TOURMALINE

Understanding the Genetic Validation for IL-6 Inhibition in Cardiovascular Disease

November 1, 2024

Investor Presentation

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Agenda

Opening Remarks	**Sandeep Kulkarni, MD** Co-Founder & CEO, Tourmaline Bio
Genetic Validation in Drug Development	**Dipender Gill MD, PhD** Founder & CEO, Sequoia Genetics
Pacibekitug in Cardiovascular Disease	**Emil deGoma, MD** SVP Medical Research, Tourmaline Bio
Q&A	

Tourmaline key highlights

An IL-6 renaissance is underway: new insights emerging about a broad range of indications where IL-6 may be clinically validated

Pacibekitug (also referred to as TOUR006) has demonstrated best-in class potential: long-acting, low immunogenicity, and low-volume subcutaneous administration observed in clinical trials to date

A late-stage clinical company: pivotal Phase 2b spiriTED TED trial and Phase 2 TRANQUILITY CV trial ongoing, pivotal Phase 3 TED trial also expected to commence in 2H 2024

Accomplished leadership team: extensive experience developing and commercializing antibodies for immune and inflammatory diseases

Well-financed: cash expected to fund operations into 2027, enabling the delivery of key anticipated milestones for both strategic paths

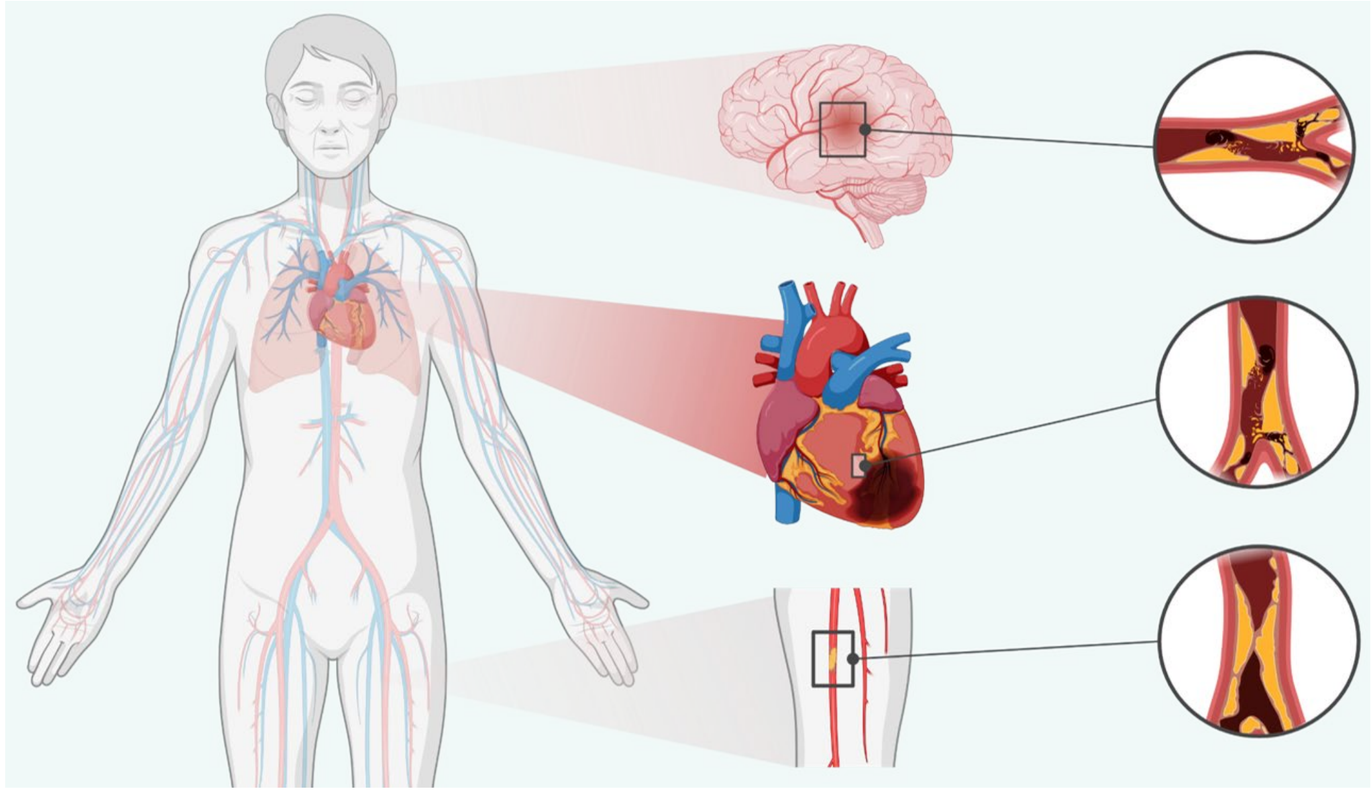
Convergence of human evidence supports therapeutic potential of IL-6 inhibition for atherosclerotic cardiovascular disease (ASCVD)

Human genetic evidence

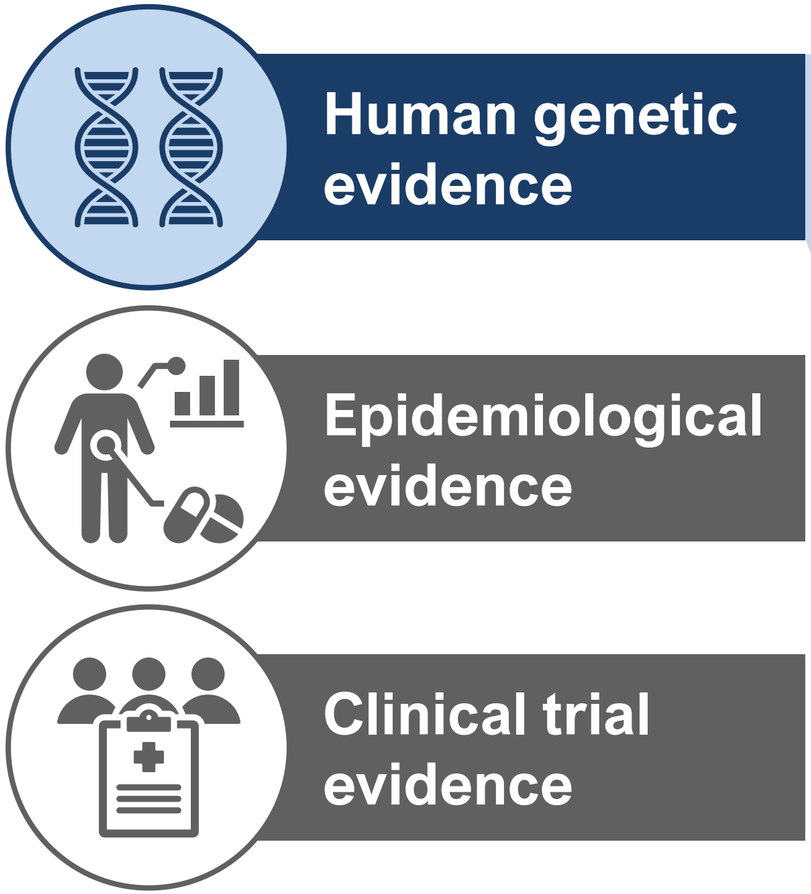
Epidemiological evidence

Clinical trial evidence

Evidence suggests IL-6 may drive ASCVD risk



Convergence of human evidence supports therapeutic potential of IL-6 inhibition for atherosclerotic cardiovascular disease (ASCVD)



- Informs ***causal*** association between genetic variants and outcomes
- Widely used approach to prioritize targets in cardiovascular disease

Today’s objectives

- Present the rationale and assumptions underlying genetic validation analyses
- Demonstrate how genetic validation can help reduce risk and inform drug development decisions
- Review the body of genetic validation supporting IL-6 as a therapeutic target for cardiovascular disease

Agenda

Opening Remarks	**Sandeep Kulkarni, MD** Co-Founder & CEO, Tourmaline Bio
Genetic Validation in Drug Development	**Dipender Gill MD, PhD** Founder & CEO, Sequoia Genetics
Pacibekitug in Cardiovascular Disease	**Emil deGoma, MD** SVP Medical Research, Tourmaline Bio
Q&A	

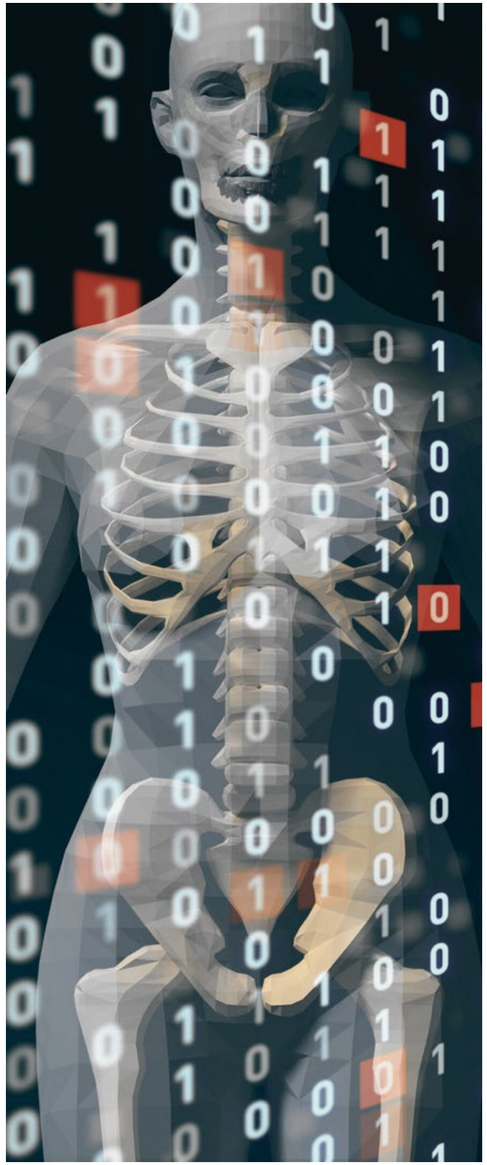
November 2024

The drug business: an ecosystem primed for disruption through human genetics

Presented by:

Dipender Gill

CEO & Founder, Sequoia Genetics



Agenda

Background

Human genetics in drug development

Published examples

Interleukin-6 signaling

Background: **About me**

Dr. Dipender Gill MD, PhD

CEO & Founder, Sequoia Genetics

Complementary training across clinical medicine, genetic epidemiology and drug development

>260 research publications

H-index **>47**

UNIVERSITY OF OXFORD

Clinical Medicine, University of Oxford

Intercalated degree in medical sciences

2005-2011

IMPERIAL

NHS

Clinical Academic, Imperial College London

Clinical Academic, Imperial College London

- Consultant Physician specializing in Internal Medicine and Clinical Pharmacology
- Research into leveraging human genetic data to unravel disease mechanisms and inform development of therapeutic targets

2011-2022

IMPERIAL

PhD in Genetic Epidemiology, Imperial College London

Intensively researching the power of genetic insights to inform drug development efforts

2017-2020

novo nordisk

Specialist, Genetics Department, Novo Nordisk

One of the first members of the newly formed Genetics Department, pioneering implementation of statistical genetic insights to inform drug development

2020-2022

novo nordisk

Principal Portfolio Scientist, Chief Scientific Advisor Office, Novo Nordisk

Responsible for optimizing incorporation of human-centric evidence across the Novo Nordisk R&D portfolio

2022-2023

LCP powering possibility

Lead for Integrated Omics, Lane, Clark & Peacock

Successfully created a new service area that leveraged molecular insights to improve the efficiency of drug discovery and development efforts

2023-2024

Sequoia GENETICS

CEO & Founder, Sequoia Genetics

At the forefront of leveraging human genetic data to unravel disease biology and inform on all aspects of drug development.

April 2024

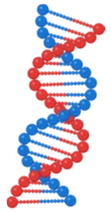
Background: **Genetics in Drug Development**

Drug development is slow and expensive

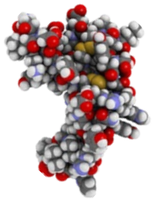
34
drugs approved by the FDA per year [1]

12
years to take a drug to market [2]

$1.1 billion
investment on average [2]

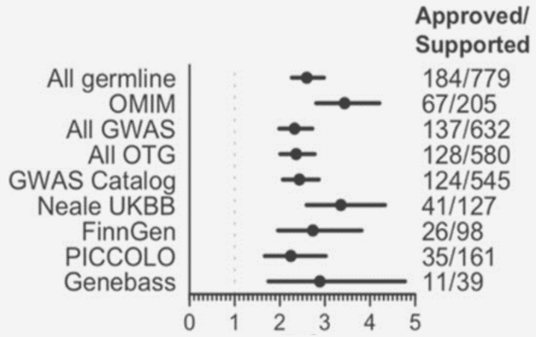


Genes code for proteins, which make up the majority of drug targets.



Random genetic variation in the genes coding for protein drug targets can be used to study their effects.

Targets with genetic support are more than twice as likely to make it to market [3]



Only now is there the breadth and depth of genomic data available to impactfully inform drug discovery and development efforts.

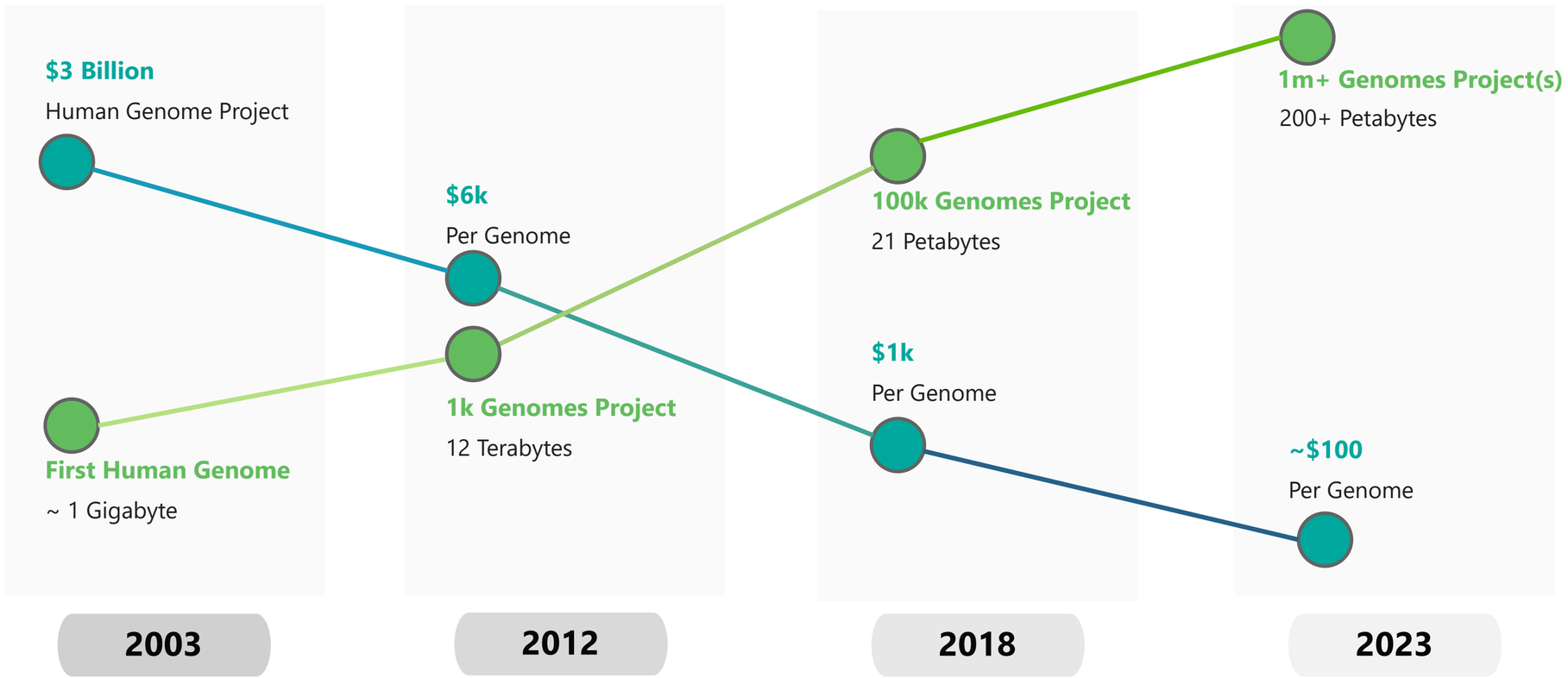
Published genetic associations over time [4]
(depicted per chromosome)

1. Mullard, 2023. Nature Rev. Drug Discovery, 22. | 2. Wouters, 2020. JAMA, 323(9). | 3. Minikelet al. 2024. Nature. | 4. https://www.ebi.ac.uk/gwas

Background: **An Explosion in Bioinformatics Data**

Cost of Sequencing

Size of Flagship Genome Projects

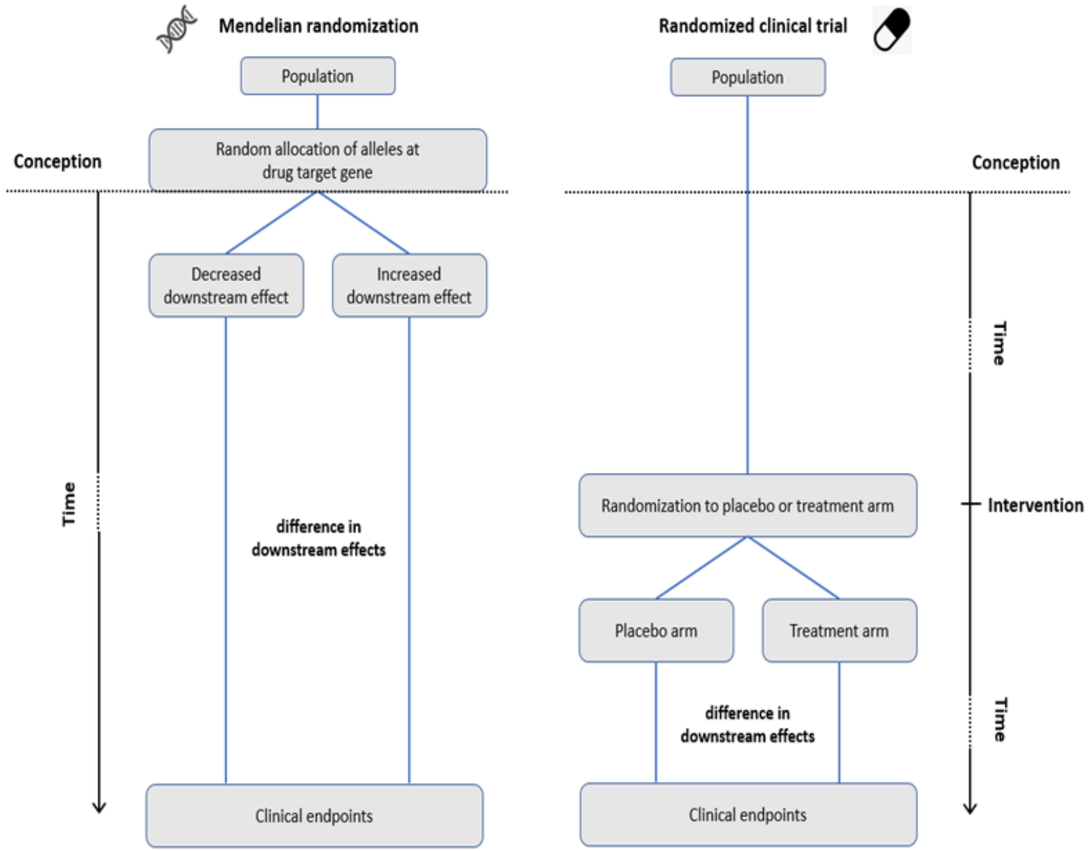


The rapid increase in genome sequencing data, expected to reach 40 exabytes by 2025[1], is outpacing the capacity of current analysis pipelines.

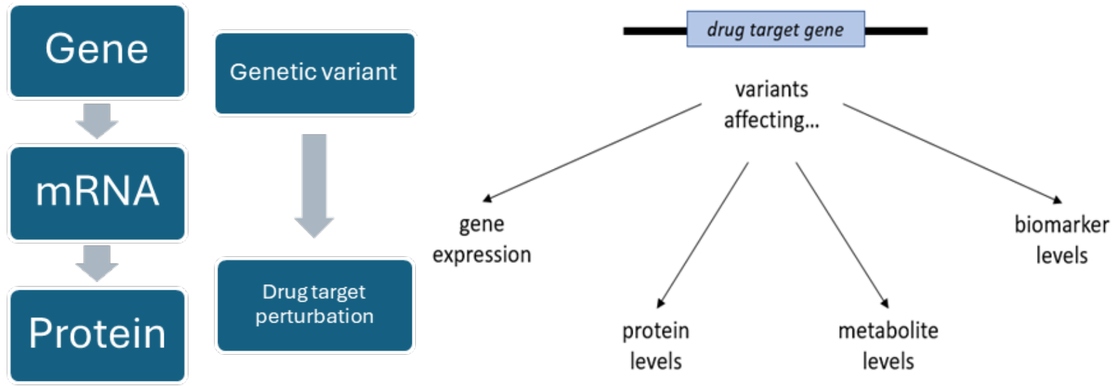
1. https://blogs.nvidia.com/blog/how-ai-is-transforming-genomics/

Genetic data can be leveraged to draw causal inferences that inform all stages of drug development

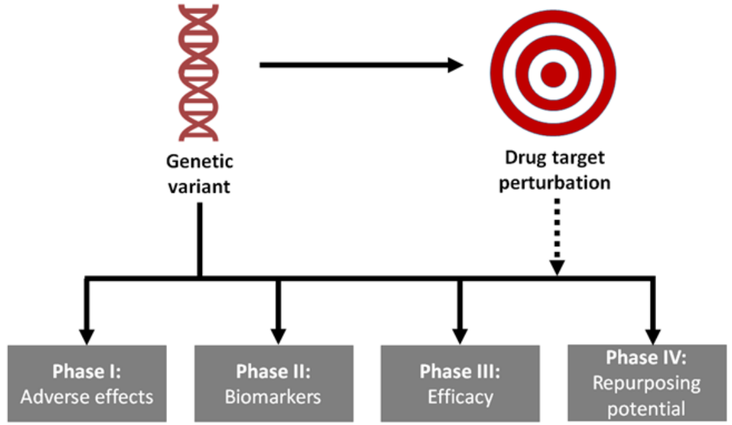
1 The random allocation of genetic variants at conception means that their associations are devoid of confounding from environmental factors or reverse causation, analogous to treatment allocation in an RCT



2 Genes code for proteins and thus variants can inform on the effects of perturbing drug target proteins

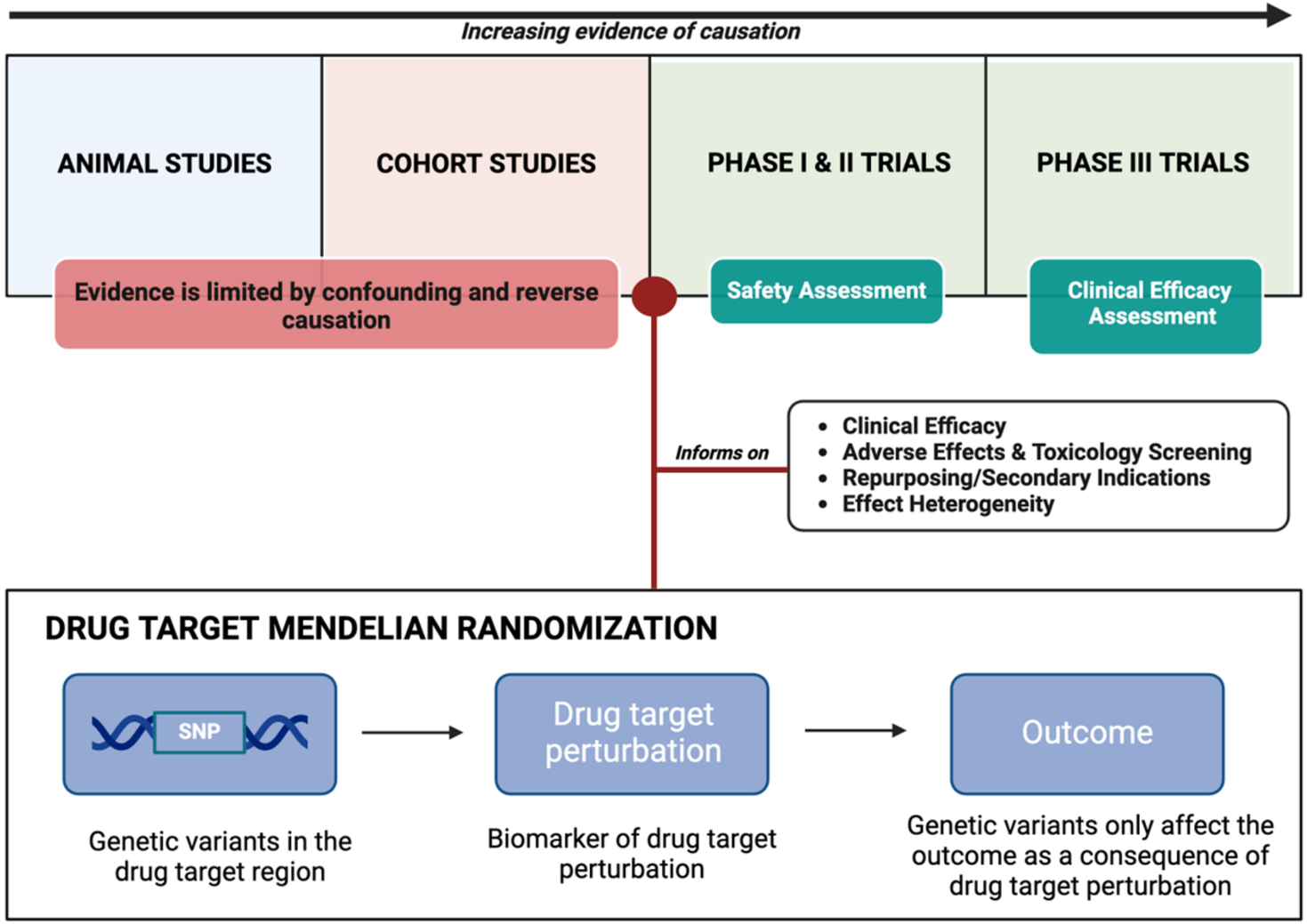


3 Genetic variants that mimic drug effects can be leveraged to inform on all stages of drug development

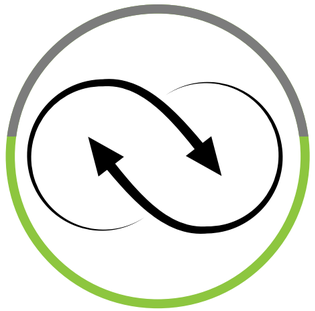


Gill D, et al. Mendelian randomization for studying the effects of perturbing drug targets. Wellcome Open Res. 2021 Feb 10;6:16.

Drug target Mendelian randomization can be used to infer the causal effect of perturbing drug targets



What can we study?



Interaction with other risk factors

Dose-response relationships

Secondary indications and adverse effects

Efficacy and comparison with other drug targets

Biomarkers of target engagement and mediating effects

Heterogeneity across population subgroups.

Tissue specific effects.

Ask the relevant questions

Biological and clinical expertise.

Design appropriate analyses

Knowledge of relevant data availability and statistical methods for study design.

Interpret the results to inform drug development

Translating the findings to directly inform key decisions.

Optimizing the impact of human genetic data requires seamless integration of biological, statistical and translational expertise.

Factor XI

Stroke
Volume 49, Issue 11, November 2018; Pages 2761-2763
https://doi.org/10.1161/STROKEAHA.118.022792
BRIEF REPORTS

Genetically Determined FXI (Factor XI) Levels and Risk of Stroke

Dipender Gill, MD, Marios K. Georgakis, MD, Mike Laffan, MD, PhD, Maria Sabater-Lleal, PhD, Rainer Malik, PhD, Ioanna Tzoulaki, PhD, Roland Veltkamp, MD*, and Abbas Dehghan, MD, PhD*

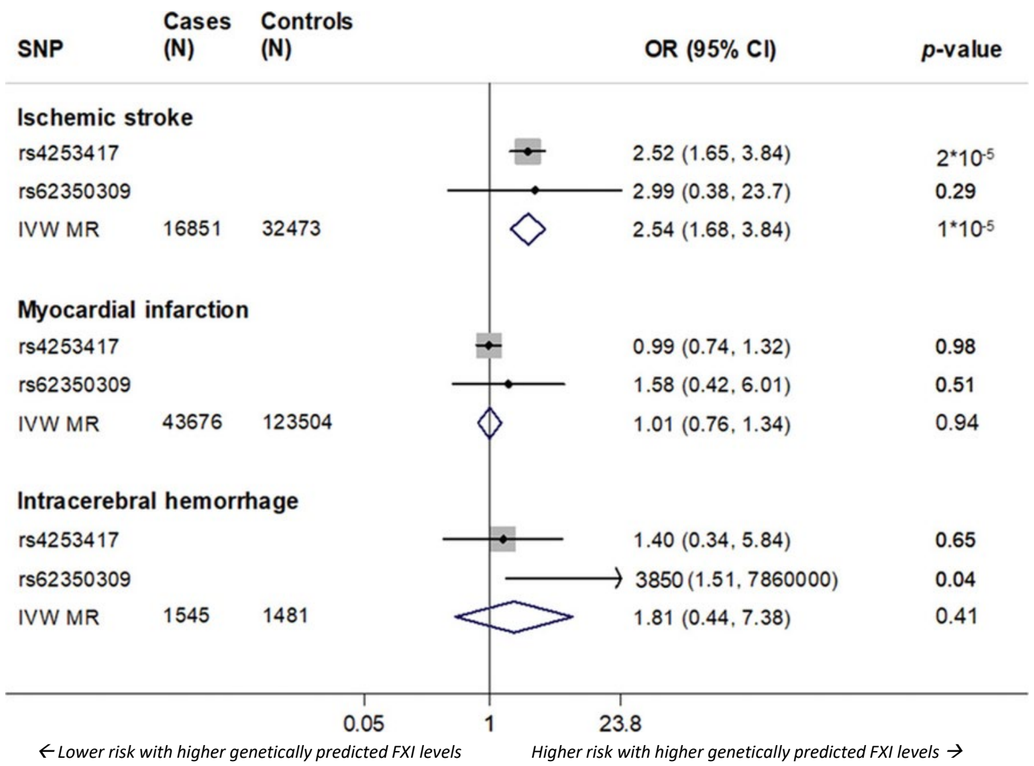


Figure 1. Forest plot of the individual single-nucleotide polymorphism (SNP) and pooled Mendelian randomization (MR) estimates for the association of genetically predicted FXI (factor XI) levels and risk of ischemic stroke, myocardial infarction, and intracerebral hemorrhage. IVW indicates inverse variance; and OR, odds ratio.

Stroke
Volume 50, Issue 11, November 2019; Pages 3004-3012
https://doi.org/10.1161/STROKEAHA.119.026545
CLINICAL SCIENCES

Leveraging Human Genetics to Estimate Clinical Risk Reductions Achievable by Inhibiting Factor XI

Benjamin Georgi, PhD, Johanna Mielke, PhD, Mark Chaffin, MSc, Amit V. Khera, MD, Lian Gelis, PhD, Hardi Mundl, MD, J.J.J. van Giezen, PhD, Patrick Ellinor, MD, PhD, Sekar Kathiresan, MD, Karl Ziegelbauer, PhD, and Daniel F. Freitag, PhD

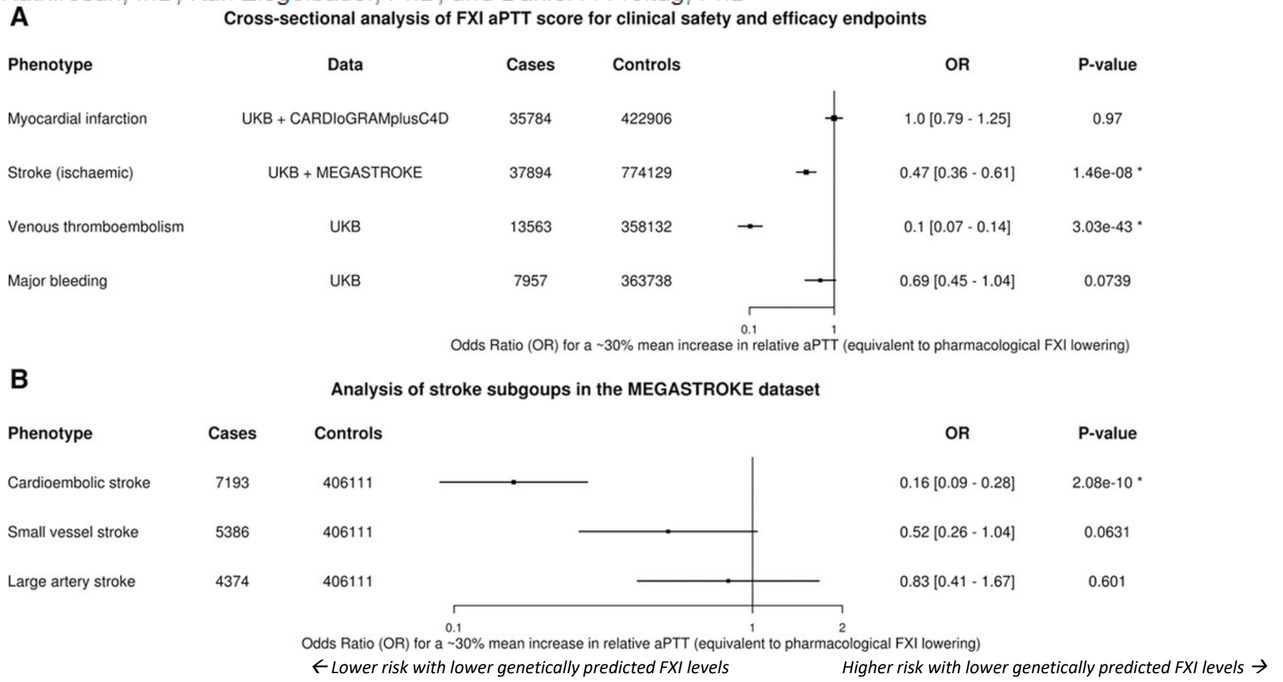
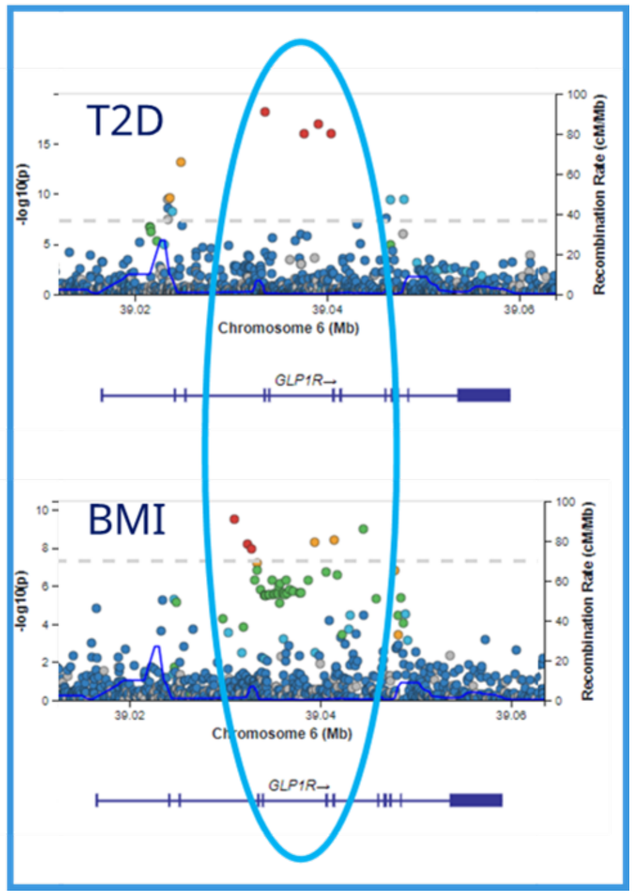


Figure 2. Cross-sectional analyses of the genetic factor XI (FXI) score for clinical end points and ischemic stroke subtypes. A, Association of the FXI genetic score with 4 primary safety and efficacy outcomes (United Kingdom Biobank [UKB], external genetics consortia). After correcting for testing 4 primary outcomes (Bonferroni threshold=0.05/4=0.01), we observe significant associations of the FXI genetic score, expressed as a 30% relative increase in activated partial thromboplastin time (aPTT), with venous thromboembolism (odds ratio [OR]=0.1 [0.07–0.14], $P=3.03\times10^{-43}$) and ischemic stroke (OR=0.47 [0.36–0.61]; $P=1.5\times10-8$) and (B) cross-sectional analysis of CCS ischemic stroke subgroups from the MEGASTROKE dataset. Integration of MEGASTROKE effect sizes for 2 common FXI SNPs (rs4253417, rs1593) by fixed-effect meta-analysis showed significant risk reduction for the cardioembolic stroke subtype (OR=0.16 [0.09–0.28]; $P=2.08\times10^{-10}$).

Human genetics support GLP1R in T2D and obesity and inform repurposing

ARTICLES
https://doi.org/10.1038/s41588-020-0637-y
nature genetics

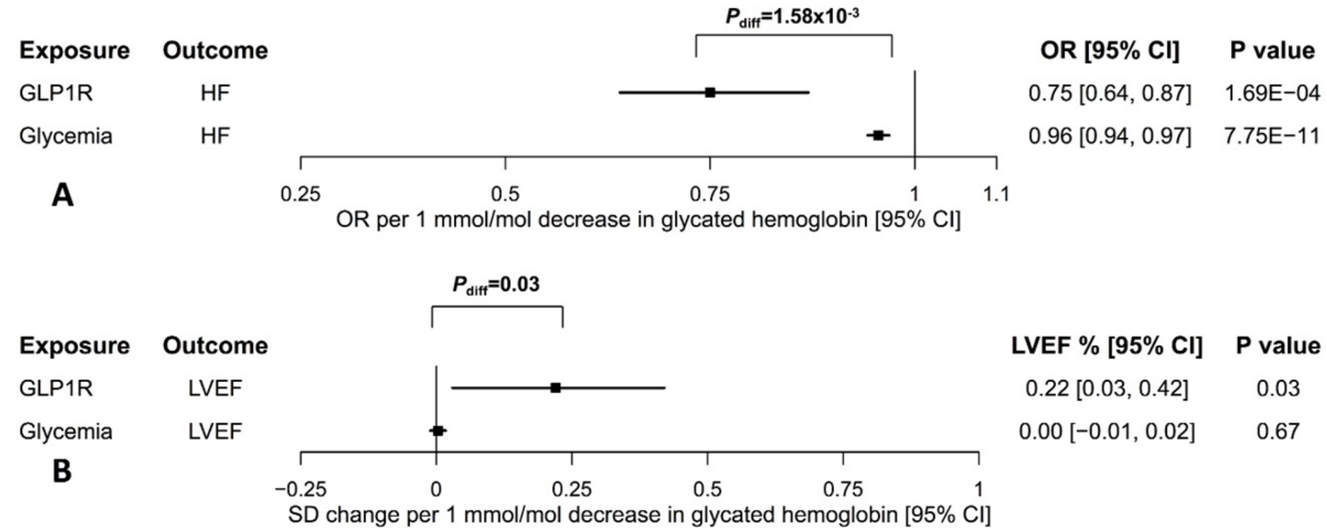
Discovery of 318 new risk loci for type 2 diabetes and related vascular outcomes among 1.4 million participants in a multi-ancestry meta-analysis



Journal of the American Heart Association
Volume 10, Issue 13, 6 July 2021
https://doi.org/10.1161/JAHA.120.020331
BRIEF COMMUNICATION

Genetic Evidence for Repurposing of GLP1R (Glucagon-Like Peptide-1 Receptor) Agonists to Prevent Heart Failure

Iyas Daghlas, BS ; Ville Karhunen, PhD ; Devleena Ray, BSc ; Verena Zuber, PhD ; Stephen Burgess, PhD ; Philip S. Tsao, PhD ; Julie A. Lynch, PhD, RN ; Kyung Min Lee, PhD ; Benjamin F. Voight, PhD ; Kyong-Mi Chang, MD ; Emma H. Baker, PhD ; Scott M. Damrauer, MD ; Joanna M. M. Howson, PhD ; Marijana Vujkovic, PhD, MSCE ; Dipender Gill, BMBCh, PhD



Daghlas I, …, **Gill D.** Genetic Evidence for Repurposing of GLP1R (Glucagon-Like Peptide-1 Receptor) Agonists to Prevent Heart Failure. J Am Heart Assoc. 2021 Jul 6;10(13):e020331.

Circulation
Volume 140, Issue 4, 23 July 2019; Pages 270-279
https://doi.org/10.1161/CIRCULATIONAHA.118.038814
ORIGINAL RESEARCH ARTICLE

Use of Genetic Variants Related to Antihypertensive Drugs to Inform on Efficacy and Side Effects

Dipender Gill, MD*, Marios K. Georgakis, MD*, Fotios Koskeridis, MSc, Lan Jiang, MS, Qiping Feng, PhD, Wei-Qi Wei, MD, PhD, Evropi Theodoratou, PhD, Paul Elliott, FMedSci, Joshua C. Denny, MD, MS, Rainer Malik, PhD, Evangelos Evangelou, PhD, Abbas Dehghan, MD, PhD, Martin Dichgans, MD†, and Ioanna Tzoulaki, PhD†

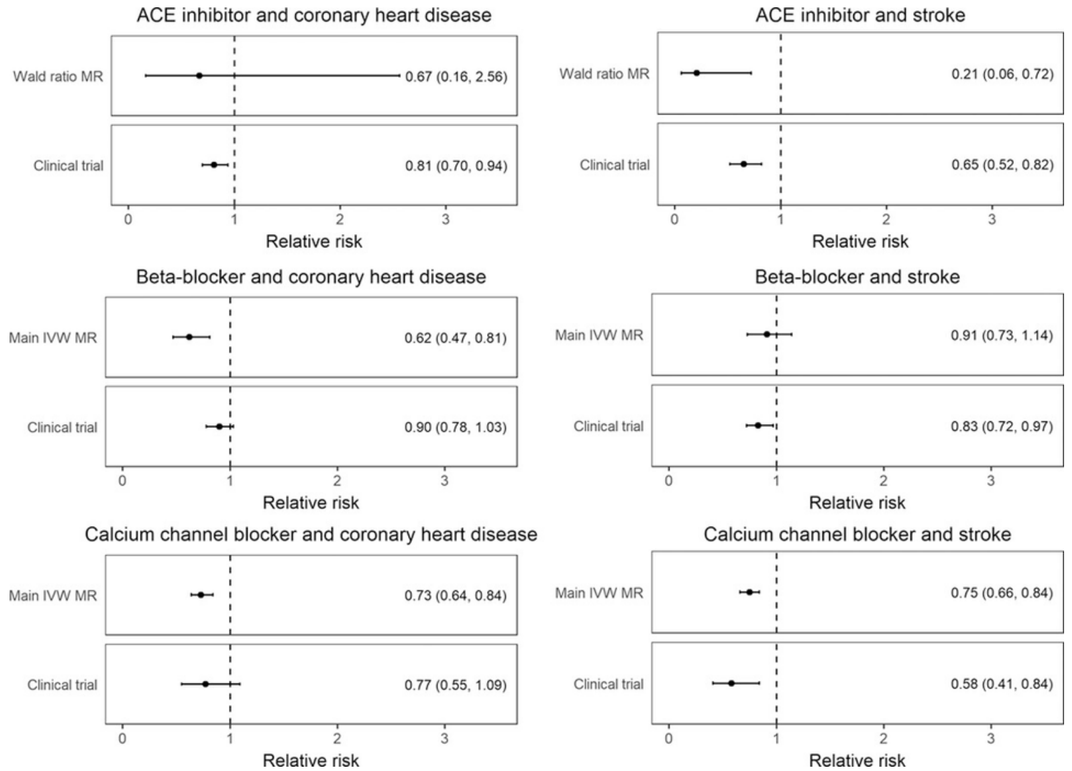


Figure 1. MR estimates for the effect of genetically lower systolic blood pressure through the ACE inhibitor, β-blocker, and calcium channel blocker variants, respectively, on risk of coronary heart disease and stroke, compared with randomized, controlled trial meta-analysis results. ACE indicates angiotensin-converting enzyme; IVW, inverse variance weighted; and MR, Mendelian randomization.

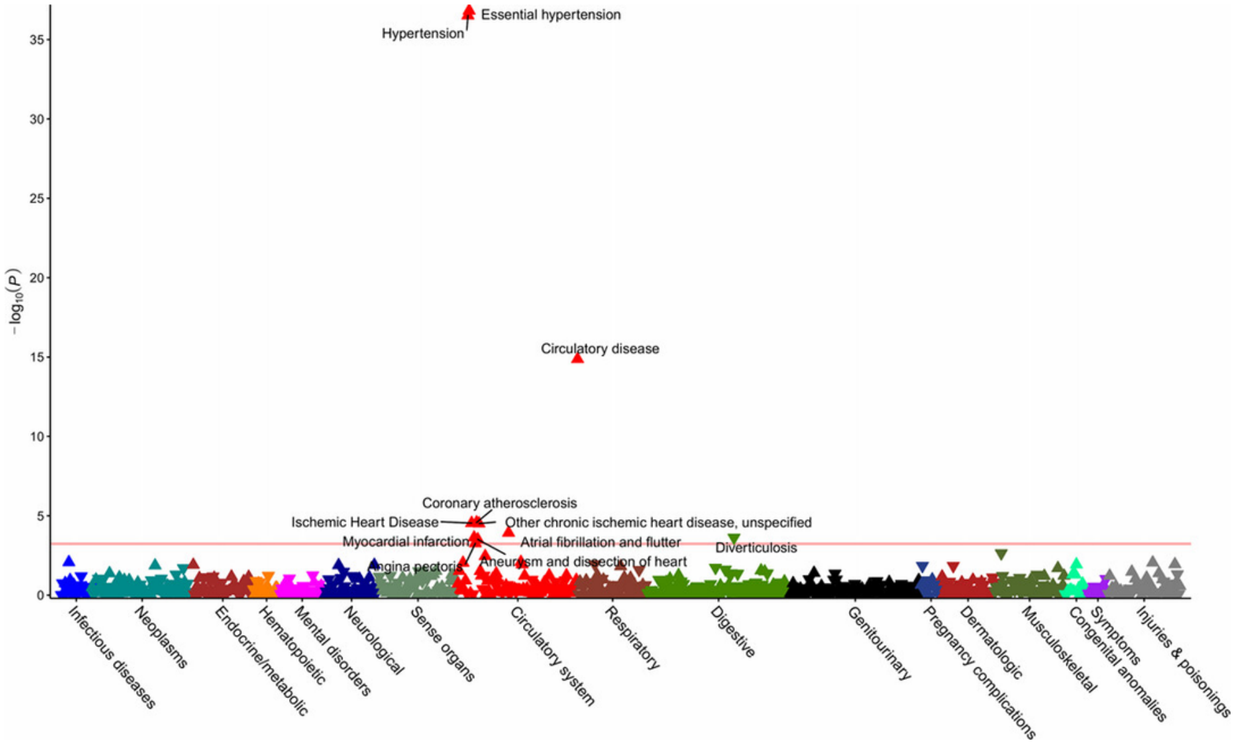


Figure 4. Phenome-wide association study of the standardized genetic risk score for calcium channel blockers. The horizontal line depicts the 5% false-discovery rate threshold.

Ardissino et al. BMC Medicine (2022) 20:288
https://doi.org/10.1186/s12916-022-02483-1

Safety of beta-blocker and calcium channel blocker antihypertensive drugs in pregnancy: a Mendelian randomization study

RESEARCH ARTICLE Open Access

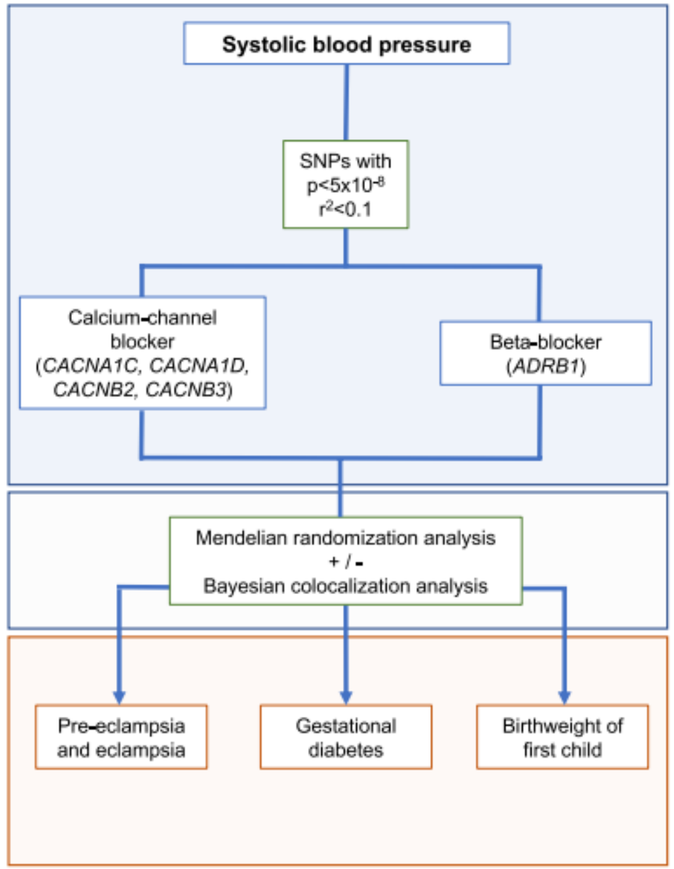


Fig. 3 Study design fowchart

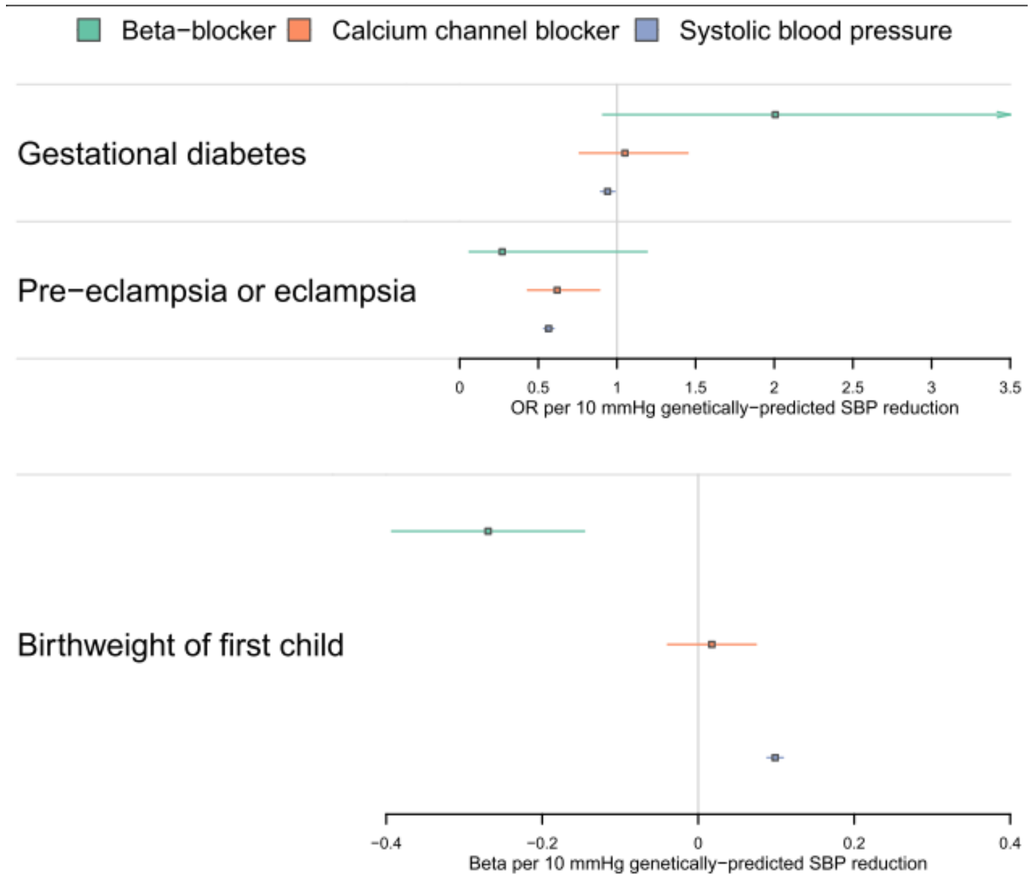
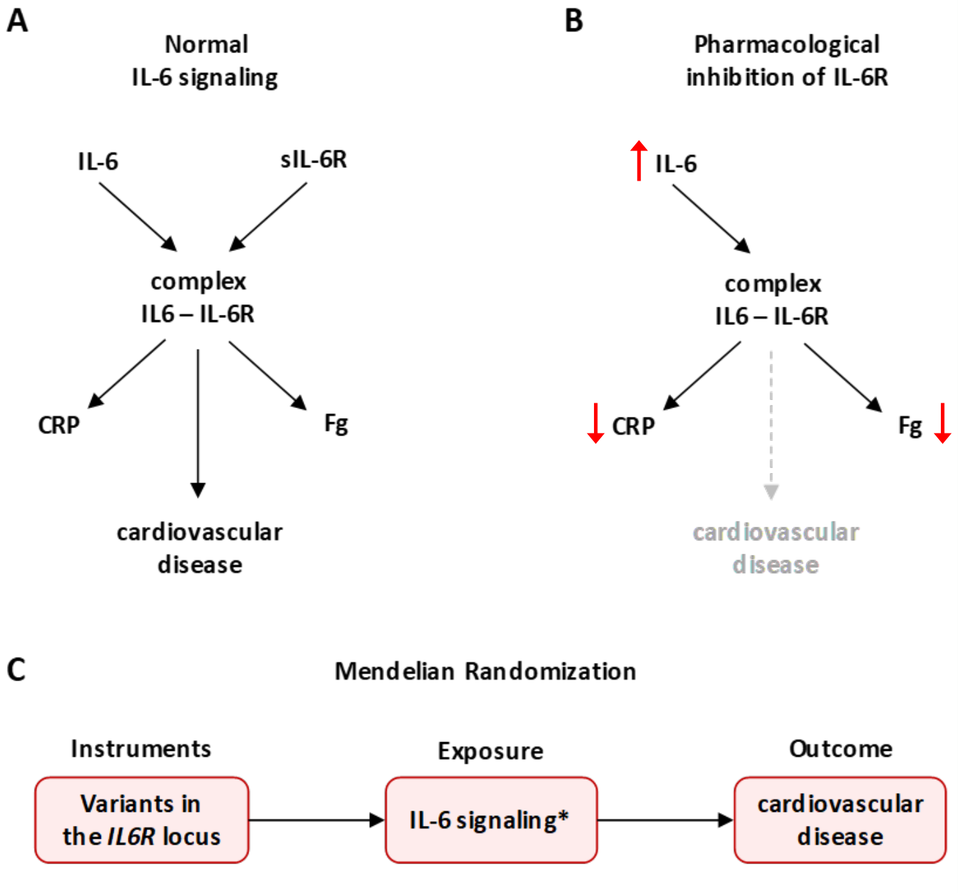


Fig. 1 Mendelian randomization estimates (scaled to 10-mmHg systolic blood pressure reduction) for beta-blocker and calcium channel blocker drug efects, and systolic blood pressure reduction by any mechanism

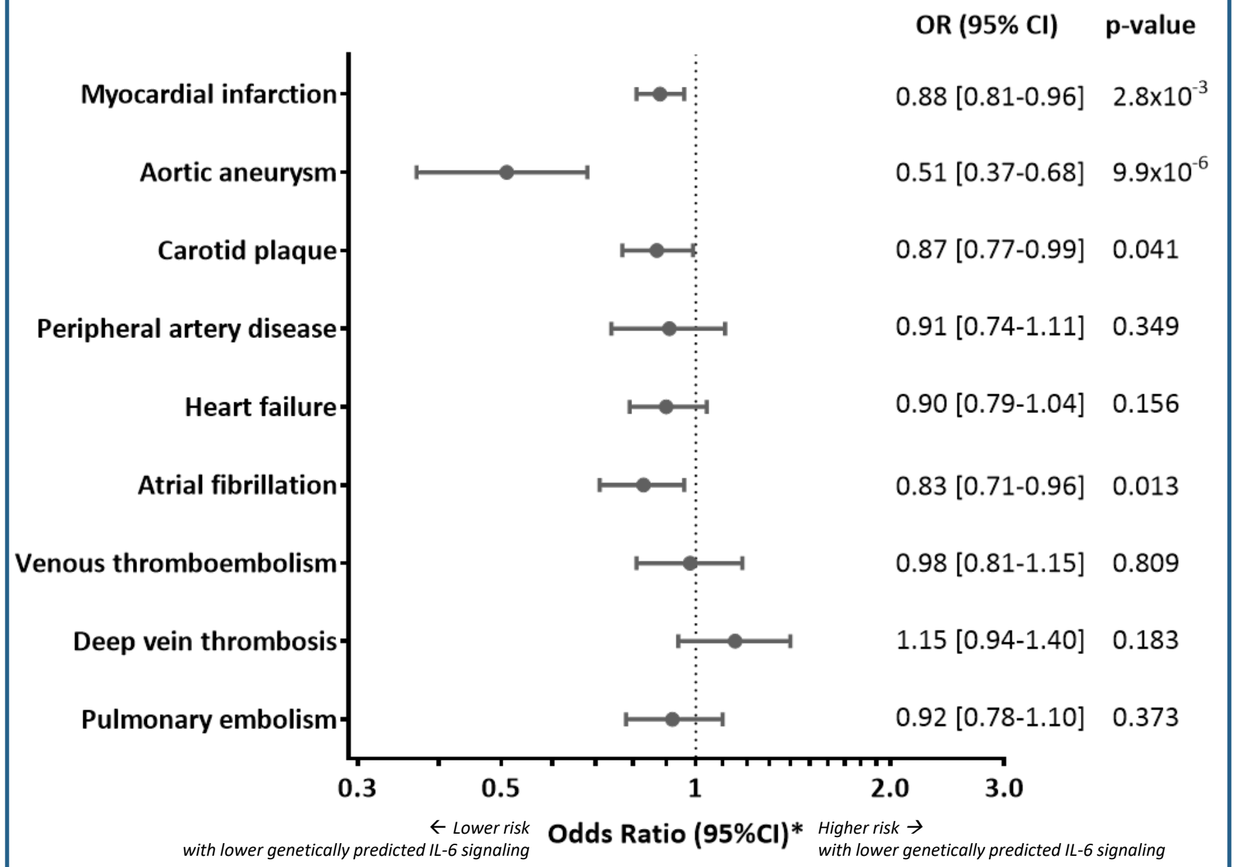
Ardissino M, …S, **Gill D.** Safety of beta-blocker and calcium channel blocker antihypertensive drugs in pregnancy: a Mendelian randomization study. BMC Med. 2022 Sep 6;20(1):288.

Interleukin-6 (IL6) signaling

Interleukin-6 signalling



Cardiovascular outcomes with lower genetically predicted IL-6 signaling



Georgakis MK, Malik R, **Gill D,** et al. Interleukin-6 Signaling Effects on Ischemic Stroke and Other Cardiovascular Outcomes: A Mendelian Randomization Study. Circ Genom Precis Med. 2020 Jun;13(3):e002872.

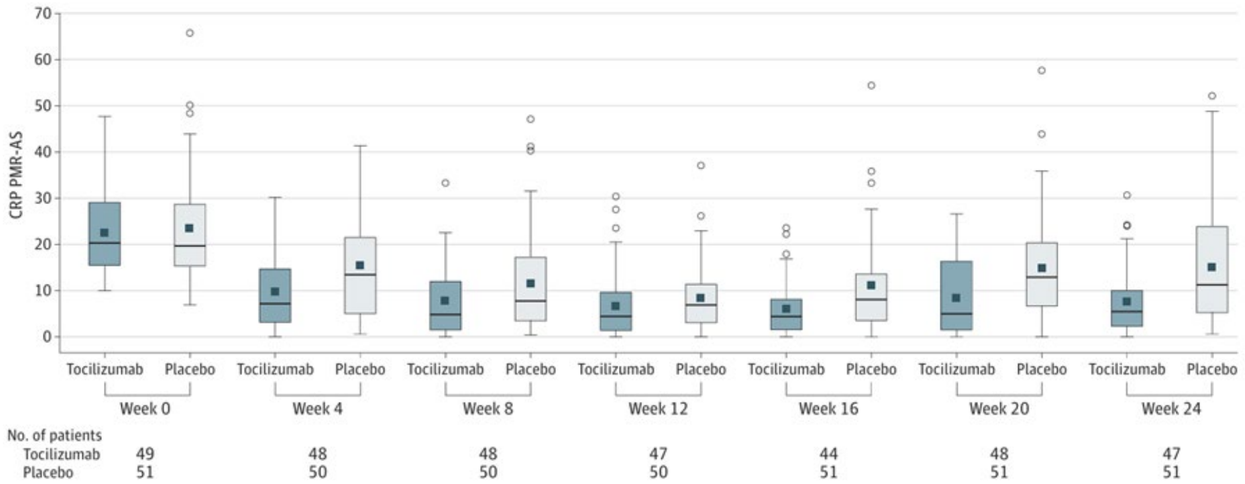
Interleukin-6 signaling

IL6 signaling is an approved target for rheumatoid arthritis, with strong human genetic evidence supporting its efficacy

Figure 1 Mendelian randomisation estimates of the effect of genetically proxied interleukin-6 receptor inhibition on polymyalgia rheumatica.

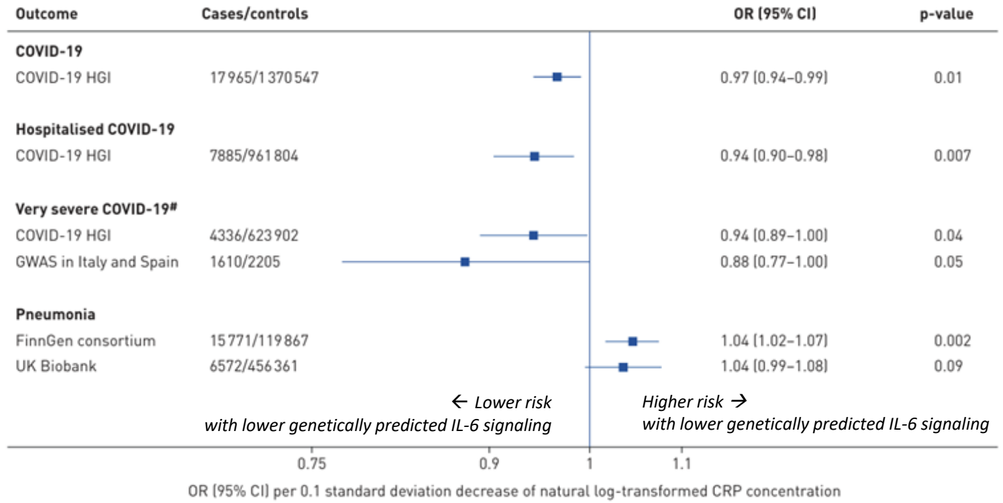
Ann Rheum Dis October 2022 Vol 81 No 10

Zhao SS, **Gill D**. Ann Rheum Dis. **14 June 2022**

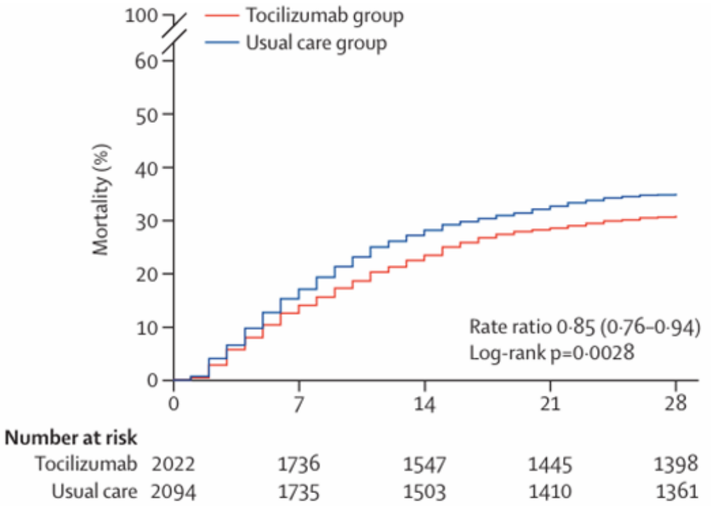


Devauchelle-Pensec V, et al. JAMA. **20 September 2022**

Similar genetic evidence anticipated efficacy of IL6 signalling for polymyalgia rheumatica and COVID-19 was published by us before conclusive clinical trial evidence was available



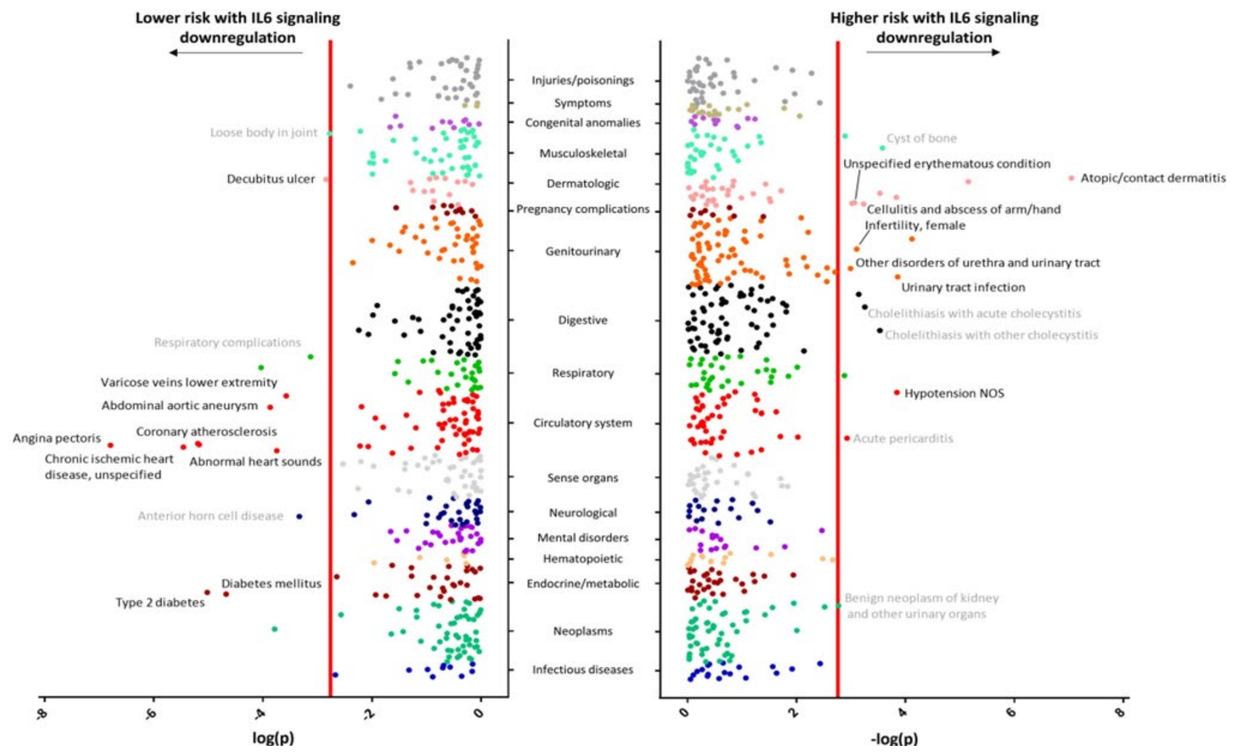
Larsson SC, Burgess S, **Gill D**. Eur Respir J. **14 Jan 2021**



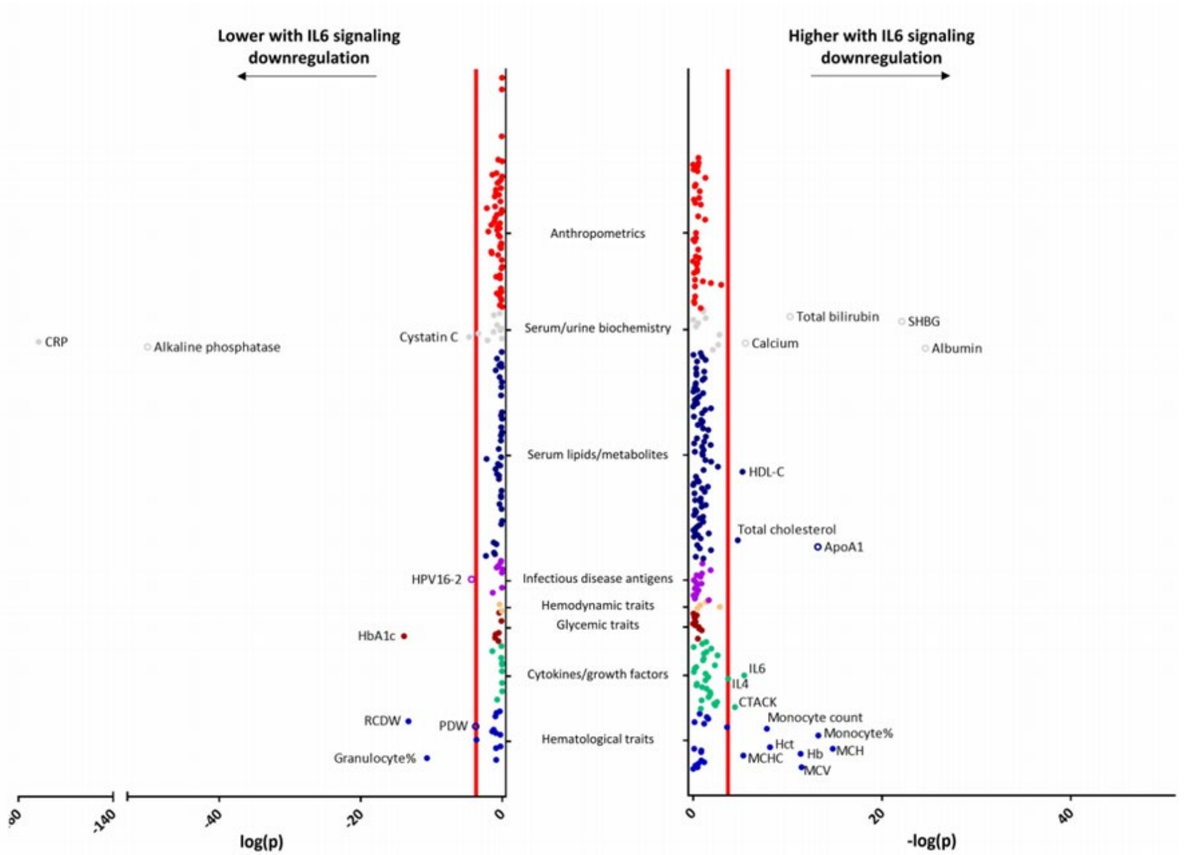
RECOVERY Collaborative Group. Lancet. **1 May 2021**

Rapid hypothesis-free interrogation

Phenome-wide association study



Biomarker-wide association study



Georgakis MK, Malik R, Li X, **Gill D**, et al. Genetically Downregulated Interleukin-6 Signaling Is Associated With a Favorable Cardiometabolic Profile: A Phenome-Wide Association Study. Circulation. 2021 Mar 16;143(11):1177-1180.

Associations of genetically predicted IL-6 signaling with cardiovascular disease risk across population subgroups

BMC Medicine

RESEARCH ARTICLE

Open Access

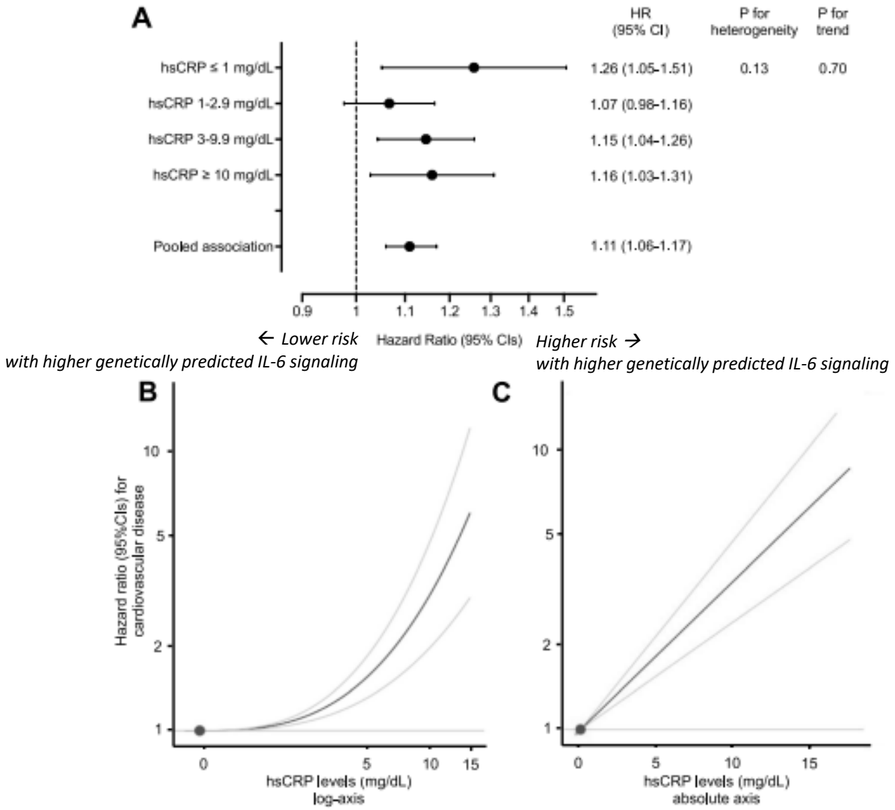


Fig. 1 Associations between genetically predicted IL-6R-mediated signaling and risk of incident cardiovascular disease across measured hsCRP levels. A Mendelian randomization analyses stratified by baseline hsCRP levels. The hazard ratios are scaled for 1 mg/dL increment in absolute hsCRP levels. The p-values for heterogeneity and for trend are derived from the Cochran Q statistic and linear meta-regression analyses across deciles of measured hsCRP. B, C Mendelian randomization analyses of genetically predicted IL6R-mediated signaling and CVD risk across B) ln-transformed measured hsCRP levels and C) absolute measured hsCRP levels. For B, C, results are obtained from fractional polynomial models across associations derived for deciles of measured hsCRP levels. The reference is set to the minimum hsCRP value in the UK Biobank sample (0.08 mg/dL). The p-values for non-linearity are 0.001 for ln-transformed hsCRP levels and 0.99 for absolute hsCRP levels. For all graphs, the residual values of hsCRP are used to stratify, as determined in models regressing the genetic risk score for IL-6 signaling on measured hsCRP levels

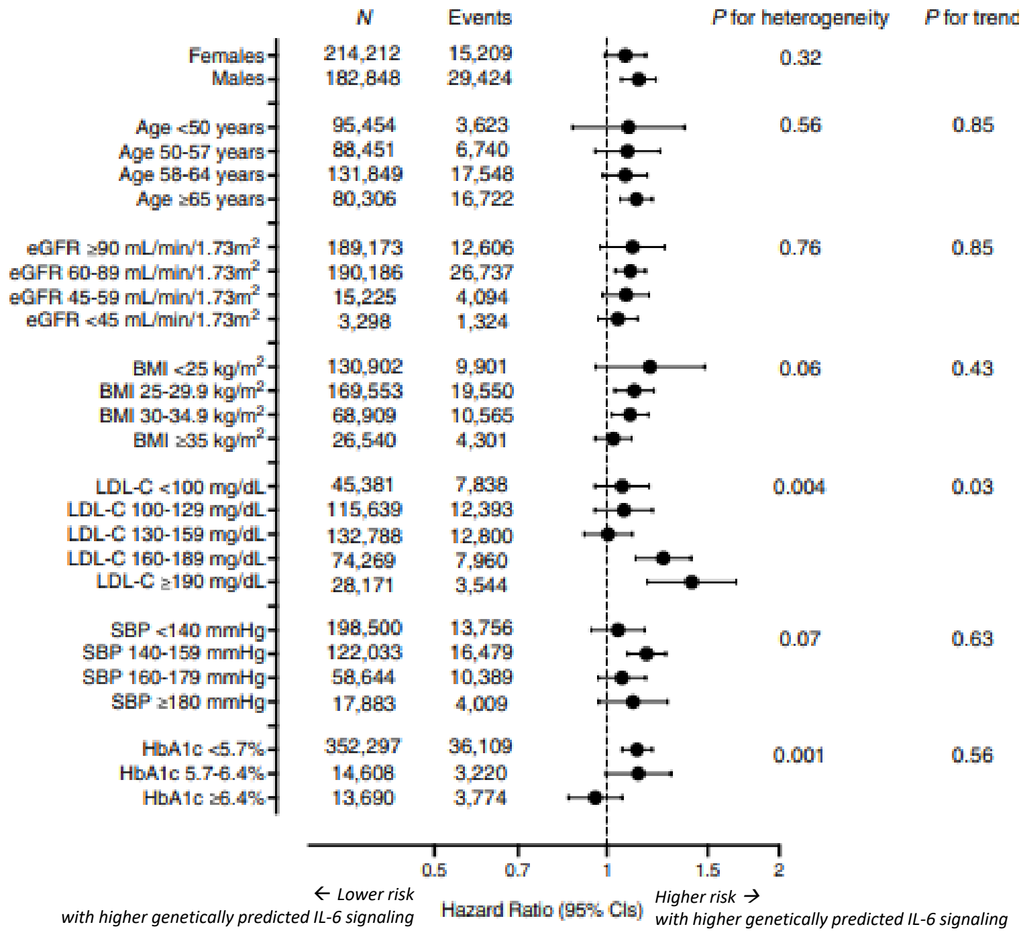


Fig. 2 Association between genetically predicted IL-6R-mediated signaling activity and risk of cardiovascular disease across clinically relevant subgroups. The hazard ratios are scaled on 1 mg/dL increment in absolute hsCRP levels. The p-values for heterogeneity and for trend are derived from the Cochran Q statistic and linear meta-regression analyses across strata of the diferent measured variables. For all variables except for age and sex, the residual values are used to stratify, as determined in models regressing the genetic score for IL-6 signaling on these variables

Georgakis MK, …, **Gill D.** Associations of genetically predicted IL-6 signaling with cardiovascular disease risk across population subgroups. BMC Med. 2022 Aug 11;20(1):245.

Agenda

Opening Remarks	**Sandeep Kulkarni, MD** Co-Founder & CEO, Tourmaline Bio
Genetic Validation in Drug Development	**Dipender Gill MD, PhD** Founder & CEO, Sequoia Genetics
Pacibekitug in Cardiovascular Disease	**Emil deGoma, MD** SVP Medical Research, Tourmaline Bio
Q&A	

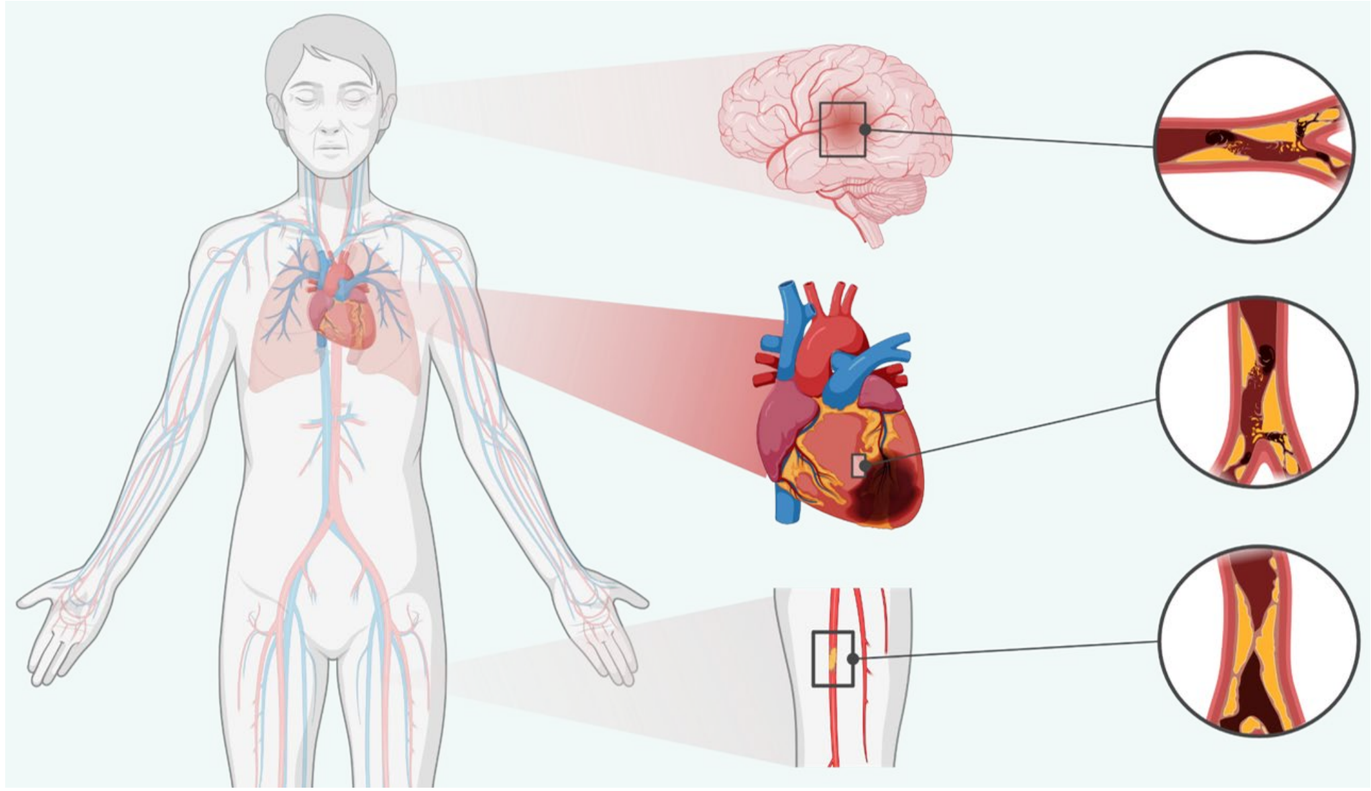
Convergence of human evidence supports therapeutic potential of IL-6 inhibition for ASCVD

Human genetic evidence

Epidemiological evidence

Clinical trial evidence

Evidence suggests IL-6 may drive ASCVD risk

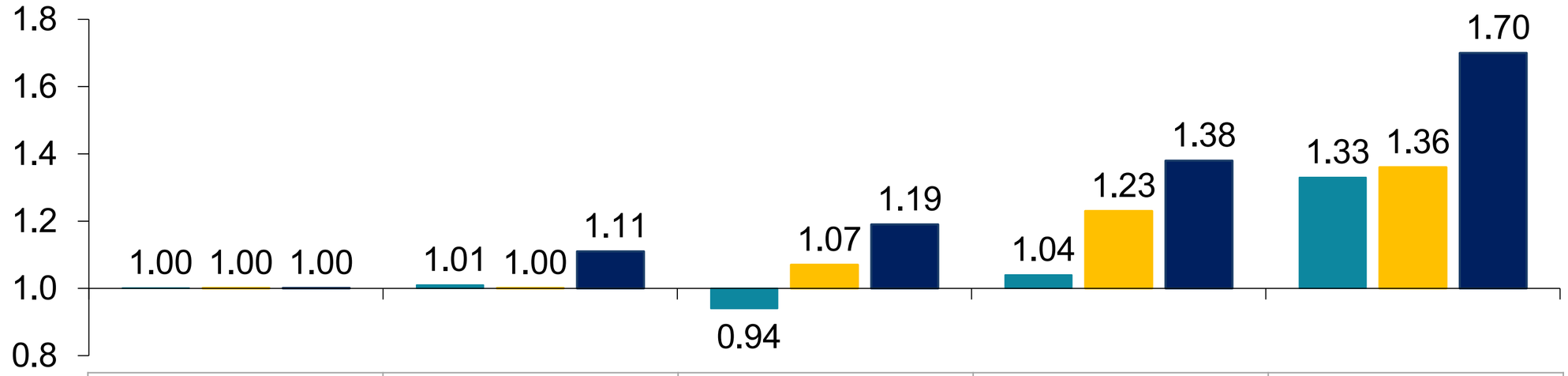


ASCVD: atherosclerotic cardiovascular disease

Emerging evidence suggests that hs-CRP is more strongly associated with MACE than both LDL and Lp(a)

Late breaking data presented at European Society of Cardiology 2024 Congress and simultaneously published in the New England Journal of Medicine

30-year longitudinal data from the Women's Health Study[1]
(n=27,929)



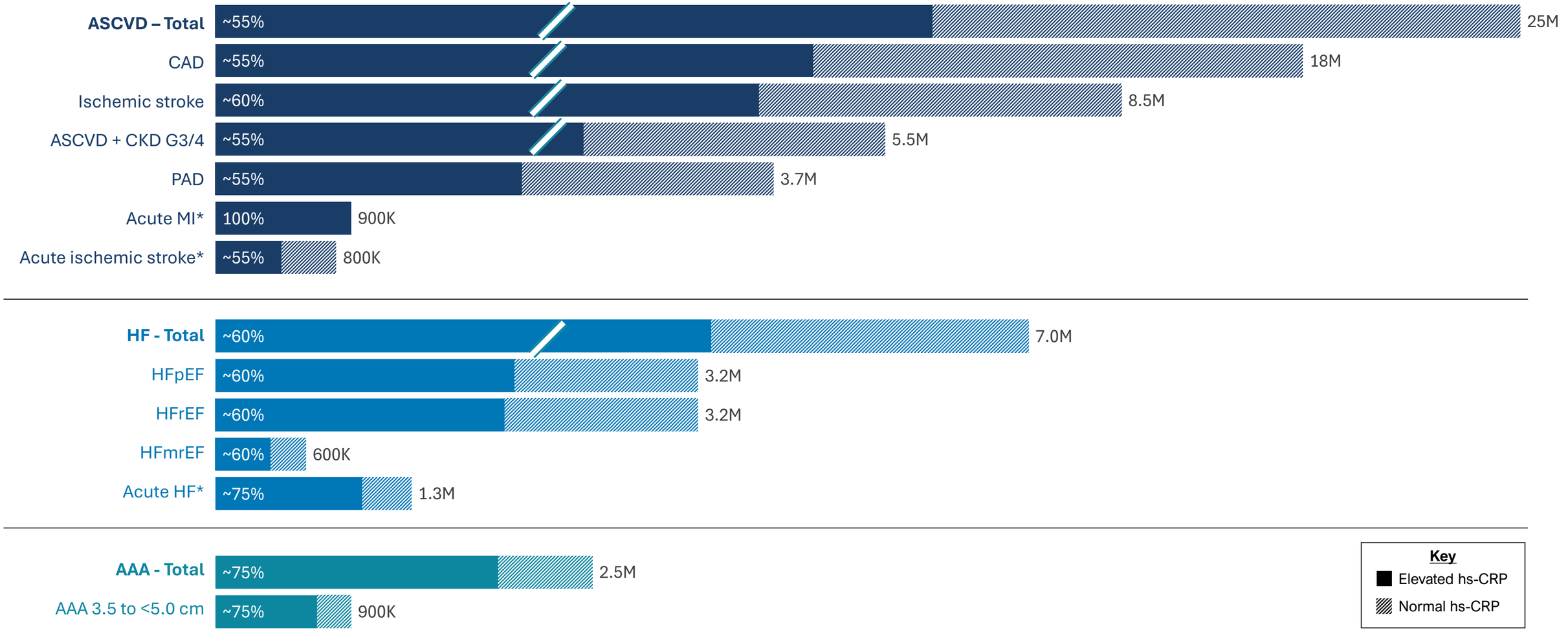
	Quintile (reference)	Quintile 2	Quintile 3	Quintile 4	Quintile 5
hs-CRP mg/L baseline	<0.65	0.65 to <1.47	1.47 to <2.75	2.75 to <5.18	≥5.18
LDL-C mg/dL baseline	<96.1	96.1 to <113.5	113.5 to <129.7	129.7 to <150.7	≥150.7
Lp(a) mg/dL baseline	<3.6	3.6 to <7.6	7.6 to <15.5	15.5 to <44.1	≥44.1

[1]Women's Health Study. MACE: CV death, MI, stroke, coronary revascularization. Increased risk defined as 1-relative risk, compared to lowest quintile of Lp(a) and hs-CRP population, adjusted for age, initial randomization treatment group, smoking (current, past, never), presence of diabetes, and Framingham blood pressure categories. Table 2. Ridker et al, NEJM (2024).

IL-6 inhibition has the potential to address millions of patients across a wide range of inflammation mediated CV conditions

Estimated US prevalence (2024)[1]

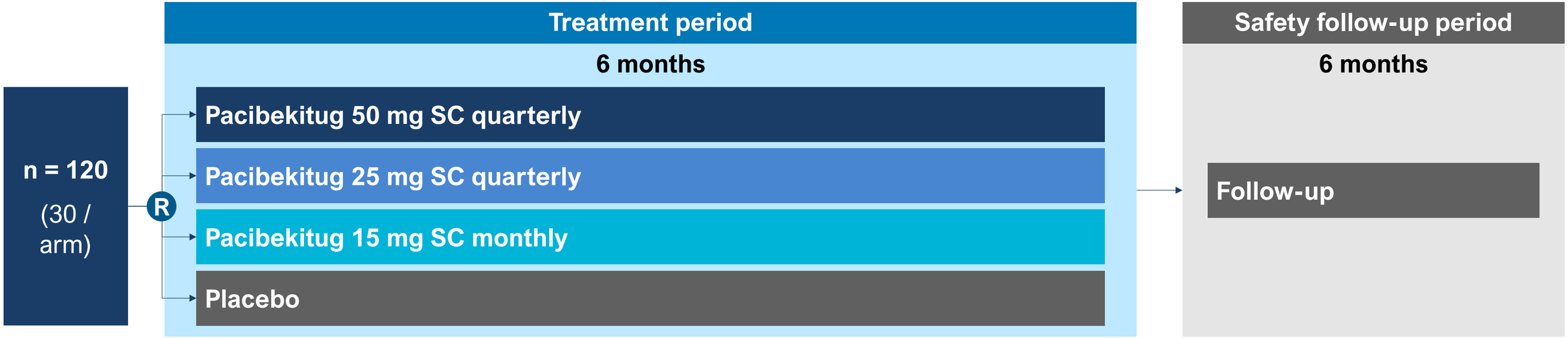
Populations are not mutually exclusive



[1]Publications available upon request. *Annual incidence
AAA: abdominal aortic aneurysm. ASCVD: atherosclerotic cardiovascular disease. CAD: coronary artery disease. CKD: chronic kidney disease. HF: heart failure. HFmrEF: Heart Failure with Mid-Range Ejection Fraction. HFpEF: heart failure with preserved ejection fraction. HFrEF: heart failure with reduced ejection fraction. MI: myocardial infarction. PAD: peripheral artery disease.

TRANQUILITY Phase 2 trial supporting development in ASCVD

Double-blinded, placebo-controlled Phase 2 trial (NCT06362759)



Study population:

- CKD stage G3-4 (eGFR 15-59 ml/min/1.73m^2)
- hs-CRP ≥2 mg/L and <15 mg/L
- Exclude patients at higher risk for safety complications (e.g., immunocompromised patients)

Primary efficacy endpoint:

- Change from baseline in hs-CRP

Additional endpoints:

- Other pharmacodynamic markers: serum amyloid A, fibrinogen, lipoprotein(a), and other biomarkers
- Safety and tolerability

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