholesterol < 130 mg/dl
- High-sensitivity CRP < 2 mg/liter and LDL cholesterol ≥ 130 mg/dl
- High-sensitivity CRP < 2 mg/liter and LDL cholesterol < 130 mg/dl



No. at Risk	Years					
—	5,992	5,785	5,443	5,040	4,515	3,238
—	8,072	7,923	7,591	7,161	6,611	4,989
—	5,071	4,990	4,791	4,523	4,181	3,211
—	8,804	8,702	8,504	8,220	7,783	6,325

B High-Sensitivity CRP and Lipoprotein(a)

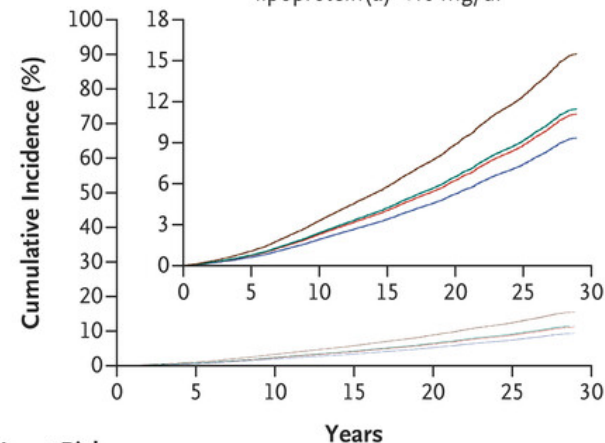
- High-sensitivity CRP ≥ 2 mg/liter and lipoprotein(a) ≥ 40 mg/dl
- High-sensitivity CRP ≥ 2 mg/liter and lipoprotein(a) < 40 mg/dl
- High-sensitivity CRP < 2 mg/liter and lipoprotein(a) ≥ 40 mg/dl
- High-sensitivity CRP < 2 mg/liter and lipoprotein(a) < 40 mg/dl



No. at Risk	Years					
—	3,098	3,001	2,834	2,626	2,371	1,758
—	10,855	10,623	10,122	9,510	8,698	6,433
—	2,938	2,886	2,787	2,651	2,488	1,966
—	10,857	10,735	10,440	10,029	9,419	7,524

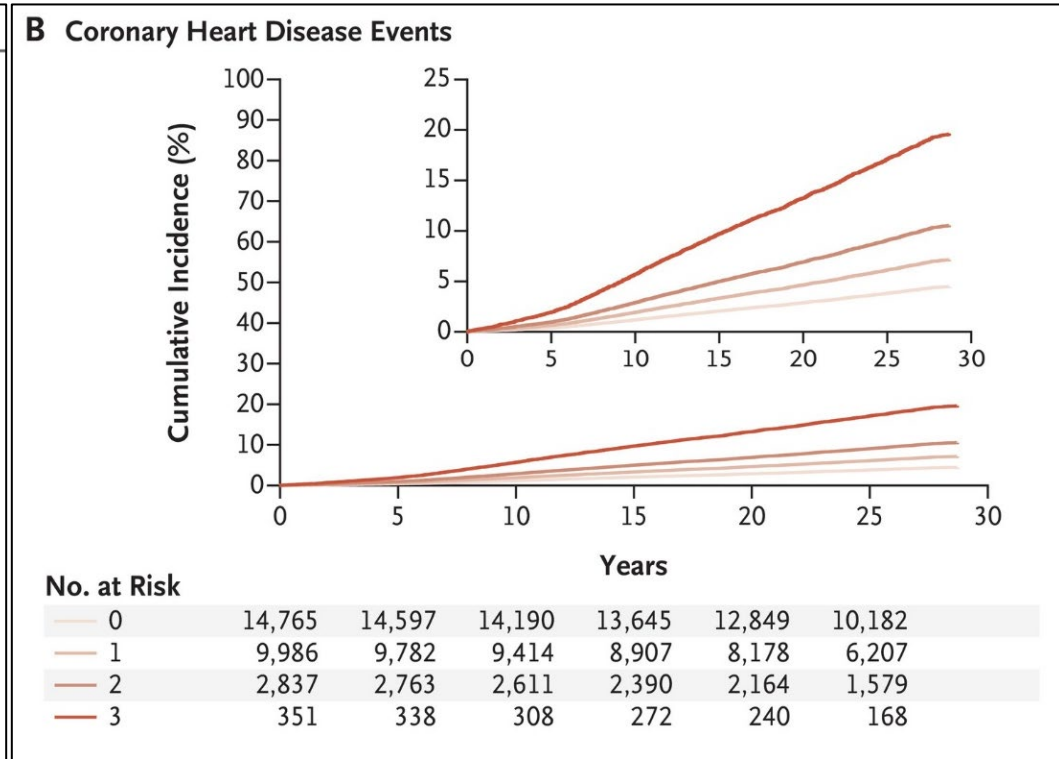
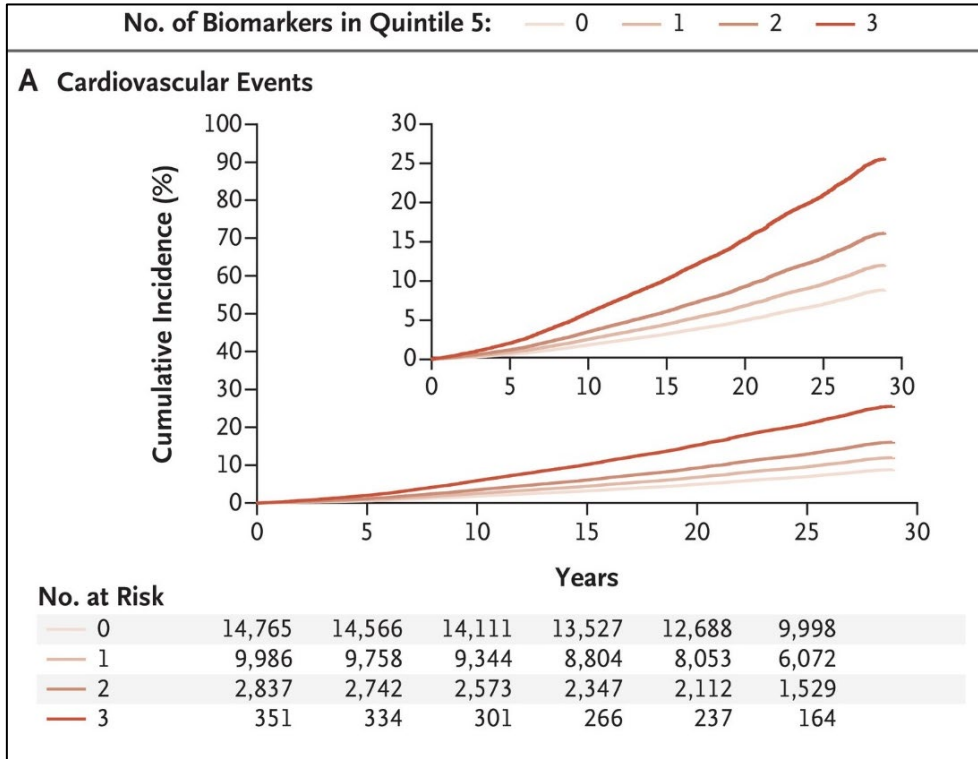
C LDL Cholesterol and Lipoprotein(a)

- LDL cholesterol ≥ 130 mg/dl and lipoprotein(a) ≥ 40 mg/dl
- LDL cholesterol ≥ 130 mg/dl and lipoprotein(a) < 40 mg/dl
- LDL cholesterol < 130 mg/dl and lipoprotein(a) ≥ 40 mg/dl
- LDL cholesterol < 130 mg/dl and lipoprotein(a) < 40 mg/dl

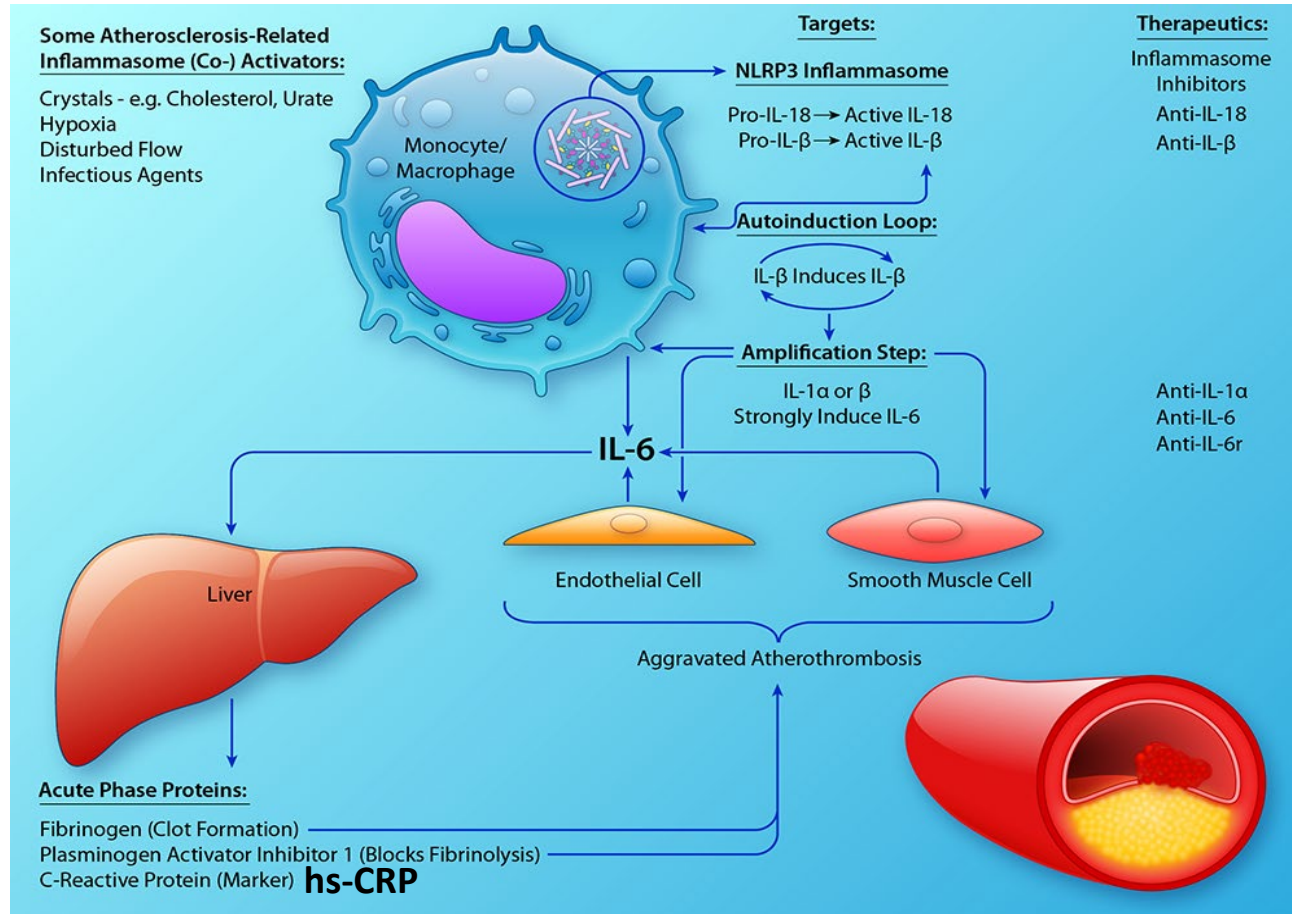


No. at Risk	Years					
—	2,931	2,838	2,659	2,457	2,234	1,667
—	8,048	7,877	7,519	7,058	6,422	4,755
—	3,105	3,049	2,962	2,820	2,625	2,057
—	13,664	13,481	13,043	12,481	11,695	9,202

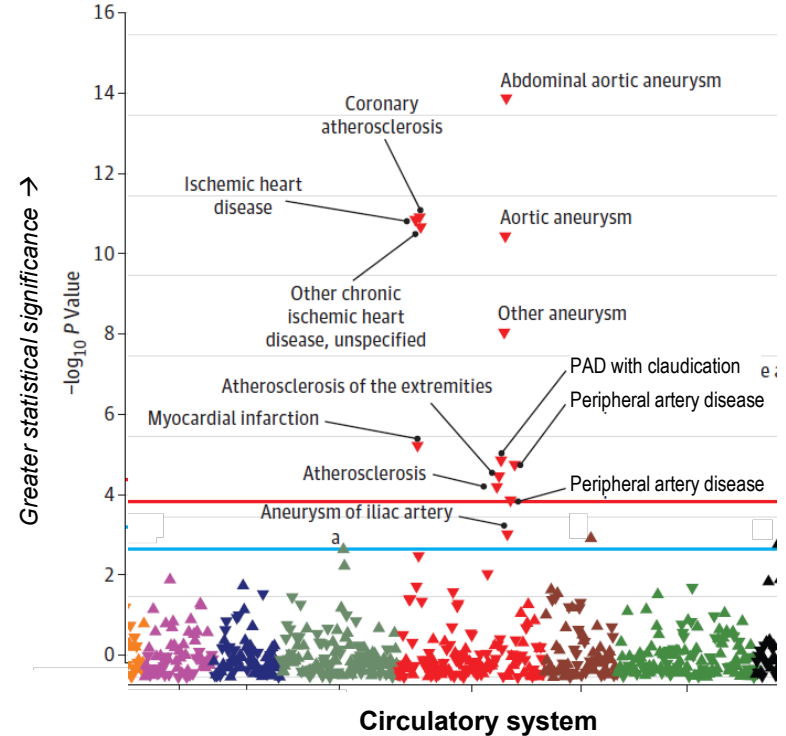
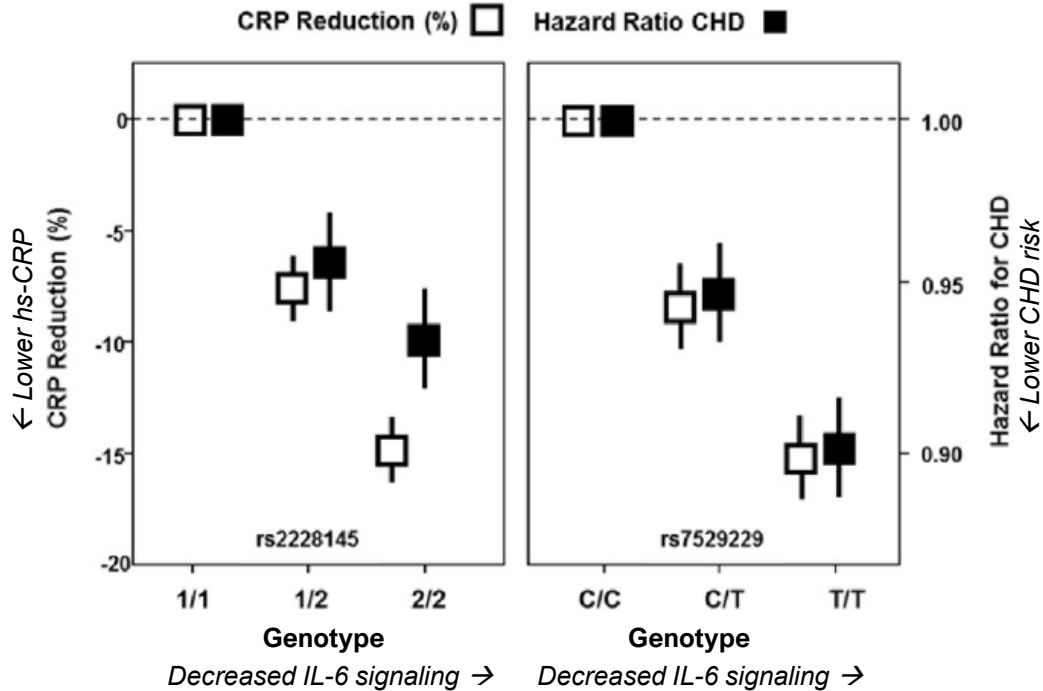
Inflammation – An Additive Risk Factor



Inflammatory Pathways



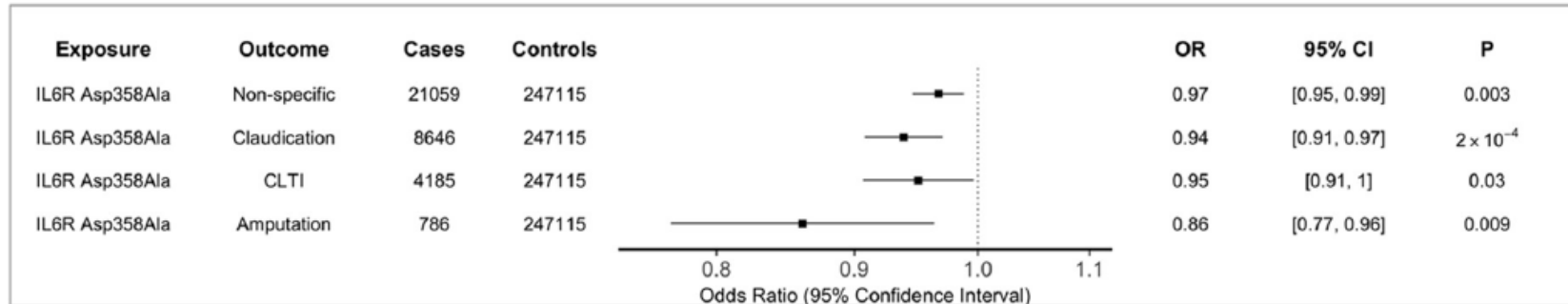
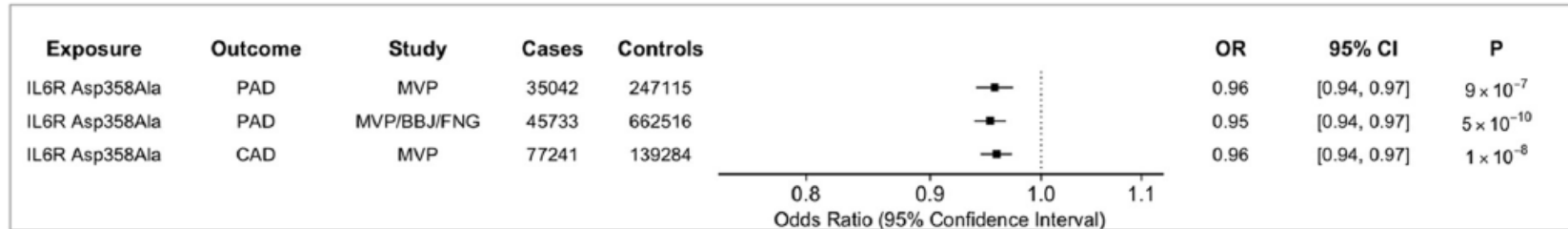
IL-6R variant (\downarrow CRP 9%) associated with a significantly lower risk of ASCVD in multiple human studies



Sarwar et al., Lancet (2012). Swerdlow et al., Lancet (2012). Figures Adapted from Ridker et al., Circ Res (2021) and Cai et al., JAMA Cardiol (2018). ASCVD: atherosclerotic cardiovascular disease, CHD: coronary heart disease, CRP: C-reactive protein, IL: interleukin.

Rationale for IL-6 inhibition in PAD: Human Genetic Data

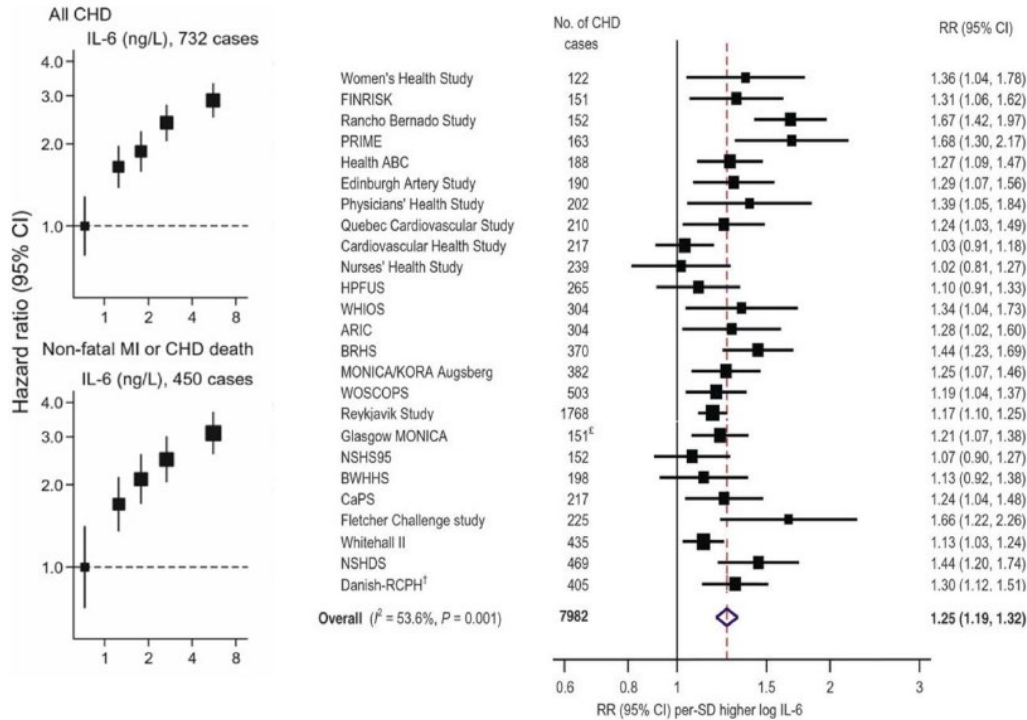
IL6R variant mimicking low-dose anti-IL-6R mAb associated with decreased risk of PAD



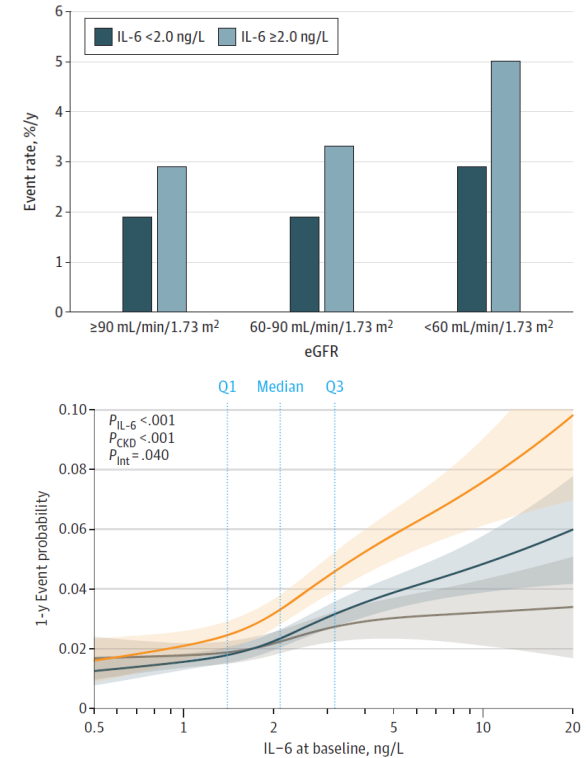
Levin et al., Circ Res (2021). CAD: coronary artery disease. CLTI: chronic limb threatening ischemia. CI: confidence interval, IL: interleukin, mAb: monoclonal antibody, PAD: peripheral artery disease, OR: odds ratio.

Epidemiological studies of IL-6 and ASCVD

IL-6 levels and incident CHD risk (29 prospective studies)¹



IL-6 levels and MACE in CKD²



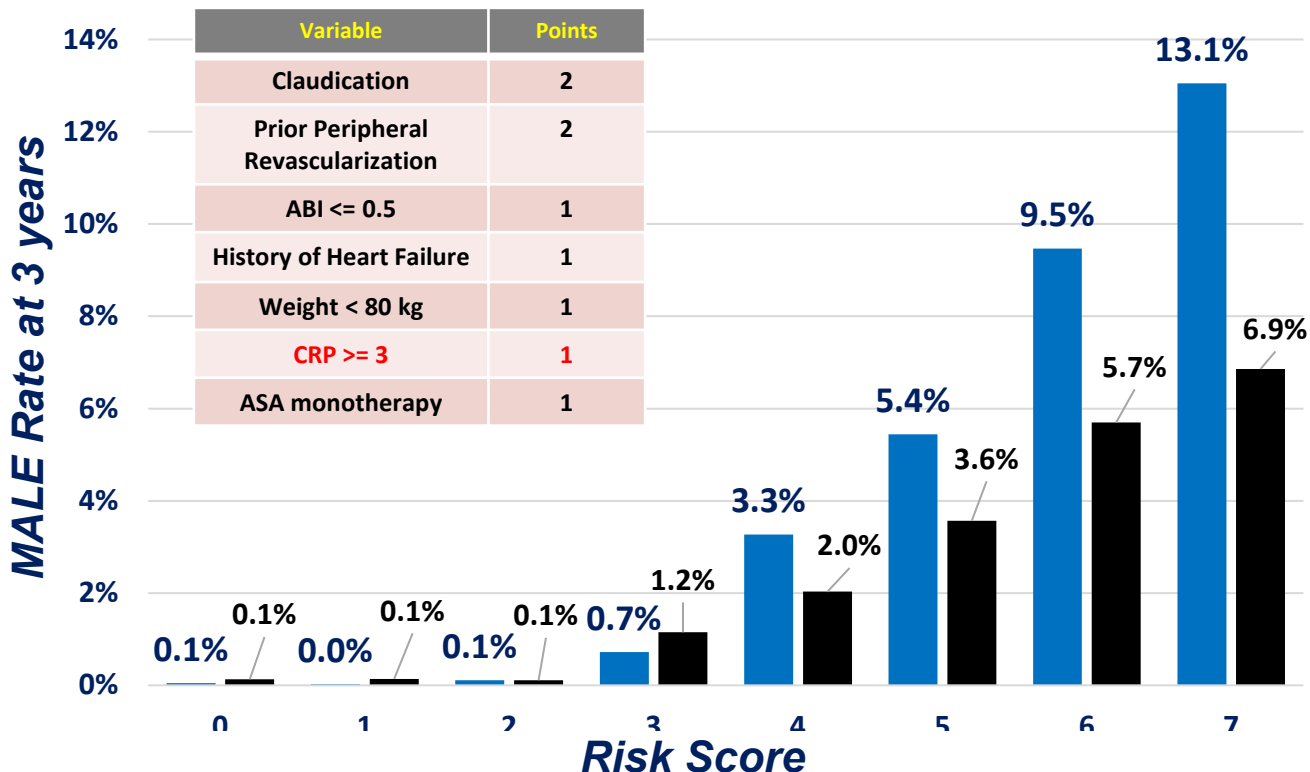
¹Ridker & Rane, Circ Res (2021) adapted from Kaptoge et al., Eur Heart J (2014). ²Batra et al, JAMA Cardiol (2021). ASCVD: atherosclerotic cardiovascular disease, CHD: coronary heart disease, CI: confidence interval, CKD: chronic kidney disease, eGFR: estimated glomerular filtration rate, IL: interleukin, MACE: major adverse cardiovascular event, MI: myocardial infarction, RR: relative risk.

CRP an Independent Predictor of Acute Limb Ischemia

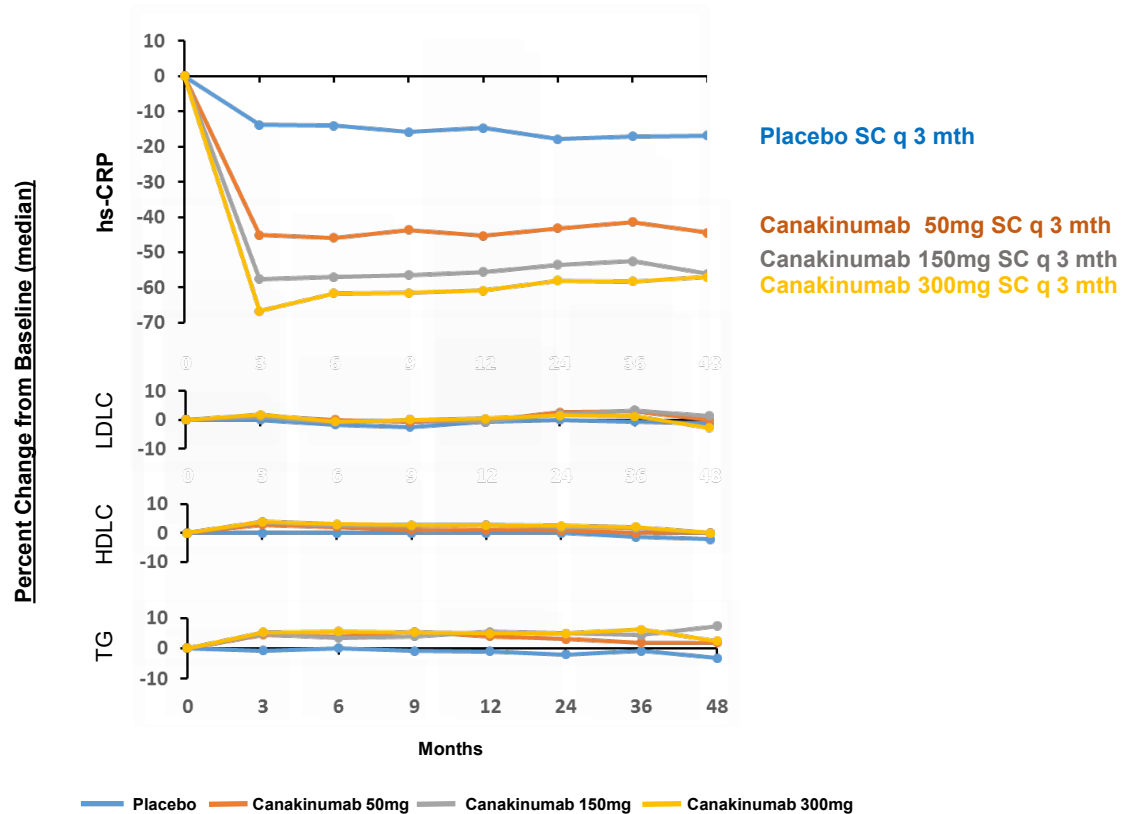
PAD

C-Statistic 0.82

■ Placebo ■ Vorapaxar



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

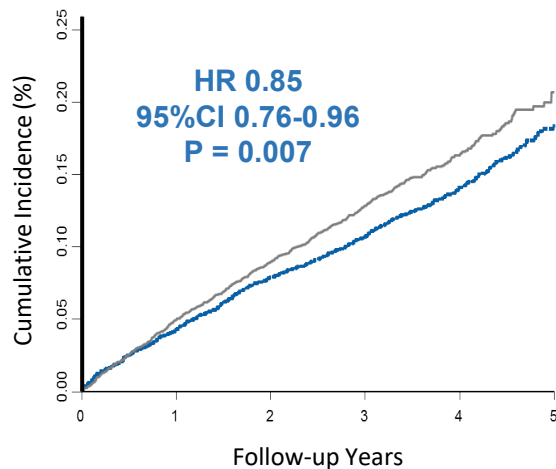


Ridker PM, Everett BM et al. N Engl J Med. 2017;377:1119-31. hs-CRP: high sensitivity C-reactive protein. LDLC: low-density lipoprotein cholesterol. HDLC: high-density lipoprotein cholesterol. TG: triglycerides. SC: subcutaneous

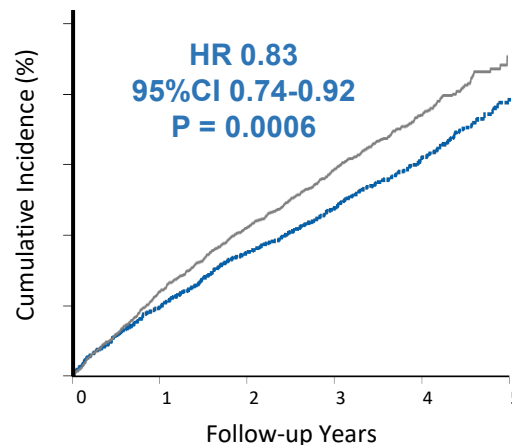
CANTOS: Primary Cardiovascular Endpoints

— Placebo SC q 3 months
— Canakinumab 150/300 mg SC q 3 months

MACE



MACE - Plus



35 - 40% reductions in hs-CRP and IL-6
No change in LDLC

Ridker PM, Everett BM et al. N Engl J Med. 2017;377:1119-31. MACE: major adverse cardiovascular events. hs-CRP: high sensitivity C-reactive protein. LDLC: low density lipoprotein cholesterol. SC: subcutaneous.

CANTOS: Lower risk of CV mortality in subgroups achieving low on-treatment hs-CRP, low IL-6

CV mortality benefit in hs-CRP <2 mg/L¹

	Placebo (n=3182)	Canakinumab, hsCRP ≥2 mg/L at 3 months (n=2868)	Canakinumab, hsCRP <2 mg/L at 3 months (n=3484)	p _{trend} across categories
Myocardial infarction, stroke, or death from any cause				
Incidence rate (n)	5.39 (614)	5.38 (553)	3.96 (508)	..
HR ^{adj} (95% CI)	1 (ref)	0.93 (0.83–1.05)	0.73 (0.65–0.82)	..
p value	Ref	0.25	<0.0001	<0.0001
Cardiovascular death				
Incidence rate (n)	1.74 (211)	1.83 (198)	1.22 (164)	..
HR ^{adj} (95% CI)	1 (ref)	0.99 (0.82–1.21)	0.69 (0.56–0.85)	..
p value	Ref	0.95	0.0004	0.0004

CV mortality benefit in IL-6 < median²

Treatment group, on-treatment IL-6 threshold	N	Incidence rate (n) ^a	HR (95% CI)	P-value	HR ^{adj} (95% CI) ^b	P-value
MACE						
Placebo	1597	4.91 (282)	1 (ref)		1 (ref)	
Canakinumab, IL-6 ≥ median value (1.65 mg/L)	1619	5.15 (291)	1.06 (0.90–1.25)	0.49	0.90 (0.76–1.07)	0.25
Canakinumab, IL-6 < median value (1.65 mg/L)	1617	3.21 (199)	0.64 (0.54–0.77)	<0.0001	0.68 (0.56–0.82)	<0.0001
P-value for trend across categories				<0.0001		<0.0001
MACE+						
Placebo	1597	5.49 (311)	1 (ref)		1 (ref)	
Canakinumab, IL-6 ≥ median value (1.65 mg/L)	1619	5.44 (305)	1.00 (0.85–1.17)	0.97	0.87 (0.74–1.02)	0.093
Canakinumab, IL-6 < median value (1.65 mg/L)	1617	3.72 (228)	0.67 (0.57–0.80)	<0.0001	0.70 (0.59–0.84)	<0.0001
P-value for trend across categories				<0.0001		<0.0001
Cardiovascular mortality						
Placebo	1597	1.66 (103)	1 (ref)		1 (ref)	
Canakinumab, IL-6 ≥ median value (1.65 mg/L)	1619	2.26 (136)	1.38 (1.07–1.79)	0.0134	1.15 (0.88–1.51)	0.30
Canakinumab, IL-6 < median value (1.65 mg/L)	1617	0.72 (47)	0.43 (0.30–0.60)	<0.0001	0.48 (0.34–0.68)	<0.0001
P-value for trend across categories				<0.0001		0.0002

¹Ridker et al., Lancet (2018). ²Ridker et al., Eur Heart J (2018).

Current State

- **Colchicine^{1,2}**
 - **Largest trial showed no benefit**
 - **Poorly tolerated**
 - **Unclear benefit/risk for mortality**
 - **Unclear mechanism**
- **Canakinumab**
 - **Not available**
- **IL-6³**
 - **Specific**
 - **Strong pre-clinical, genetic, observational data**
 - **Programs focused on ASCVD in CKD, HFpEF, acute MI ongoing**

¹Jolly et al., NEJM 2024. ²Buckley, Libby, ATVB 2024. ³Ridker et al., Circ Res (2021). ASCVD: atherosclerotic cardiovascular disease. CKD: chronic kidney disease. HFpEF: heart failure with preserved ejection fraction. MI: myocardial infarction

Summary

- **ASCVD is the number 1 killer in the context of an aging population with more cardiometabolic disease**
- **Patients with polyvascular disease (metastatic atherosclerosis), high risk PAD, and high risk CAD are at very high risk of MACE + MALE with event rates approaching 7-10% per year¹⁻⁴**
- **Therapies targeting lipids, thrombosis, and diabetes are effective but significant residual risk remains¹⁻⁴**
- **Inflammation is an unaddressed risk factor with IL-6 as a specific target supported by extensive genetic and observational data**
- **Novel therapies targeting IL-6 hold great promise to reduce global vascular risk in patients with high risk ASCVD**

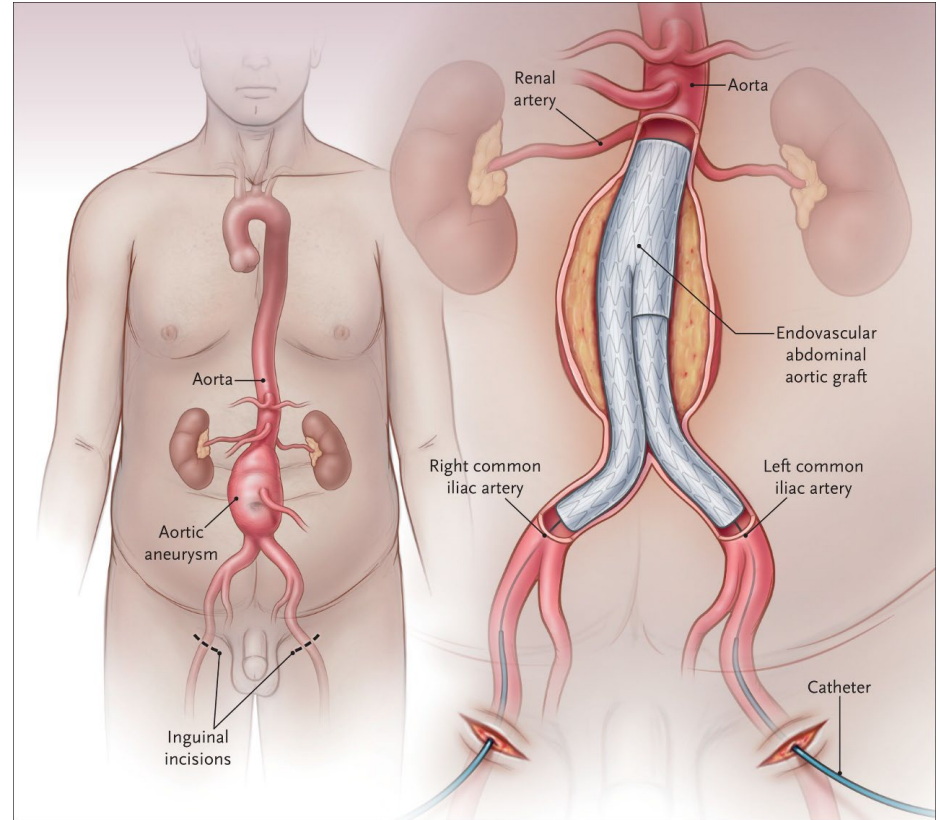
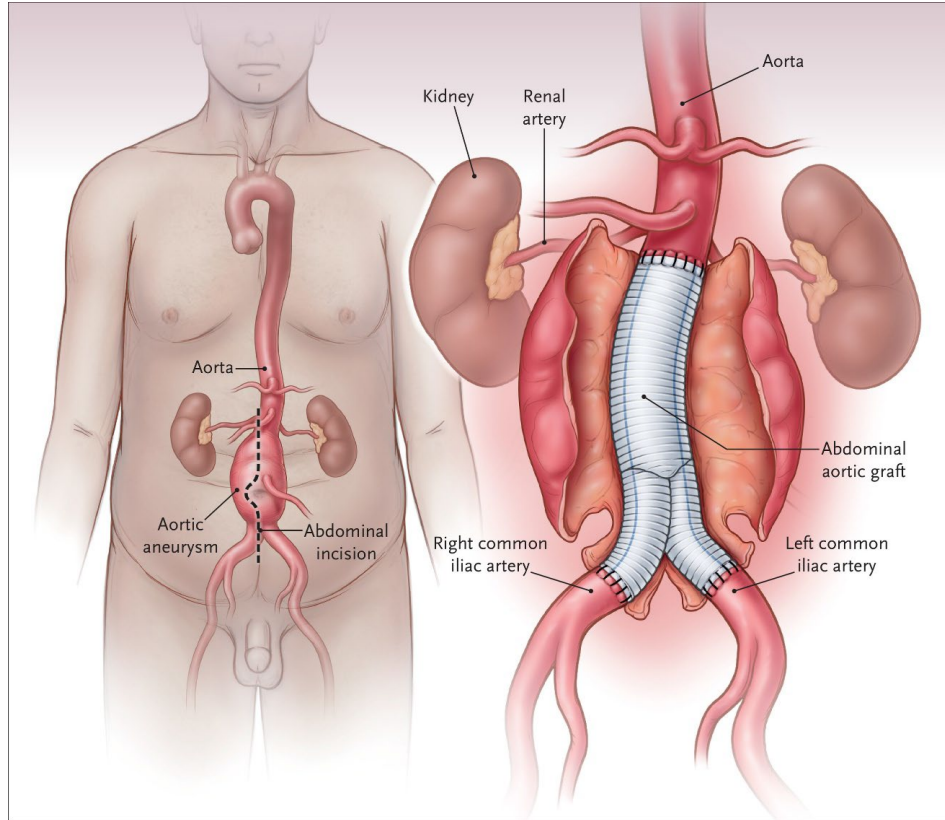
Abdominal Aortic Aneurysm

A morbid “ticking time bomb” with no available medical therapies to prevent the progression of disease

Abdominal Aortic Aneurysm

- **Affects ~ 2 million in the US**
- **Defined as an abdominal aortic diameter > 3 cm**
- **An inflammatory disease acquired in the context of age, smoking, hypertension, hypercholesterolemia**
- **A silent killer that grows asymptotically until rupture, unless detected by screening**
- **Current medical therapy is based on risk factors (e.g. smoking cessation, blood pressure lowering) but does not directly address the pathobiology of disease or halt progression**
- **Patients inevitably progress to requiring repair or rupture**

Abdominal Aortic Aneurysm



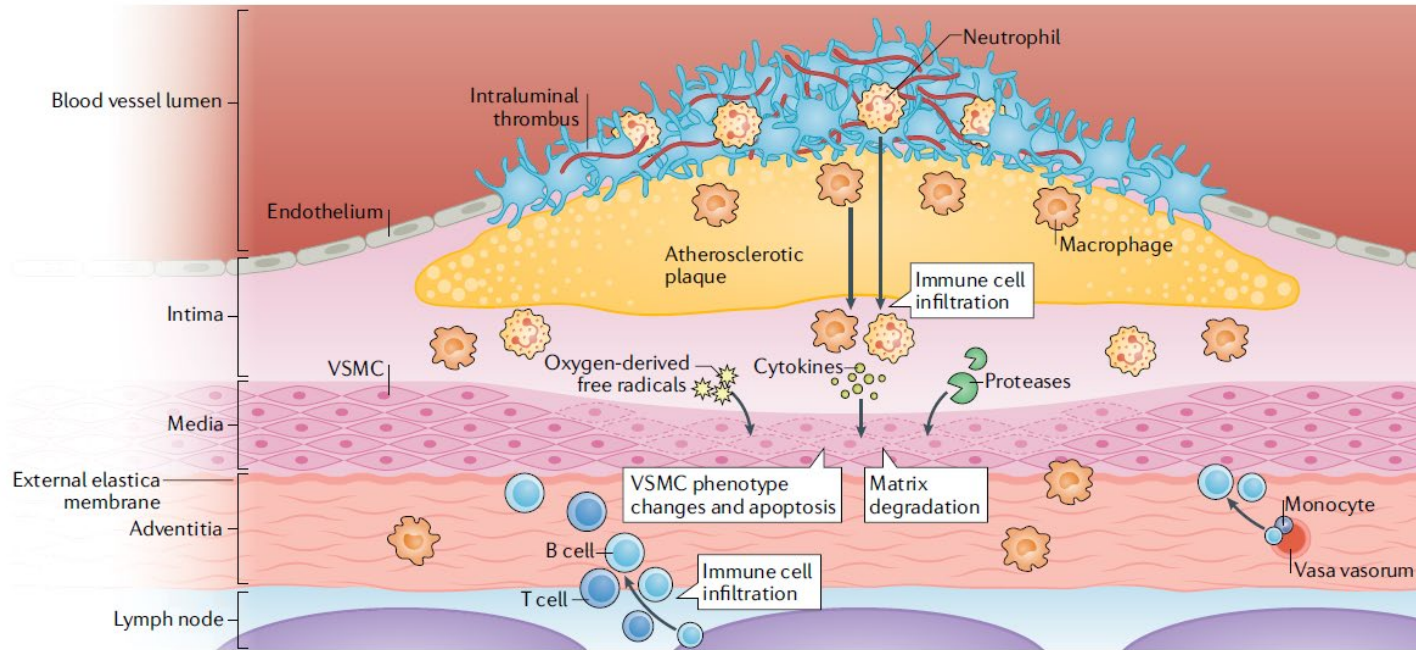
AAA prevalence estimates likely underestimate unmet need due to suboptimal adherence to screening guidelines

2022 AHA/ACC Guidelines ¹	2019 SVS Guidelines ²	2019 USPSTF Guidelines ³
<p>Recommend screening for AAA in:</p> <ul style="list-style-type: none"> Men/women ≥65y with a history of smoking or a family history of AAA Men/women <65y with multiple risk factors for AAA 	<p>Recommend screening for AAA in:</p> <ul style="list-style-type: none"> Men/women 65-75y with a history of tobacco use. Men/women 65-75y with a first-degree relative with AAA. Men/women >75y with a history of tobacco use who are in otherwise good health. 	<p>Recommend screening for AAA in:</p> <ul style="list-style-type: none"> Men 65-75y who have ever smoked Men 65-75y who never smoked but have other risk factors, such as family history

- Cochrane meta-analysis showed that AAA screening was associated with a 40% reduction in mortality⁴
- Recent analysis of a US claims database of 250 million patients reported a 39% adherence rate with AAA screening guidelines⁵
- In a US study of 65,000 patients admitted for ruptured AAA, 24% of patients with ruptured AAA were <65 years, suggesting that expansion of screening criteria are warranted⁶

¹Isselbacher et al., Circulation (2022). ²Chaikof et al., J Vasc Surg 2018. ³USPSTF, JAMA (2019). ⁴Cosford et al., Cochrane (2007). ⁵Ho et al., J Vasc Surg (2023). ⁶Dansey et al., J Vasc Surg (2021). AAA: abdominal aortic aneurysm.

Inflammation is considered critical to the pathogenesis of AAA



Chronic aortic inflammation

- Neutrophils, macrophages, T and B lymphocytes, enter aortic wall
- Cytokines potentiate inflammation
- Inflammatory response increases vasculotoxic factors, eg, proteases, oxygen-derived free radicals

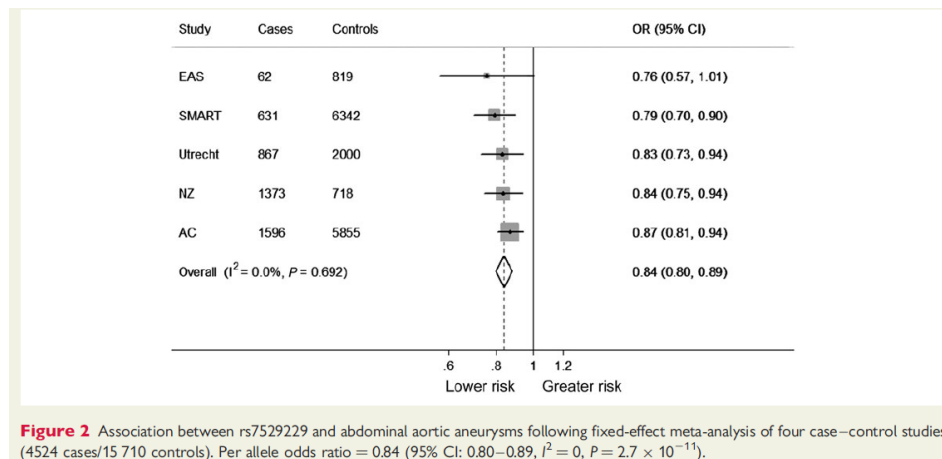
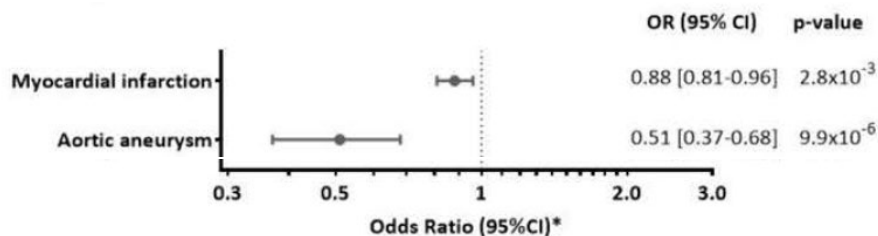
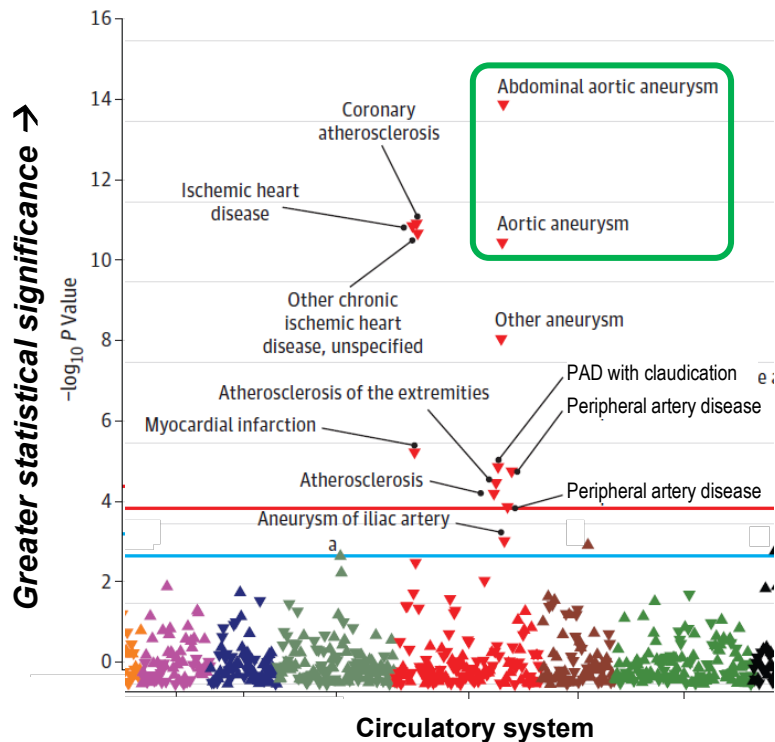


Aortic wall destruction

- Breakdown of extracellular matrix
- Vascular smooth muscle death

Human genetic studies of IL-6 and abdominal aortic aneurysm

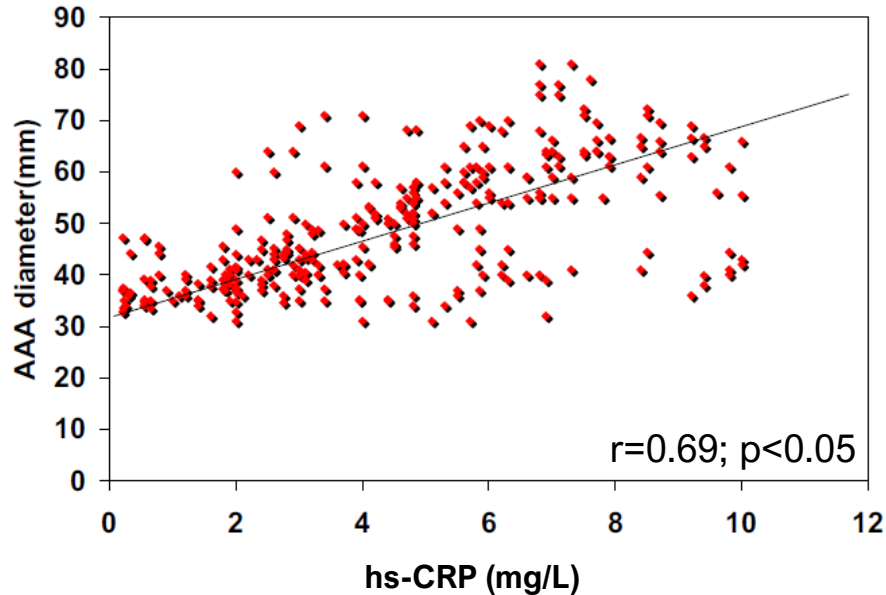
Genetic variant of downregulated IL-6 signaling associated with significant reduction in risk of AAA



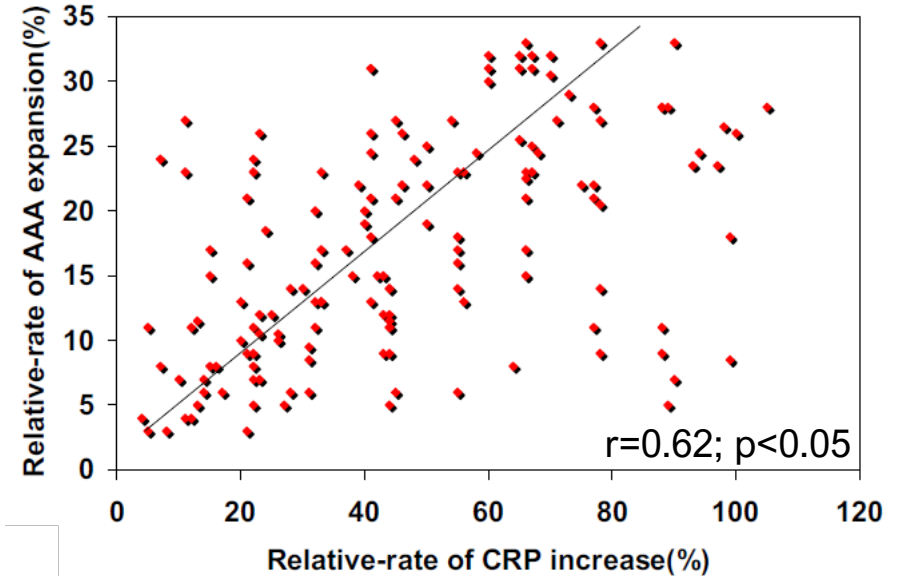
Cai et al., JAMA Cardiol (2018). Georgakis et al., Circ Genom Precis Med (2020). Harrison et al., Eur Heart J (2013). AAA: abdominal aortic aneurysm.

Epidemiological studies of hs-CRP and abdominal aortic aneurysm

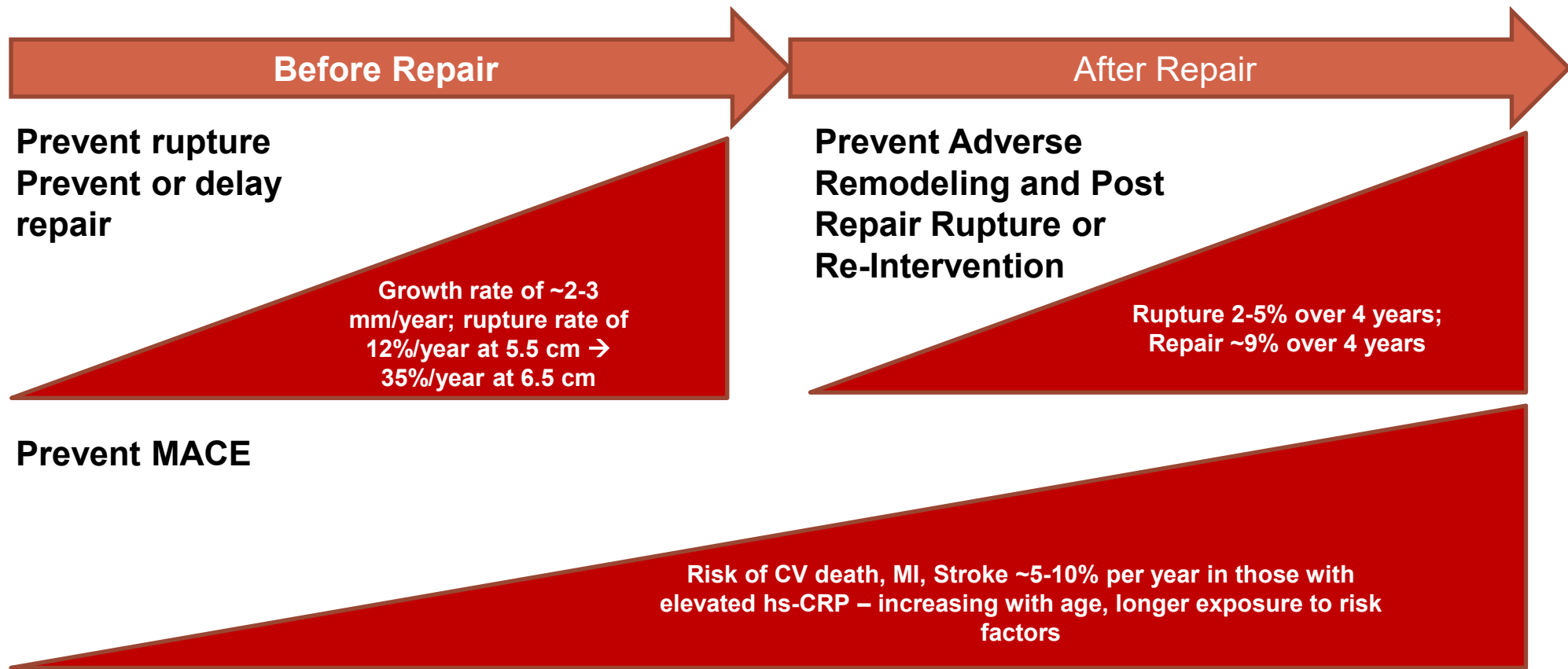
Higher hs-CRP levels associated with larger AAA



Changes in hs-CRP associated with changes in AAA size



Potential for Broad Vascular Benefits & AAA Disease Modification Before and After Repair



Agenda

Carrying pacibekitug momentum into 2025

Sandeep Kulkarni, MD
Co-Founder & CEO

Addressing residual inflammatory risk in CV diseases

Marc P. Bonaca, MD, MPH
*University of Colorado
CPC Clinical Research*

Pioneering the next frontier in CV with IL-6 inhibition

Emil deGoma, MD
SVP, Medical Research

Pacibekitug's practice-changing potential in CV

Gerhard Hagn
SVP, Head of Commercial & BD

Confirming pacibekitug's best-in-disease opportunity in TED

Gerhard Hagn
SVP, Head of Commercial & BD

Q&A

Our vision is to lower CV-related morbidity and mortality in patients with high inflammatory risk through IL-6 inhibition...

To achieve this vision, we plan to...

Bring pacibekitug to high-risk ASCVD patients
as a targeted anti-inflammatory therapy

Expand pacibekitug use beyond patient
populations currently studied in clinical trials

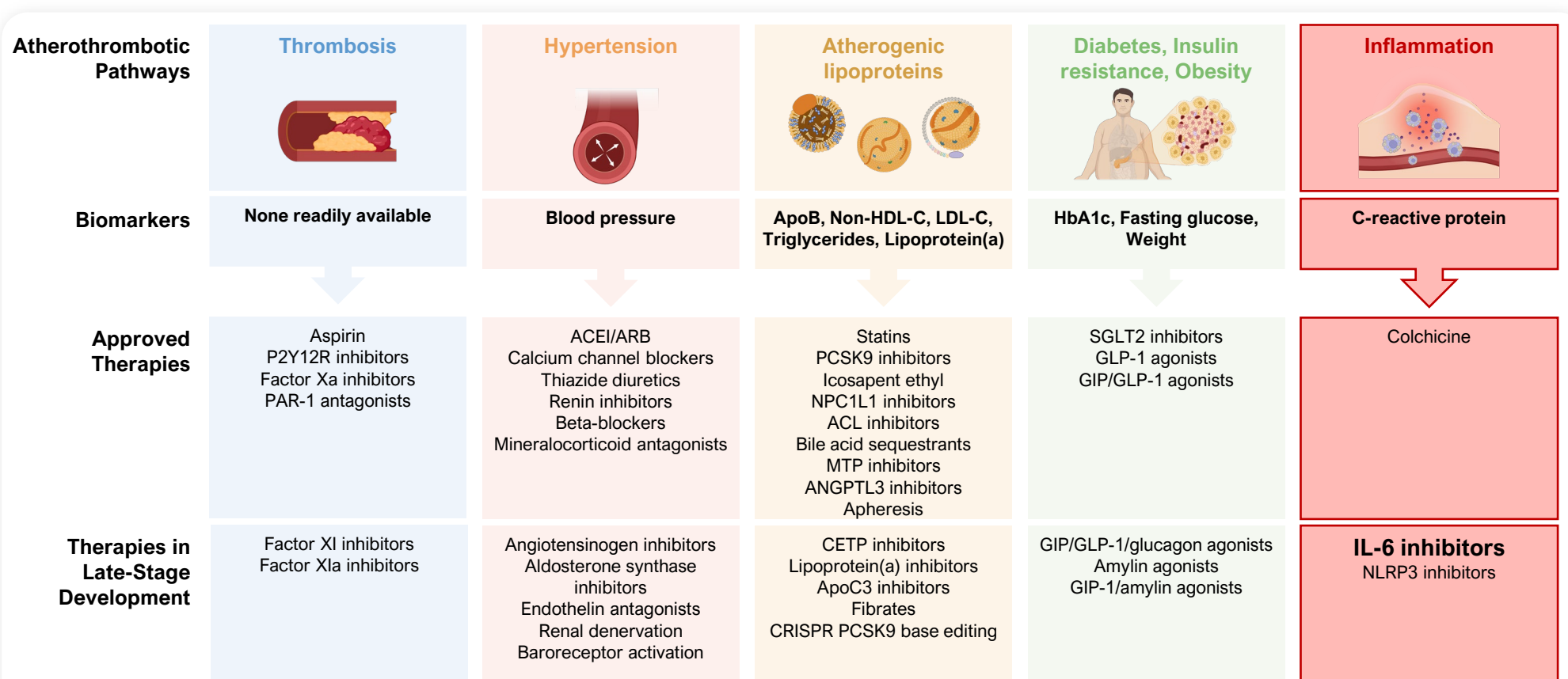
Support increased **testing of hs-CRP** by leveraging
activities of others in a **targeted manner**

Improve adherence and real-world effectiveness
through **quarterly administration** of pacibekitug

Innovate CV trial designs and ultimately patient care
by **engaging with our CV SAB** and other experts

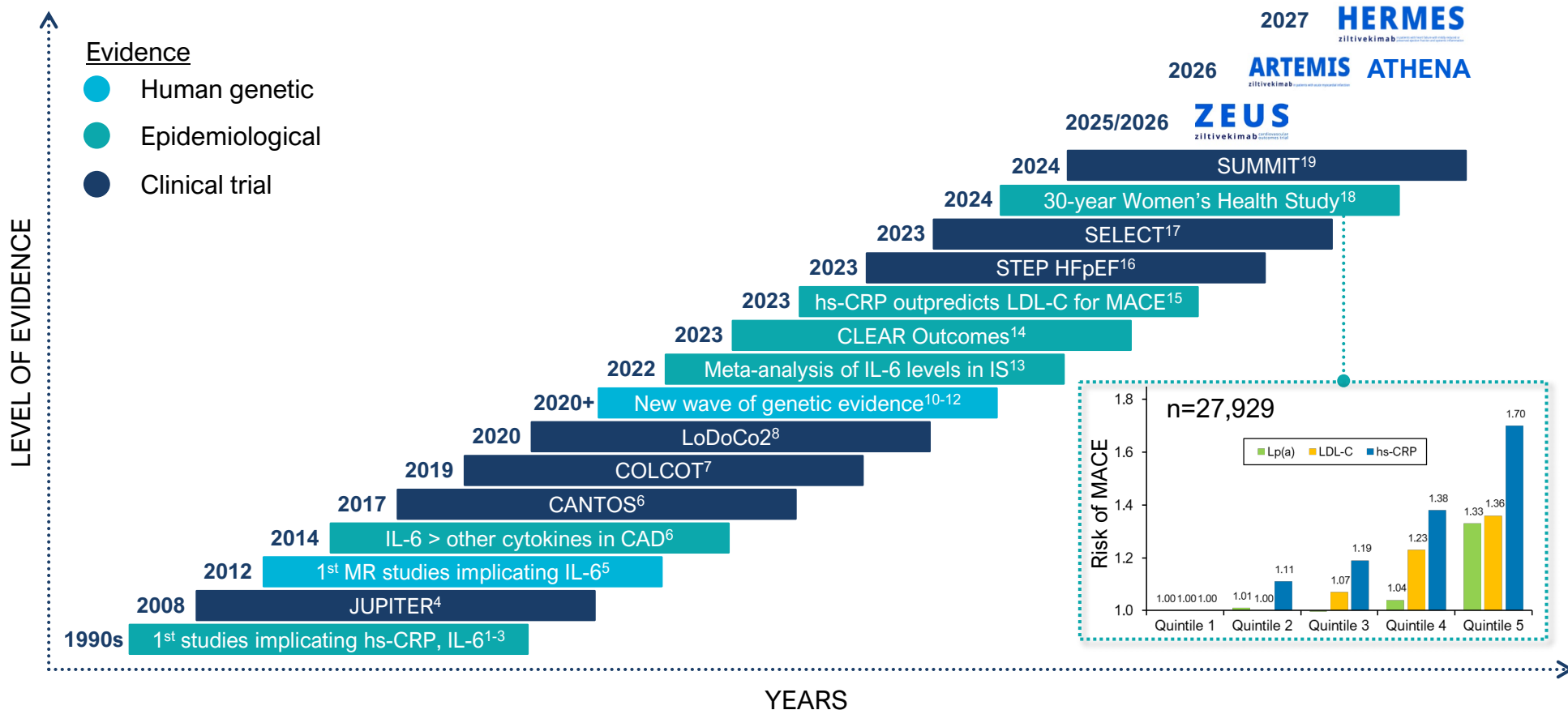
...so that millions of CV patients live healthier and longer lives

Reducing inflammation: the next frontier for cardiovascular disease



List of therapies not exhaustive. ACEI: angiotensin-converting enzyme inhibitor. ACL: adenosine triphosphate-citrate lyase. ANGPTL3: angiopoietin-like protein 3. ApoB: apolipoprotein B. ApoC3: apolipoprotein C3. ARB: angiotensin receptor blocker. CETP: Cholesteryl ester transfer protein. CRISPR: clustered regularly interspaced short palindromic repeats. GIP: gastric inhibitory polypeptide. GLP-1: glucagon-like peptide-1. IL-6: Interleukin-6. MTP: microsomal triglyceride transfer protein. NLRP3: nucleotide-binding domain, leucine-rich-containing family, pyrin domain-containing-3. NPC1L1: Niemann-Pick C1-Like 1. PAR: protease-activated receptors. PCSK9: proprotein convertase subtilisin/ kexin type 9. P2Y12R: purinergic 2Y type 12 receptor. SGLT2: sodium-glucose cotransporter 2.

After decades of accumulating evidence, we are now approaching a potential paradigm shift in cardiovascular inflammation



Mechanism matters: compelling human evidence for IL-6 inhibition in CV diseases



Human genetic evidence¹⁻⁵

The interleukin-6 receptor as a target for prevention of coronary heart disease: a mendelian randomisation analysis

The Interleukin-6 Receptor Mendelian Randomisation Analysis (IL6R MR) Consortium*

RESEARCH LETTERS

A Missense Variant in the IL-6 Receptor and Protection From Peripheral Artery Disease

Interleukin-6 receptor pathways in coronary heart disease: a collaborative meta-analysis of 82 studies

IL6R Genetics Consortium and Emerging Risk Factors Collaboration*

RESEARCH LETTER

Interleukin-6 Signaling Effects on Ischemic Stroke and Other Cardiovascular Outcomes

A Mendelian Randomization Study

Research Letter

Genetically Proxied IL-6 Receptor Inhibition and Coronary Artery Disease Risk in a Japanese Population

Sizheng Steven Zhao^{1,2}, Dipender Gill²



Epidemiological evidence⁶⁻⁹

ORIGINAL ARTICLE

Inflammation, Cholesterol, Lipoprotein(a), and 30-Year Cardiovascular Outcomes in Women

Paul M Ridker, M.D., M. Vinayaga Moorthy, Ph.D., Nancy R. Cook, Sc.D.,

Inflammation and cholesterol as predictors of cardiovascular events among patients receiving statin therapy: a collaborative analysis of three randomised trials

Paul M Ridker, Deepak L Bhatt, Anura D Pradhan, Robert J Glynn, Jean G MacFadyen, Steven E Nissen, on behalf of the PROMINENT, REDUCE-IT,

Inflammatory cytokines and risk of coronary heart disease: new prospective study and updated meta-analysis

Stephen Kaptoge^{1*}, Sreenivasa Rao Kondapally Seshasai², Pei Gao¹, Daniel F. Freitag¹,

Current Atherosclerosis Reports (2025) 27:12
https://doi.org/10.1007/s11883-024-01259-7

REVIEW

IL-6 and Cardiovascular Risk: A Narrative Review

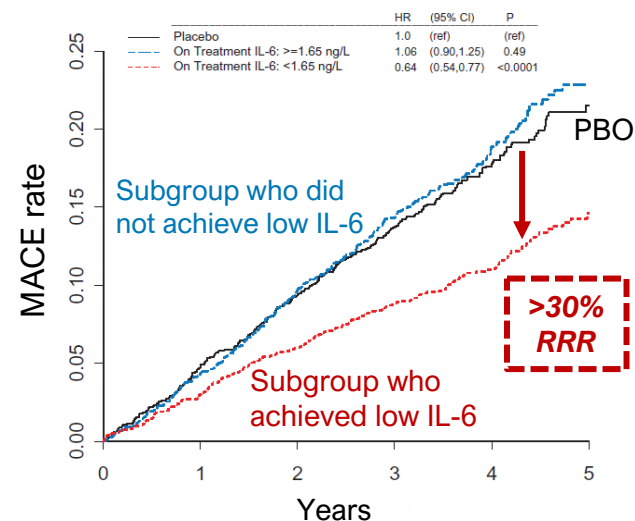
Nehal N. Mehta¹ · Emil deGoma² · Michael D. Shapiro³

Accepted: 4 November 2024
© The Author(s) 2024



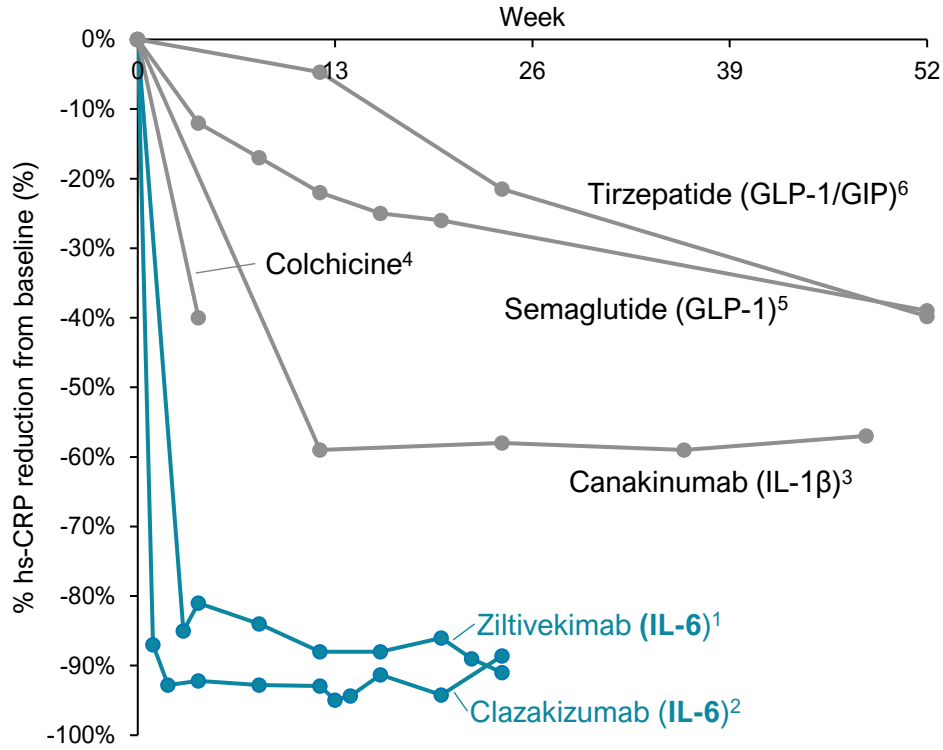
Clinical trial evidence¹⁰⁻¹³

CANTOS (canakinumab)¹²

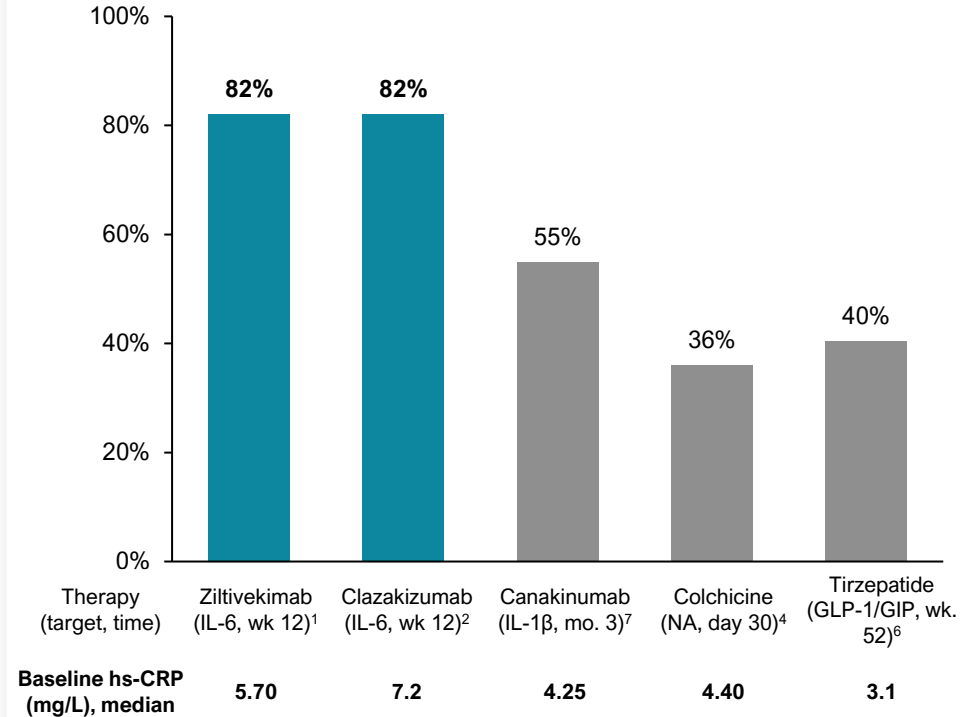


IL-6 inhibition has produced rapid and robust hs-CRP reductions in patients with established or at high-risk of CVD

Percent reduction in hs-CRP

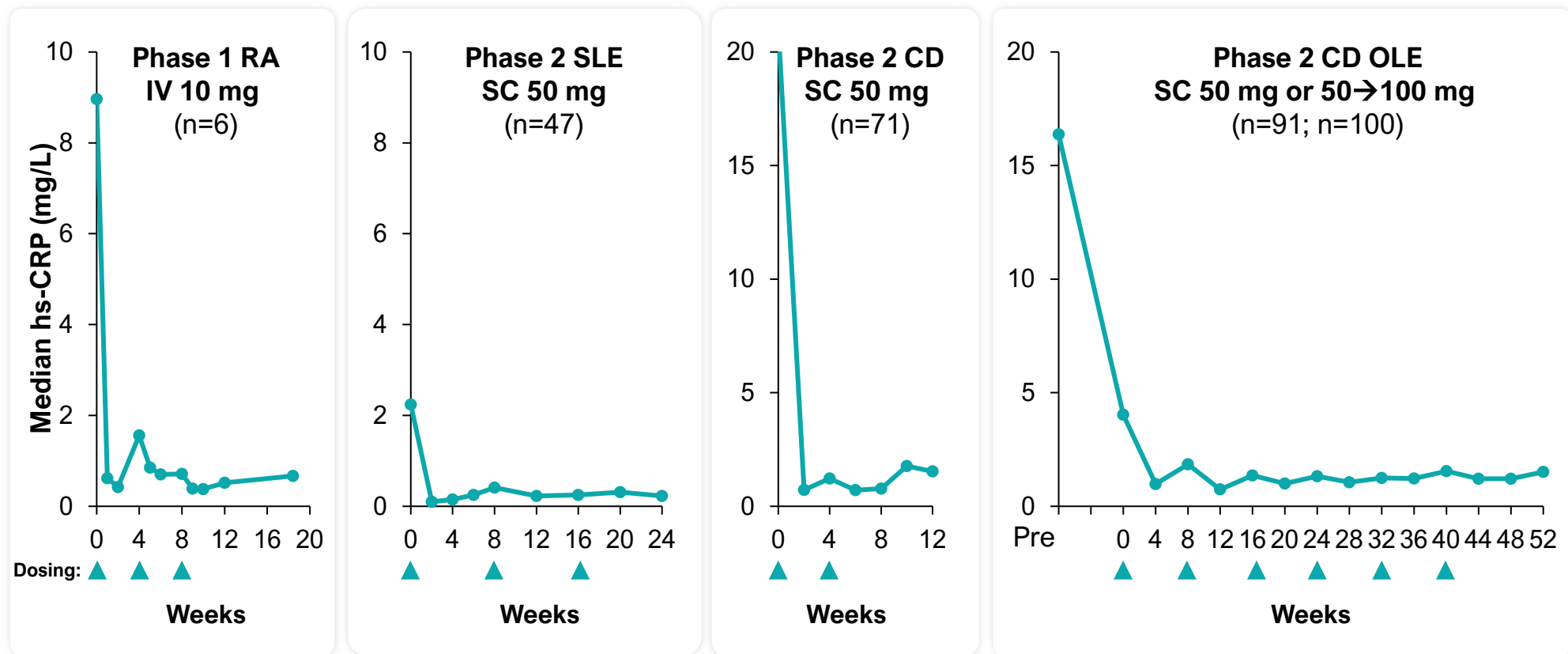


% of patients with hs-CRP <2 mg/L



¹RESCUE: Ridker et al., Lancet (2021). Ziltivekimab 15mg q4w arm. ²Chertow et al., Nat Med (2024). Clazakizumab 5mg q4w arm. ³CANTOS: Ridker et al., N Eng J Med (2017). 150mg q3m arm. ⁴Fiolet et al., PLOS ONE (2020). Colchicine 0.5mg QD. ⁵SELECT: Plutzky et al., EAS Congress (2024). Semaglutide 2.4mg QW maintenance. ⁶Borlaug et al., Nat Med (2024). Tirzepatide up to 15mg QW. ⁷Ridker et al., Lancet (2017). Time course values obtained by webplotdigitizer. Values are not placebo adjusted. CVD: cardiovascular disease. GIP: gastric inhibitory polypeptide. GLP-1: glucagon-like peptide-1. hs-CRP: high sensitivity C-reactive protein. Certain data in this presentation are based on a cross-trial comparison and are not based on head-to-head clinical trials. Cross trial comparisons are inherently limited and may suggest misleading similarities or differences in outcomes. Results of head-to-head comparisons may differ significantly from those set forth herein.

Pacibekitug achieved rapid and robust suppression of hs-CRP in patients with high-grade inflammatory autoimmune disorders



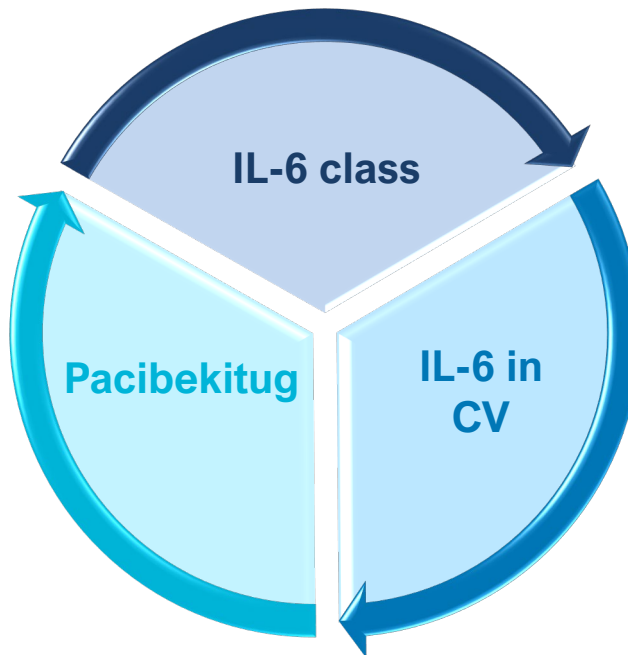
CD: Crohn's disease. hs-CRP: high sensitivity C-reactive protein. OLE: open-label extension, RA: rheumatoid arthritis, SLE: systemic lupus erythematosus. Rheumatoid arthritis: B0151002 study report. Table 14.4.7.1.1. Median baseline CRP 9.0 mg/L. Key eligibility: active disease, background methotrexate. Crohn's disease: B0151003 study report. Table 14.2.4.1.3. Median baseline hs-CRP 21.1 mg/L. Key eligibility: active disease, failed/intolerant to anti-TNF α . CD OLE B0151005 study report. Table 14.2.4.1. Median pre-baseline hs-CRP 16.4 mg/L, baseline hs-CRP 4.0 mg/L. Systemic lupus erythematosus: B0151006 study report. Table 14.3.4.1.5. Median baseline hs-CRP 2.2 mg/L.

Safety profile of IL-6 inhibition is well understood

Over 1M patients treated with IL-6 pathway inhibitors since 2010¹

Continued progress and learnings on trial monitoring and execution may further mitigate risk⁴

Existing safety data from approximately 450 study participants⁵ and reviewed by FDA

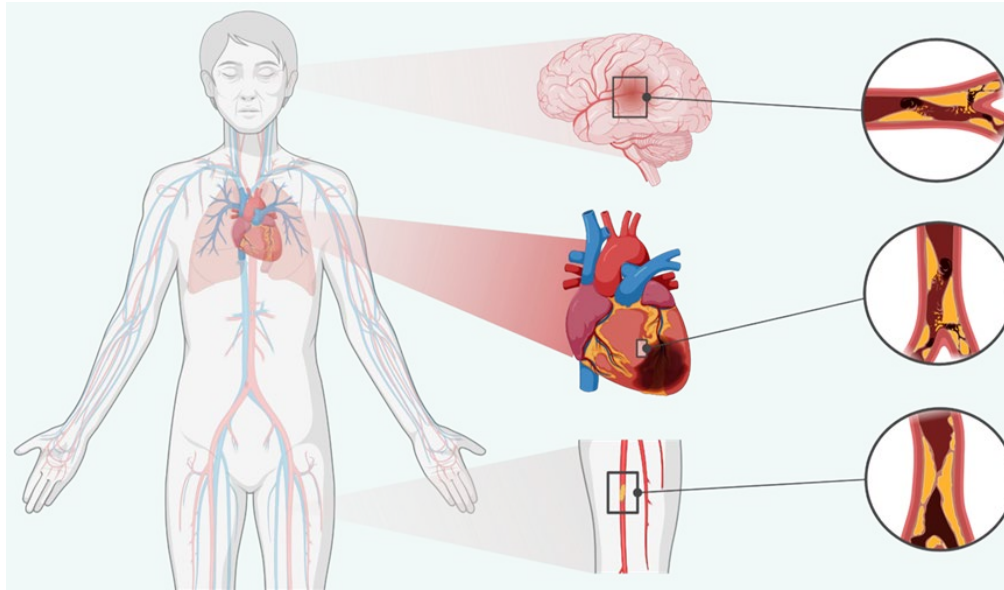


Lower rates of class AEs observed in CV populations in Ph2 studies vs. autoimmune diseases²

Phase 3 CV outcome trials of IL-6 inhibitors continue with no major safety amendments reported³

ASCVD:

Our lead CV indication with potentially practice-changing impact



Cerebrovascular disease

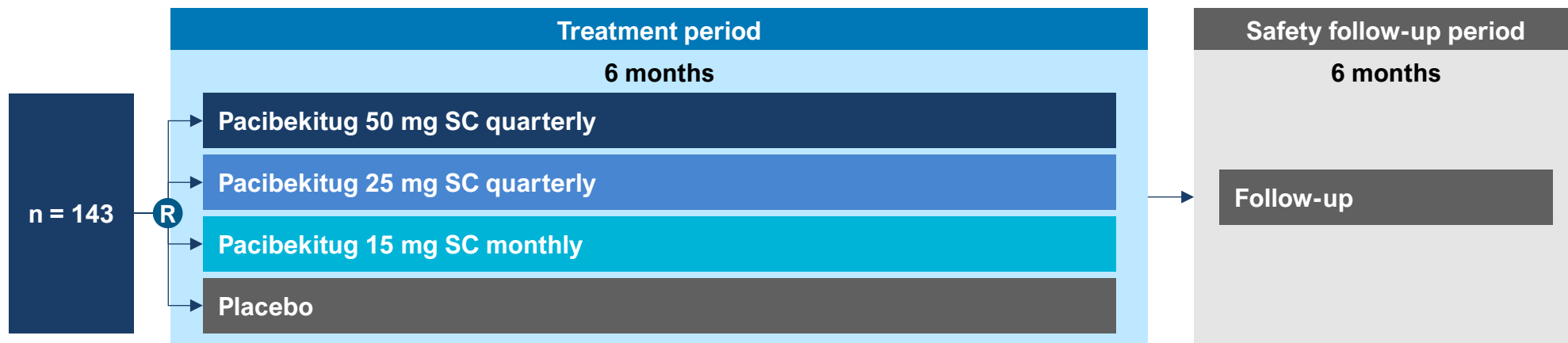
Coronary artery disease

Peripheral artery disease

- ACSVD continues to be the **leading cause of death** globally¹
- With **significant, persistent unmet need** for targeted anti-inflammatory therapy²

TRANQUILITY⁶ Phase 2 trial supporting development in ASCVD

Double-blinded, placebo-controlled Phase 2 trial (NCT06362759) | Status: **over-enrollment completed**



Study population:

- CKD stage 3-4 (eGFR 15-59 ml/min/1.73m²) or UPCR>200 mg/g
- hs-CRP ≥2 mg/L and <15 mg/L
- Exclude patients at higher risk for safety complications (e.g., immunocompromised patients)

Primary pharmacodynamic endpoint:

- Change from baseline in hs-CRP through Day 90

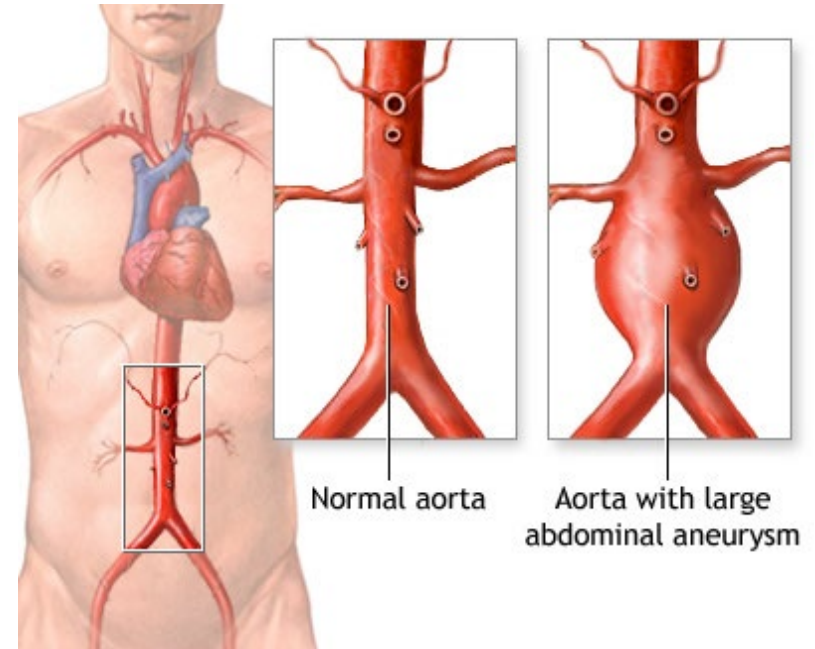
Additional endpoints:

- Percent of participants who achieve hs-CRP <2 mg/L
- Other pharmacodynamic markers, including lipoprotein (a)
- Safety and tolerability

AAA:

A high-mortality, first-in-disease opportunity for pacibekitug

- High-risk vascular disease with **significant unmet need in approximately 2M people in US¹**
- **Strong strategic fit** with ASCVD due to overlapping prescribers
- Progressive disease with increasing risk of **rupture, usually a fatal event²**
- **In less than 5 years**, majority of medium-sized AAA grow to threshold for surgical repair^{3,4}
- Surgical repair, recommended for large AAA to prevent rupture, is **associated with complications⁵⁻⁹**



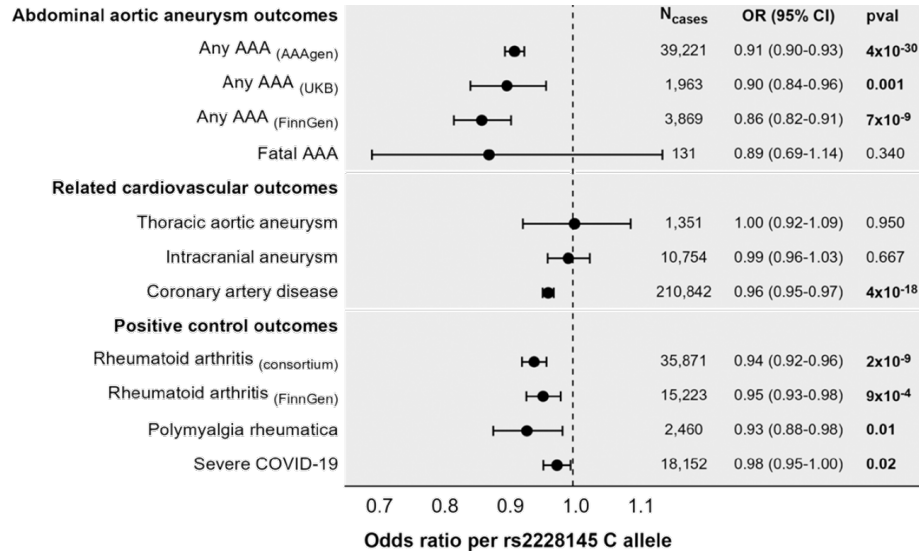
No FDA approved treatment

Compelling evidence supports IL-6 inhibition to slow AAA growth



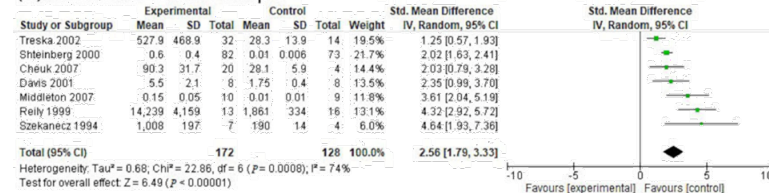
Human genetic evidence

Genetic variant associated with reduction in risk of AAA¹



Epidemiological evidence

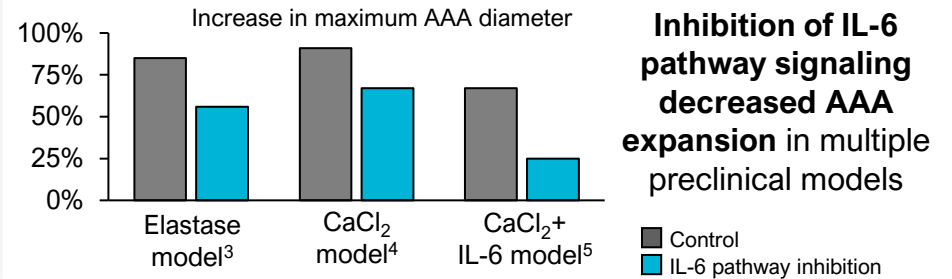
(D) IL-6 studies - Tissue sample



Higher IL-6 levels associated with AAA²



Experimental evidence

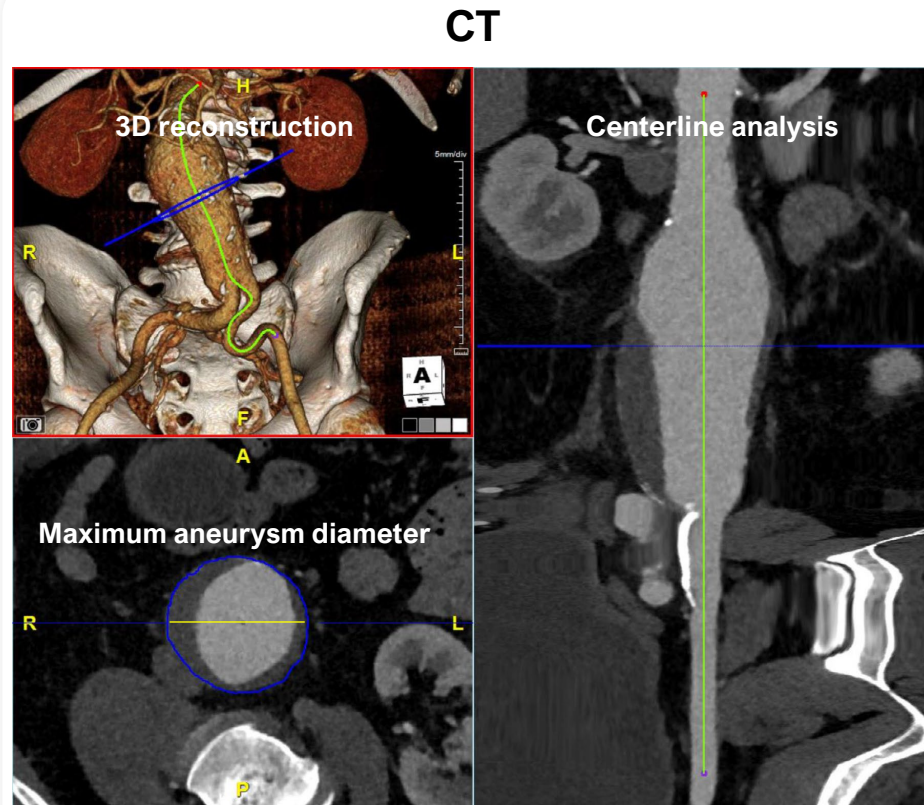


Phase 2 PoC study expected to use imaging to evaluate the ability of pacibekitug to inhibit AAA growth

- Serial imaging is the foundation of clinical care¹
- Phase 2 PoC expected to use multimodality imaging to efficiently characterize pacibekitug

Next steps:

- TRANQUILITY topline data in Q2 2025
- Alignment with FDA on Phase 2 PoC design
- Details to be shared prior to study start



Agenda

Carrying pacibekitug momentum into 2025

Sandeep Kulkarni, MD
Co-Founder & CEO

Addressing residual inflammatory risk in CV diseases

Marc P. Bonaca, MD, MPH
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Pioneering the next frontier in CV with IL-6 inhibition

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Pacibekitug's practice-changing potential in CV

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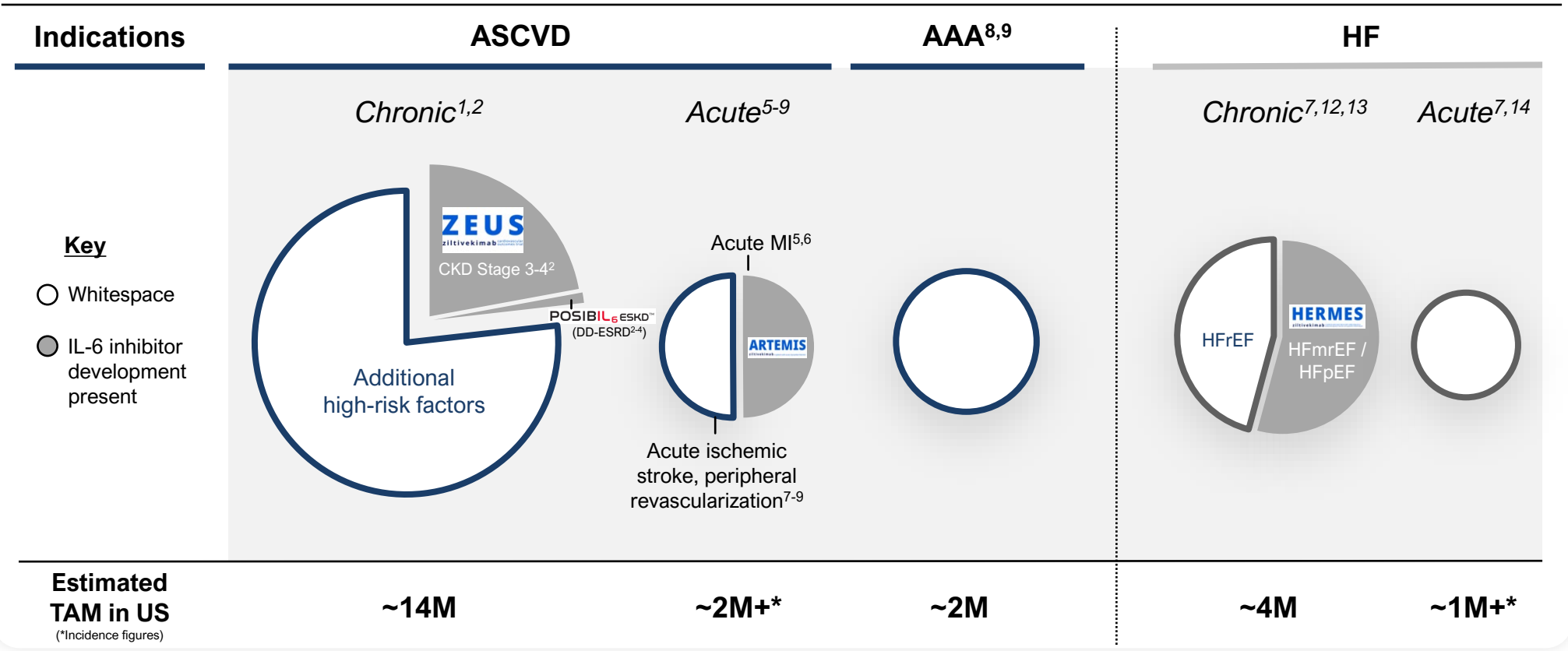
Q&A

Unlike other cardiovascular / metabolic MOAs, there is scarcity value in the IL-6 class

<p>IL-6 (3)</p>	<p>TOURMALINE</p>  							
<p>Lp(a) (7)</p>	      							
<p>NLRP3 (7+)</p>	       <p>...</p>							
<p>GLPs (11+)</p>	           <p>...</p>							

Potentially over 20M CV patients with residual inflammatory risk in the US

Estimated US CV populations with residual inflammatory risk (hs-CRP > 2 mg/L)



¹Gu et al., Am J Prev Cardiol (2022). ²Nanna et al., Circulation (2022). ³NIDDK "Kidney Disease Statistics for the United States" Accessed 11/21/24. ⁴Cozzolino et al., Nephrol Dial Transplant (2018). ⁵Masoudi et al., J Am Coll Cardiol (2017). ⁶Alexander and Smith, N Eng J Med (2016). ⁷Tsao et al., Circulation (2023). ⁸Columbo et al., Circ (2023). ⁹Guez et al., Am J Roentgenol (2019). ¹⁰Stuntz, Cardiology (2016). ¹¹De Haro et al., J Vasc Surg (2016). ¹²Ferreira et al., Int J Cardiol (2024). ¹³Defilippi et al., J Card Fail (2023). ¹⁴Kalogeropoulos et al., J Card Fail (2014). AAA: abdominal aortic aneurysm. ASCVD: atherosclerotic cardiovascular disease. CKD: chronic kidney disease. DD-ESRD: dialysis-dependent end stage renal disease. HF: heart failure. HFmrEF: heart failure with mildly reduced ejection fraction. HFpEF: heart failure with preserved ejection fraction. HFrEF: heart failure with reduced ejection fraction. hs-CRP: high sensitivity C-reactive protein. MI: myocardial infarction. TAM: Total addressable market. Figure sizes are directional and not to scale. Figures are estimates rounded to the nearest million based on internal market research and have not been verified by any independent source.

Our approach to differentiation within IL-6 class is three-pronged



Quarterly Dosing



Pacibekitug¹



Ziltivekimab

Best-in-Class – where we compete



Development Strategy

- **First-in-class:** Target ASCVD populations currently not covered by ziltivekimab
- **First-in-disease:** Tackle AAA, a very high unmet need opportunity

Being First – where we lead

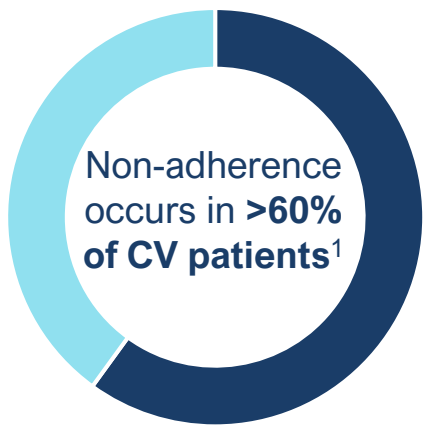


**Fast
Learner**

External CV outcomes trials provide critical insights to **drive additional differentiation**



Less frequent dosing drives greater adherence in CVD which profoundly improves patient outcomes



Cardiac Outcomes² & Mortality²



Hospitalization³



Economic Implications⁴



Dosing Frequency

Adherence



Weekly vs. daily SC

Patients on weekly Ozempic were **30% more adherent** than on daily Victoza⁵

2 / year SC vs. weekly oral

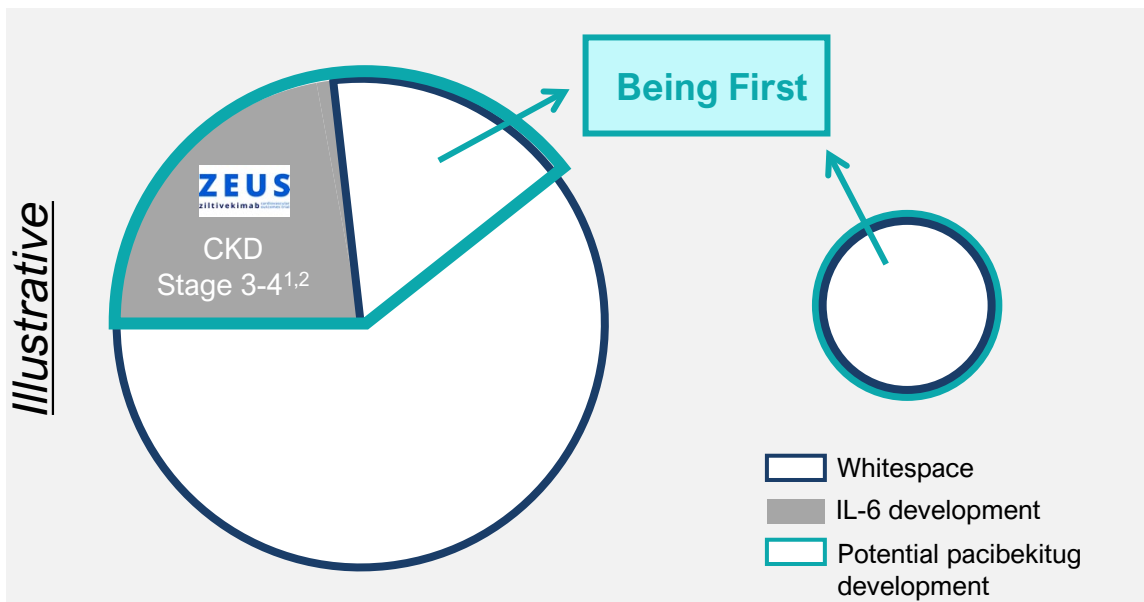
Patients on 2 / year Prolia were **29% more adherent** than on weekly orals at year 2⁶



We strategically assess first-in-class and first-in-disease patient populations for clinical development

ASCVD* (first-in-class)

AAA** (first-in-disease)













*Only chronic ASCVD displayed for illustrative purposes

**Exact target population dependent on AAA strategy and Phase 2 trial design

Strategic selection criteria:

1. Compelling genetic, epidemiological, and clinical evidence
2. High and persistent risk of CV-related morbidity and mortality
3. Overlapping prescriber bases with validated motivation to treat with IL-6

Successful cardiometabolic brands have gained advantage over first-to-market class competitors

Differentiation Strategy	Analog Market	Brands  = In-class follower	Relative Performance <i>US Peak Year Sales¹</i>	Summary
 Dosing	GLP-1 Type 2 diabetes		~\$3B	In the context of a broader blockbuster arms-race, Eli Lilly successfully promoted Trulicity's weekly dosing advantage over daily Victoza to overtake Novo Nordisk's first-gen GLP-1 (despite limited clinical differentiation) ahead of semaglutide launch
			~\$6B	
 Strategy	SGLT2 Type 2 diabetes		~\$1.5B	Boehringer Ingelheim / Eli Lilly moved aggressively and strategically to unlock remaining white space in increasingly crowded Type 2 diabetes market, securing their supremacy in the high-opportunity new cardiologist channel with first-in-class CV outcomes
			~\$5B	
 Fast Learner	Factor Xa Anticoagulation		~\$2.5B	After Xarelto missed superiority vs. warfarin in their pivotal, BMS / Pfizer delayed their own launch to increase sample size and achieve superiority, which they were able to promote in US alongside other clinical advantages to later dominate the market
			~\$8.5B	

TRANQUILITY topline results, if positive, are expected to unleash multiple attractive paths for pacibekitug in CV inflammation

TRANQUILITY⁶

Aims to demonstrate

Rapid and robust hs-CRP reduction
Quarterly dosing
Safety profile in high-risk patients



Q2 2025

Expected to enable

Dose selection for subsequent trials
EoP2 FDA meeting
Phase 3-readiness in ASCVD
AAA Phase 2 PoC trial preparation



H2 2025

TRML with partner

CVOTs in ASCVD & beyond

TRML with financing

CVOT in ASCVD



2026

Agenda

Carrying pacibekitug momentum into 2025

Sandeep Kulkarni, MD
Co-Founder & CEO

Addressing residual inflammatory risk in CV diseases

Marc P. Bonaca, MD, MPH
*University of Colorado
CPC Clinical Research*

Pioneering the next frontier in CV with IL-6 inhibition

Emil deGoma, MD
SVP, Medical Research

Pacibekitug's practice-changing potential in CV

Gerhard Hagn
SVP, Head of Commercial & BD

Confirming pacibekitug's best-in-disease opportunity in TED

Gerhard Hagn
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Q&A

TED: An independent shot on goal for pacibekitug with its own blockbuster potential



Autoimmune disease with heterogenous symptoms and **inflammation at the core**



Focus in 2024 has been on **spiriTED trial execution**



Market research and KOL interactions reinforce our **conviction in pacibekitug**



We expect to report **spiriTED topline data in H2 2025**

Recent conferences confirmed significant unmet need in TED...

Building Tourmaline presence and trial awareness



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Core take-aways from discussions with TED-treaters

1. Tepezza's **lack of durable response** is an increasing concern
2. Managing **AE profile remains a challenge** including hearing loss, menstrual/reproductive issues, hyperglycemia, and muscle spasms
3. Endos are starting to get more involved, yet Tepezza's **complexity represents major barrier**
4. HCPs have less enthusiasm for other IGF-1R therapies, voicing the **need for new MOAs**

...consistent with our TED market research in the US

3 most commonly-stated unmet needs

1. Lack of durability:

“Main unmet need is the uncertainty on durability of effect” – Endocrinologist¹

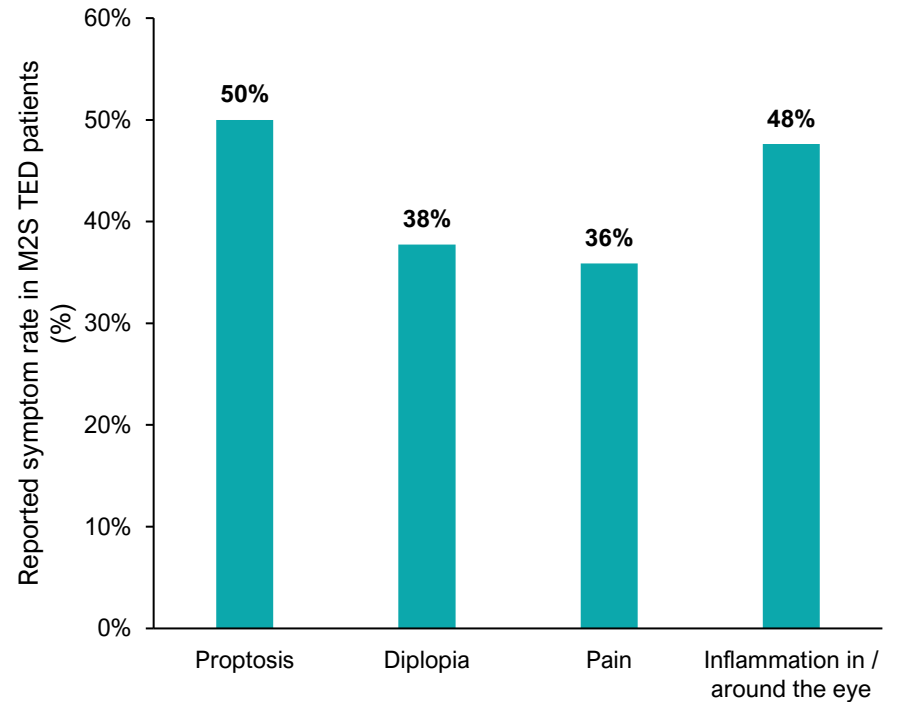
2. Management of AE profile

“Endocrinology handles the hyperglycemia. I would probably have ENT, not just audiology, involved for hearing AEs” – Oculoplastic Surgeon²

3. Complexity

“Tepezza is cumbersome to administer... filling out forms, finding infusion centers, fighting with insurance firms is labor intensive for the office” – Oculoplastic Surgeon³

Only ~50% of TED patients present with proptosis⁴



Over 50 publications support the therapeutic potential of IL-6 pathway inhibition in TED

Study Details				Key Endpoints		
First author	Year	Study type	N treated	Proptosis response rate	CAS response rate	% autoantibody reduction
Pérez-Moreiras	2021	Retro	54	78	89	75
Sánchez-Bilbao	2020	Obs	48	NR	NR	NR
Atienza-Mateo	2018	Retro	29	NR	NR	NR
Lee	2024	Prosp	19	11	47	56
Pérez-Moreiras	2014	Prosp	18	72	100	76
Pérez-Moreiras	2018	RCT	15	93	60	NS
de la Fuente Bursón	2020	Retro	15	NR	NR	NR
Pereira	2023	Retro	14	NR	NR	NR
Habroosh	2024	Prosp	13	100	31	68
Boutzios	2023	Obs	12	NR	NR	84
Pampín-Sánchez	2022	Retro	11	75	73	NR
Moi	2022	Retro	10	CI	80	75
Cortez	2022	Prosp	10	10	100	81
Silkiss	2020	CS	9	CI	56	74
Smith	2021	Retro	9	78	100	54
Bielefeld	2019	Obs	8	NR	NR	NR
Ceballos-Marcias Jose	2020	CS	8	NR	75	41
Bennedjai	2020	Retro	7	NR	NR	73
Moás	2022	Obs	7	NR	NR	92
Toro-Tobon	2023	Retro	6	50	NR	NR
de Pablo Gomez	2018	CS	5	NR	60	NR
Navarrete	2022	Retro	5	NR	NR	NR
Ribi	2017	CS	3	33	67	NR
Maldiney	2020	CS	3	67	NR	NR
Stevens	2022	Retro	3	100	67	NR
Russell	2017	CS	2	NR	0	NR
Sy	2017	CS	2	CI	50	69

Study Details				Key Endpoints		
First author	Year	Study type	N treated	Proptosis response rate	CAS response rate	% autoantibody reduction
Copperman	2019	CS	2	100	0	NR
Coy	2019	CS	2	NR	50	NR
Sierra Osorio	2020	CS	2	100	100	NR
Park	2021	CS	2	100	100	NR
Abeillon-du Payrat	2022	CS	2	100	50	NR
Butnaru	2013	CR	1	NR	100	NR
Gómez Rodríguez	2014	CR	1	NR	100	NR
Bielefeld	2017	CR	1	CI	NR	NR
Canas	2018	CR	1	100	NR	NR
Pascual-Camps	2018	CR	1	NR	NR	NR
Garreta Fontelles	2019	CR	1	NR	NR	93
Mehmet	2020	CR	1	0	NR	NR
Kaplan	2020	CR	1	NR	0	85
Cayon-Blanco	2020	CR	1	NR	100	NR
Tran	2020	CS	1	NR	NR	NR
Ruiz	2021	CR	1	NR	NR	NR
Albrashdi	2022	CR	1	100	NR	NR
Cezara	2022	CR	1	NR	0	NR
Mohamed	2022	CS	1	0	0	NR
Moleiro	2022	CR	1	100	NR	86
Almazrouei	2023	CR	1	NR	NR	NR
Cuculescu	2023	CR	1	CI	0	NR
Nirmalan	2023	CS	1	NR	NR	NR
Pramono	2023	CR	1	NR	NR	NR
Rymuza	2024	CR	1	100	0	8
Weighted Mean				68%	72%	71%
Smith 2017 (tepro Phase 2)				71%	69%	N/A
Douglas 2020 (tepro Phase 3)				83%	59%	N/A

We believe many of these reports may underestimate the true efficacy of IL-6 inhibition

- 350+ mostly steroid-refractory patients
- Late IL-6 inhibition (>9 months post symptom onset) when disease may have exited active phase
- Exposure to IL-6 inhibition may have been suboptimal (<6 months)
- Market research suggests many HCPs already routinely use IL-6 inhibitors in their practice

Proptosis response rate is generally defined in the data outlined here as a ≥ 2 mm proptosis improvement in the worse eye at baseline without any worsening in the other eye. CAS (Clinical Activity Score) response rate is generally defined in the data outlined here as a CAS of 0 or 1. Studies referenced in this table represent investigator-led studies and were not designed with the intent of generating evidence for an approval of tocilizumab or sarilumab in TED. The majority of these studies were not designed with power to detect statistical significance. Retro: retrospective. Obs: observational. Prosp: prospective. RCT: randomized controlled trial. CS: case series. CR: case report. NR: not reported. NS: not significant. CI: clear improvement. HCP: health care professional. Tepro: teprotumumab. TED: thyroid eye disease. Publications available upon request.

Pacibekitug's target product profile is expected to be well-differentiated in TED...

Target product profile in TED*

Study population		<ul style="list-style-type: none"> Moderate-to-severe active TED patients
MOA		<ul style="list-style-type: none"> IL-6 inhibition
Efficacy	Primary endpoint	<ul style="list-style-type: none"> Proptosis
	Secondary endpoints	<ul style="list-style-type: none"> Diplopia, clinical activity score (CAS), inflammation, and lid retraction
	Additional measures	<ul style="list-style-type: none"> Lower rate of relapse and retreatment Rapid time to response Lower rate of surgical intervention
Safety	Warnings & precautions	<ul style="list-style-type: none"> No anticipated risk of permanent hearing loss or warnings beyond typical IL-6 safety considerations
Dosing & administration		<ul style="list-style-type: none"> Every 8-week, low volume subcutaneous injection through pre-filled syringe Finite dosing

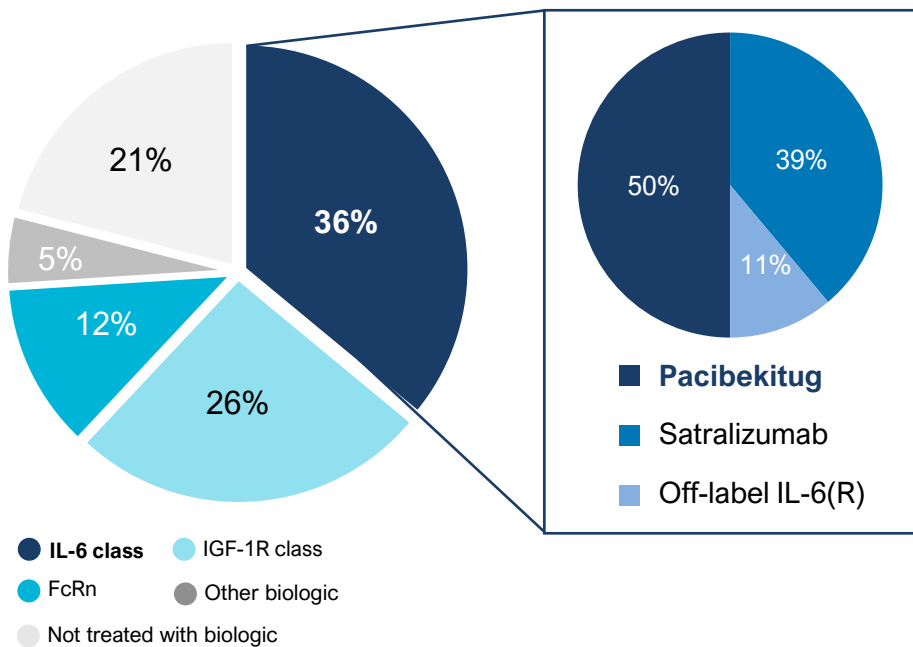
Targeted points of differentiation

- **Targeting inflammation** which is at core of disease
- **Holistic impact** on many QoL-impacting symptoms
- Emphasis on **response durability**
- **Well-tolerated** without the risk of hearing loss
- Least frequent and **most patient-friendly SC dosing**

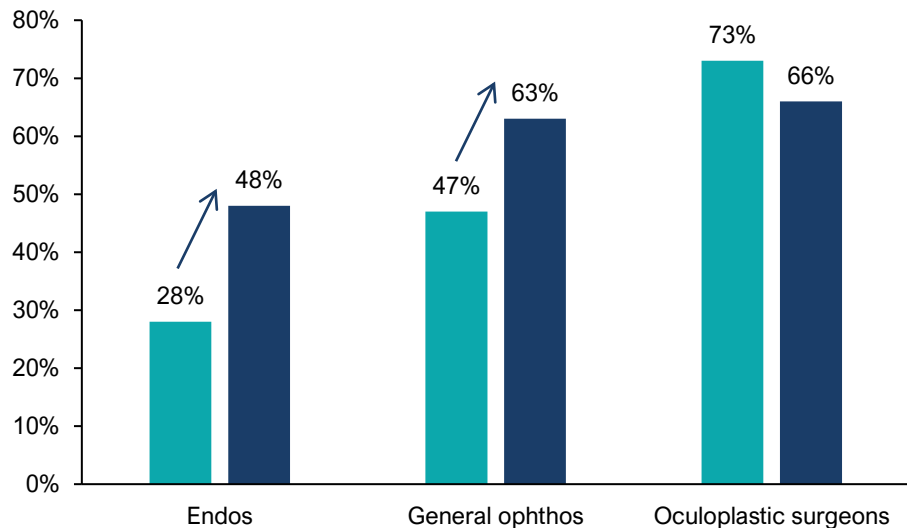
*This target product profile outlines the desired characteristics of pacibekitug in TED. It will be informed by clinical data from Phase 2b and Phase 3 and additional evidence generated from other programs including from the real world. The characteristics presented reflect outcomes that may not be representative of pacibekitug. The results of past clinical trials may not be indicative of future results, and the results of future or ongoing clinical trials may not demonstrate some or any of the characteristics presented. MOA: mechanism of action. QoL: quality of life. TED: thyroid eye disease. SC: subcutaneous

...resulting in leading market share, capitalizing on increasing Rx from endocrinologists and ophthalmologists

Pacibekitug ranked highest in future market share among 140 TED treaters in US¹



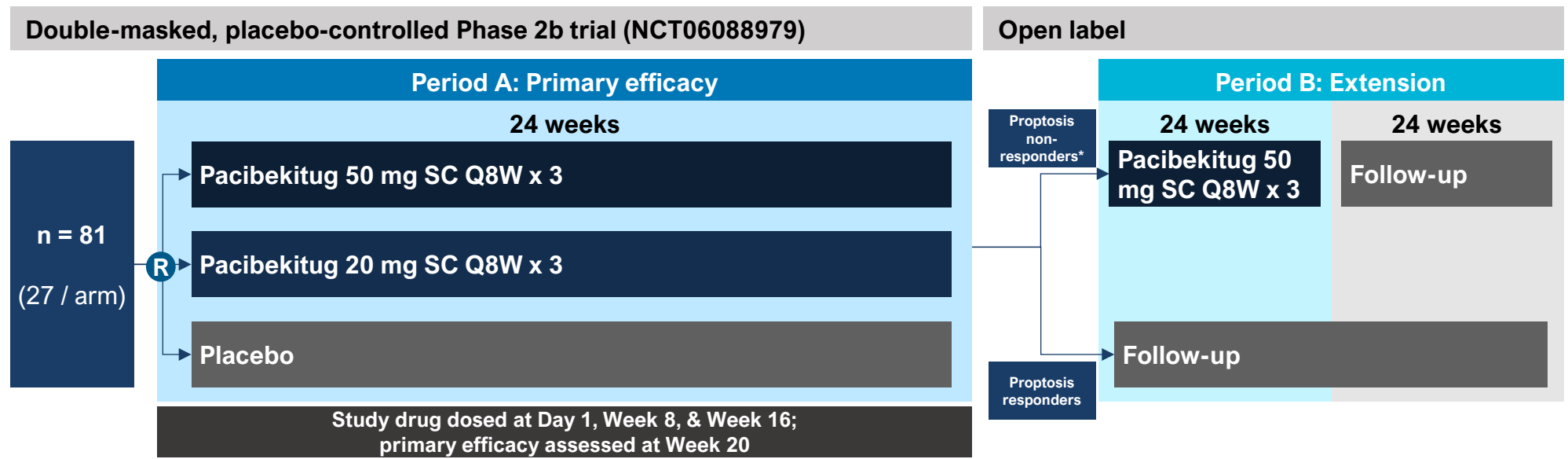
Impact on Rx if SC therapies are available¹



- I treat and manage moderate to severe active TED patients rather than referring out to another physician today
- As additional treatments become available for TED, including SC therapies, I will treat and manage moderate to severe active TED patients rather than referring out to another physician



spiriTED pivotal trial in first-line TED is ongoing



Study population:

- Moderate-to-severe TED, with proptosis ≥ 3 mm above normal (based on race and gender)
- Active phase, with symptom onset ≤ 15 months, CAS ≥ 4 and positive TSI
- First-line setting, with cap on prior corticosteroid use (< 1 g methylprednisolone or equivalent)

Primary efficacy endpoint:



- Proptosis response rate at week 20

Additional endpoints:

- CAS
- Diplopia
- QoL, safety, PK/PD/ADA

*Any patient who receives rescue therapy/intervention in Period A will not receive pacibekitug in Period B and will instead undergo follow-up only. ADA: anti-drug antibodies. CAS: clinical activity score. PD: pharmacodynamics. PK: pharmacokinetics. QoL: quality of life. SC: subcutaneous. TED: thyroid eye disease. TSI: thyroid stimulating immunoglobulin.

Key upcoming milestones

Disease focus	Indication	Milestone	Expected timing
Cardiovascular inflammation	ASCVD	 Phase 2 topline data	Q2 2025
	AAA	Phase 2 trial start	Post-TRANQUILITY topline data
Autoimmune disease	TED	 Phase 2b topline data	H2 2025

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