Novartis Biomedical Research
Cardiovascular and Metabolism
Translational Medicine

ESC Cardiovascular Round Table, Rome Italy
Revolution in Pharmacotherapy: From Herbs to Pills to Antibodies to Nucleic Acids
January 31-February 1, 2024

From Genomics to Nucleic Acid Therapeutics in Prevention & Treatment of Cardiometabolic Disease: A View from Pharma

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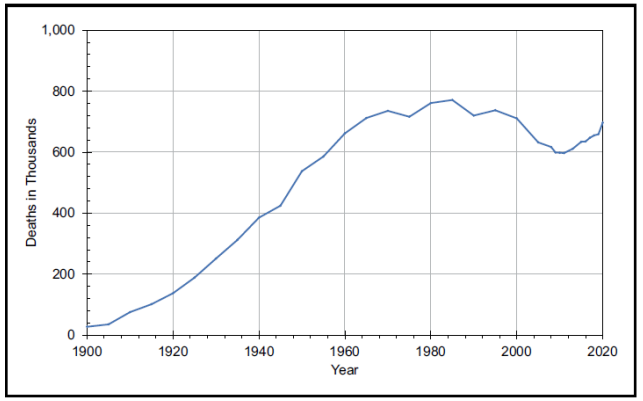
Outline: Genetics/Genomics & Nucleic Acid Rx

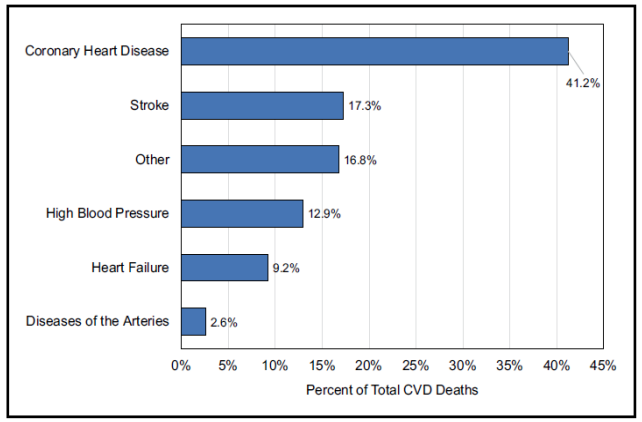
- **Human genetics / genomics has advanced our understanding** of the etiology of risk factors and CV disease and identification of cardio-metabolic disease targets, patient strata, and biomarkers
- **Genetic targets** identified by genomewide studies of cardiometabolic and its risk factors **have informed the first wave of nucleic acid-based Rx** for disease prevention and treatment
- **Novel nucleic acid Rx approaches are transforming cardiovascular therapeutics**. Lessons from ASO & siRNA trials: early phase trials (targeted at liver) can define PoM/PoC/dosing
- **Future studies** addressing risks & challenges **will enable the full potential of nucleic acid Rx** to treat, cure and ultimately prevent

Shared Public Private Mission is to Address Huge Unmet Need of CVD Morbidity & Mortality for Prevention & Treatment

Increasing deaths attributable to CVD in the USA (1900-2020)



~40% of CVD in the USA was due to coronary heart disease (1900-2020)

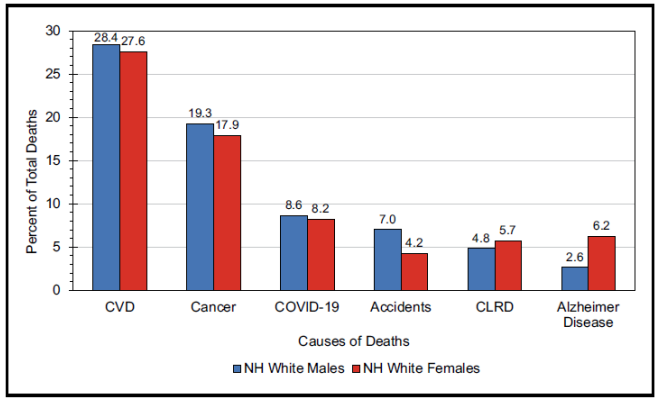


Modifiable risk factors are the top risk factors of years of life lost and death in the USA (GBD Study) 1990-2019

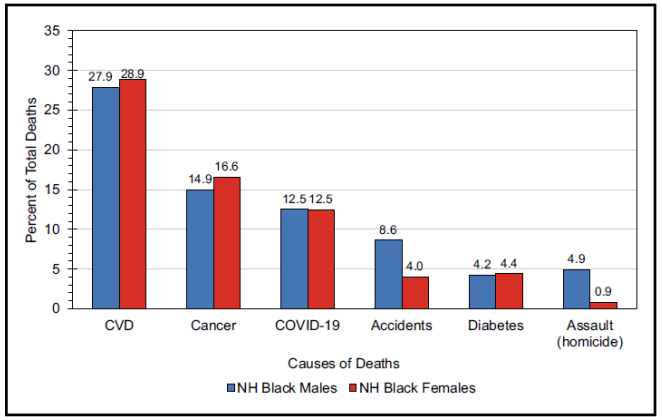
Risk factors for disability	YLL rank (for total number)		Total No. of YLLs, in thousands (95% UI)	
	1990	2019	1990	2019
Smoking	1	1	11005.06	10371.03
High SBP	2	2	8466.11	7815.63
High BMI	4	3	4994.23	7778.57
High FPG	5	4	4664.81	7121.62
Drug use	18	5	999.47	4265.41
Alcohol use	6	6	2708.90	3936.71
High LDL-C	3	7	6291.91	3863.72
Kidney dys-function	7	8	2138.32	3159.52

CVD is still the highest cause of death in males and females in USA 2020. CVD death is higher than cancer or COVID-19.

White males or females



Black males or females

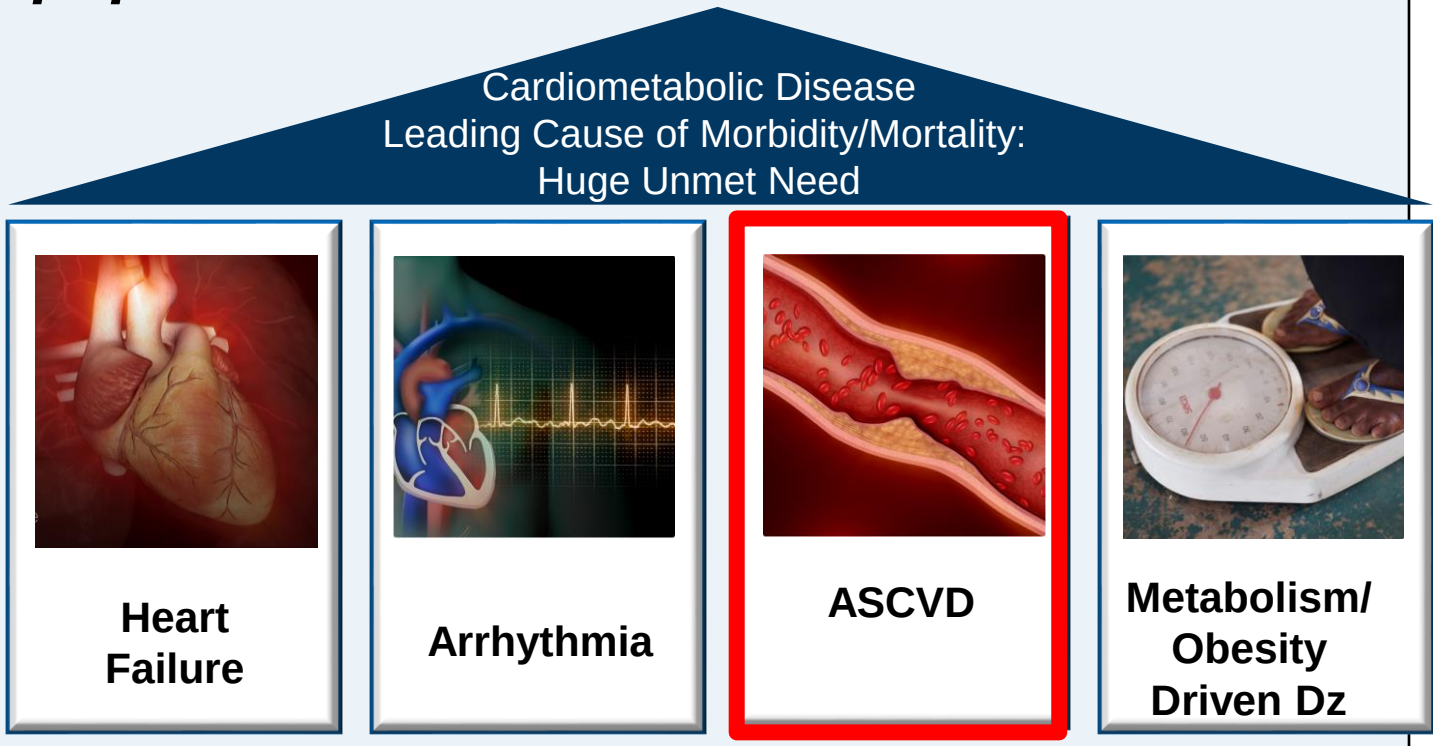


Source: Heart Disease and Stroke Statistics – 2023 Update: A report from the American Heart Association Circulation 2023. Tsao CW, Aday AW, Almarzooq ZI et al

Novartis Cardiovascular & Metabolism Focus

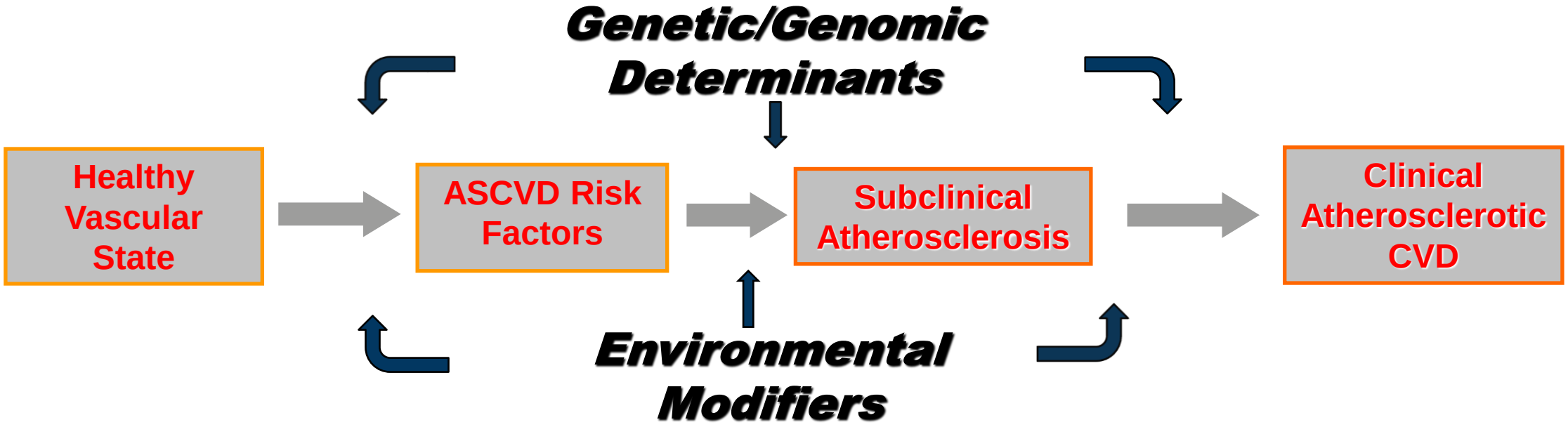
Novartis CVM Biomedical Research focuses on disease areas with high unmet need for patients and large global populations:

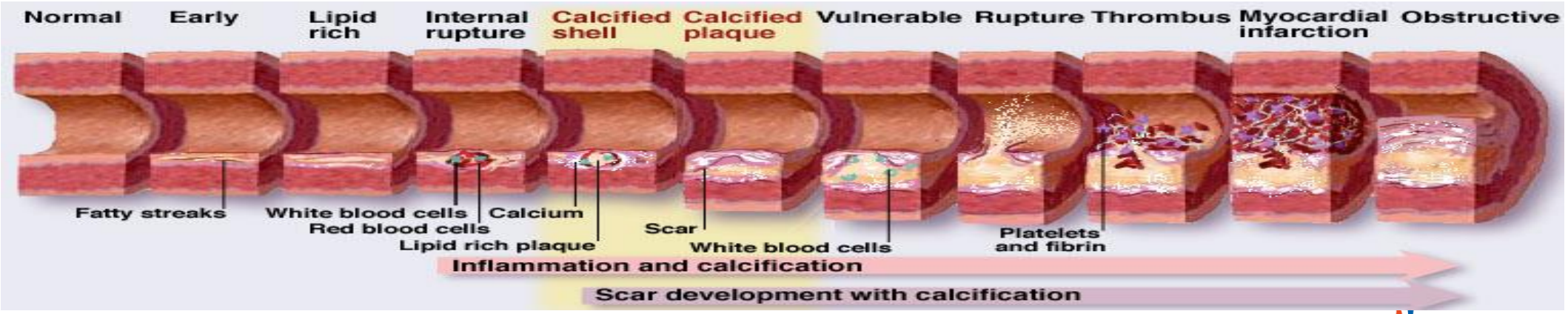
- **Heart Failure**
- **Arrhythmia**
- **Atherosclerosis**
- **Metabolism / obesity-driven diseases**



Cardiovascular & Metabolic Diseases (CVM) (www.novartis.net)

Atherosclerotic Plaque Development: From Healthy Vessel to Clinical ASCVD





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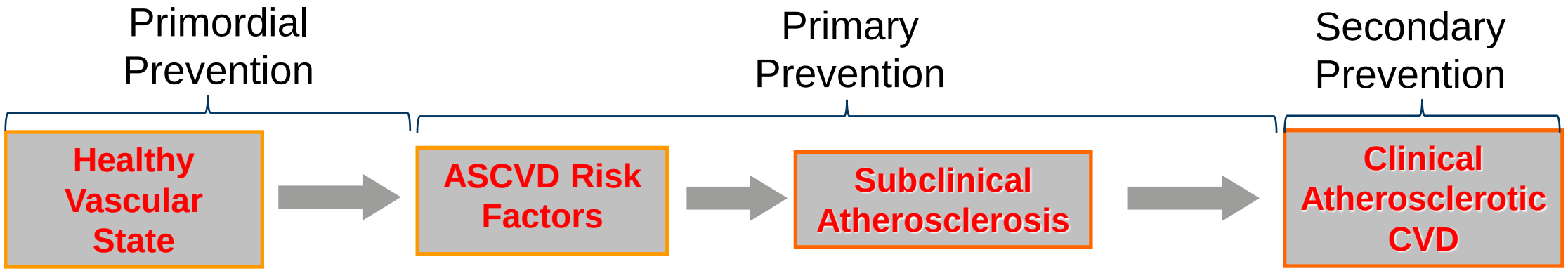
Atherosclerotic Plaque Development: From Healthy Vessel to Clinical ASCVD



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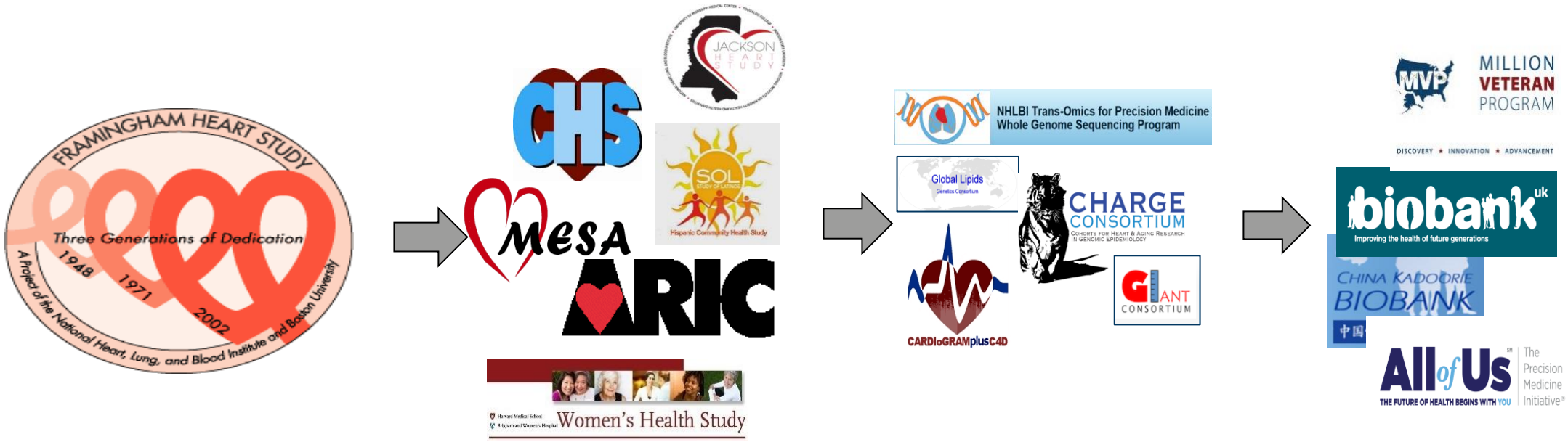
Cardiovascular Disease Biomarker & Genomics: From Framingham to Precision Medicine Cohorts

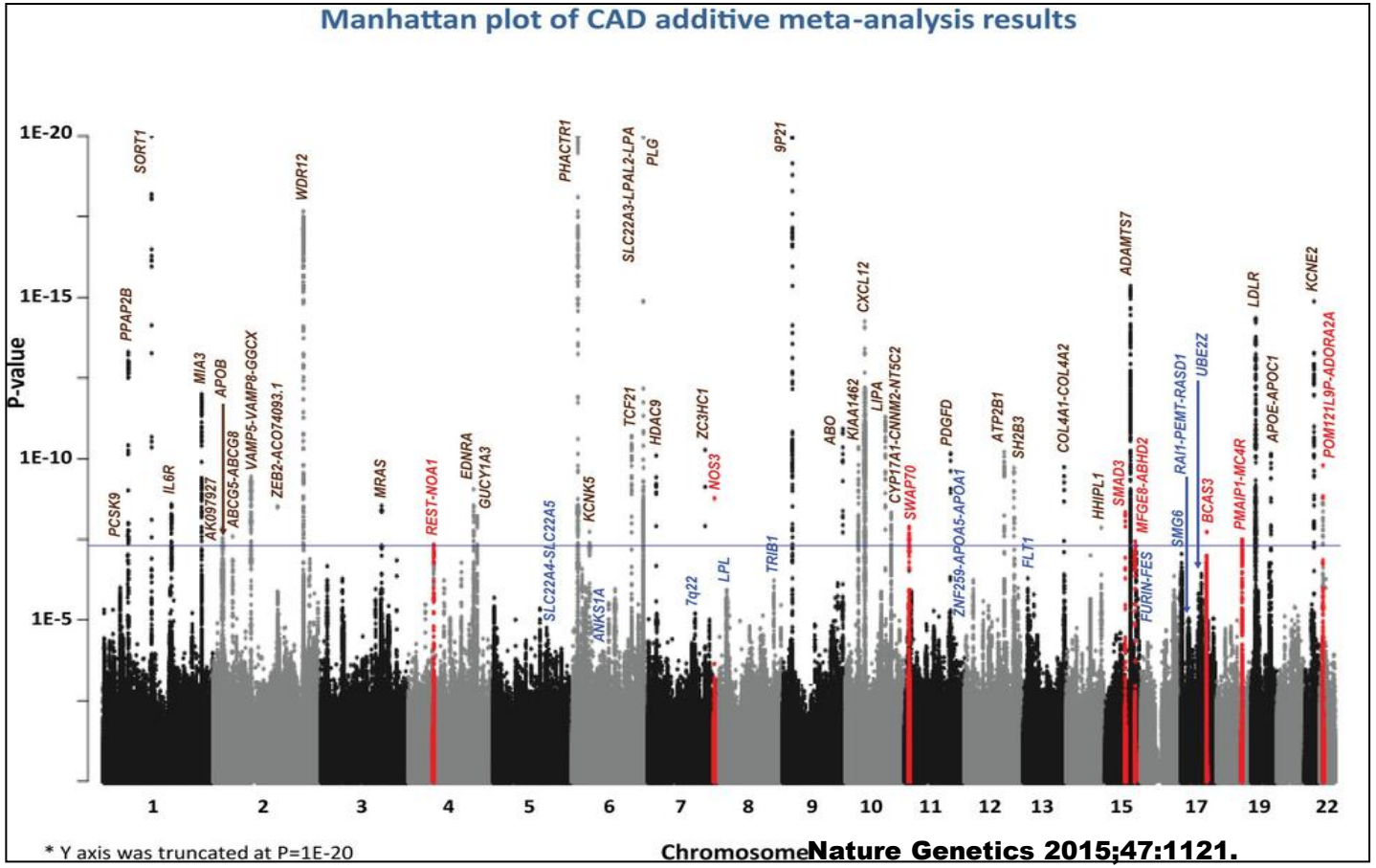
Eras of Chronic Disease Epidemiology				
Era	**Risk Factor**	**Biomarker**	**Genomic**	**Precision Med**
Era start date	**1960s**	**1990s**	**2000s**	**2015-**
Cohort design	**Single cohort**	**Single cohort, +/- multiethnic**	**Consortia of cohorts**	**Health system, mega biobank**
Sample size	**1K-10K**	**10K-100K**	**100K-500K**	**1M-10M**



O'Donnell CJ. European J Epidemiology 2020;35:1-4.

Genome Wide Studies of MI/CHD 2007-2024

Initial 9p21 Studies	• N=<25,000 • Nature & Science 2007
MIGen+	• N=25,525 • Nature Genetics 2009
CARDIo GRAM++	• N=143,677 • Nature Genetics 2011
CARDIo GRAM-PlusC4D+++	• N=194,427 • Nature Genetics 2013
CARDIOGRAM -PlusC4D+*	• N=>185,000 • Nature Genetics 2015
Cardio-Metabochip	• N=>250,000 • Nature Genetics 2017



+Kathiresan S et al. Nat. Genetics 2010;41:334.
++Schunkert H, et al. Nat. Genetics 2011;43:333.
+++Deloukas P, et al. Nat. Genetics 2013;45:25.
+* Nikpay M, et al. Nat Genetics 2015;47:1121.

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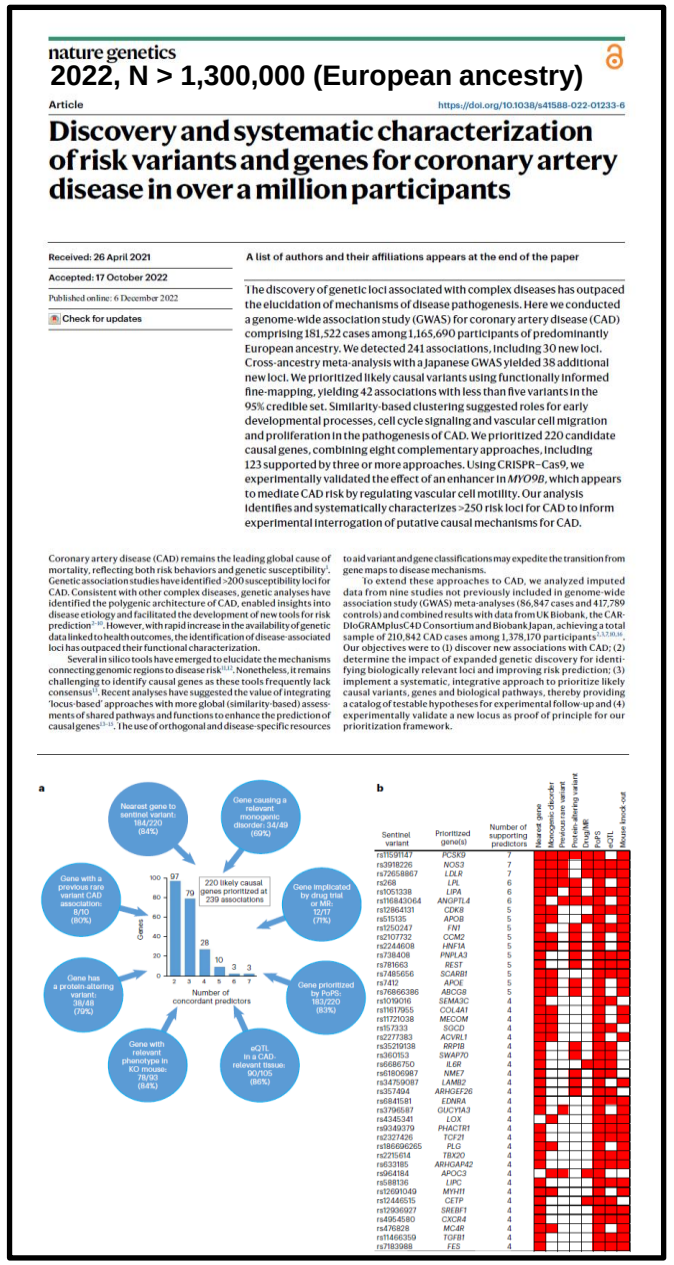

nature genetics

2022, N > 1,300,000 (European ancestry)

Article

https://doi.org/10.1038/s41588-022-01233-6

Discovery and systematic characterization of risk variants and genes for coronary artery disease in over a million participants

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A list of authors and their affiliations appears at the end of the paper

The discovery of genetic loci associated with complex diseases has outpaced the elucidation of mechanisms of disease pathogenesis. Here we conducted a genome-wide association study (GWAS) for coronary artery disease (CAD) comprising 181,522 cases among 1,165,690 participants of predominantly European ancestry. We detected 241 associations, including 30 new loci. Cross-ancestry meta-analysis with a Japanese GWAS yielded 38 additional new loci. We prioritized likely causal variants using functionally informed fine-mapping, yielding 42 associations with less than five variants in the 95% credible set. Similarity-based clustering suggested roles for early developmental processes, cell cycle signaling and vascular cell migration and proliferation in the pathogenesis of CAD. We prioritized 220 candidate causal genes, combining eight complementary approaches, including 123 supported by three or more approaches. Using CRISPR–Cas9, we experimentally validated the effect of an enhancer in *MYO9B*, which appears to mediate CAD risk by regulating vascular cell motility. Our analysis identifies and systematically characterizes >250 risk loci for CAD to inform experimental interrogation of putative causal mechanisms for CAD.

Coronary artery disease (CAD) remains the leading global cause of mortality, reflecting both risk behaviors and genetic susceptibility[1]. Genetic association studies have identified >200 susceptibility loci for CAD. Consistent with other complex diseases, genetic analyses have identified the polygenic architecture of CAD, enabled insights into disease etiology and facilitated the development of new tools for risk prediction[2–10]. However, with rapid increase in the availability of genetic data linked to health outcomes, the identification of disease-associated loci has outpaced their functional characterization.

Several in silico tools have emerged to elucidate the mechanisms connecting genomic regions to disease risk[11,12]. Nonetheless, it remains challenging to identify causal genes as these tools frequently lack consensus[13]. Recent analyses have suggested the value of integrating 'locus-based' approaches with more global (similarity-based) assessments of shared pathways and functions to enhance the prediction of causal genes[13–15]. The use of orthogonal and disease-specific resources to aid variant and gene classifications may expedite the transition from gene maps to disease mechanisms.

To extend these approaches to CAD, we analyzed imputed data from nine studies not previously included in genome-wide association study (GWAS) meta-analyses (86,847 cases and 417,789 controls) and combined results with data from UK Biobank, the CARDIoGRAMplusC4D Consortium and Biobank Japan, achieving a total sample of 210,842 CAD cases among 1,378,170 participants[1,3,7,10,16]. Our objectives were to (1) discover new associations with CAD; (2) determine the impact of expanded genetic discovery for identifying biologically relevant loci and improving risk prediction; (3) implement a systematic, integrative approach to prioritize likely causal variants, genes and biological pathways, thereby providing a catalog of testable hypotheses for experimental follow-up and (4) experimentally validate a new locus as proof of principle for our prioritization framework.

nature medicine 2022, N > 1,000,000 (diverse) ARTICLES

https://doi.org/10.1038/s41591-022-01891-3

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Large-scale genome-wide association study of coronary artery disease in genetically diverse populations

Catherine Tcheandjieu[1,2,3,4,88] ✉, Xiang Zhu[1,5,6,7,88], Austin T. Hilliard[1,88], Shoa L. Clarke[1,2,88], Valerio Napolioni[8,9], Shining Ma[5], Kyung Min Lee[10], Huaying Fang[11], Fei Chen[12], Yingchang Lu[13], Noah L. Tsao[14], Sridharan Raghavan[15,16], Satoshi Koyama[17], Bryan R. Gorman[18,19], Marijana Vujkovic[20,21], Derek Klarin[1,18,22,23,24,25], Michael G. Levin[20,21], Nasa Sinnott-Armstrong[1,11], Genevieve L. Wojcik[26], Mary E. Plomondon[27,28], Thomas M. Maddox[29,30], Stephen W. Waldo[27,28,31], Alexander G. Bick[32], Saiju Pyarajan[18,33], Jie Huang[18,34,35], Rebecca Song[18], Yuk-Lam Ho[18], Steven Buyske[36], Charles Kooperberg[37], Jeffrey Haessler[37], Ruth J. F. Loos[38], Ron Do[38,39], Marie Verbanck[38,39,40], Kumardeep Chaudhary[38,39], Kari E. North[41], Christy L. Avery[41], Mariaelisa Graff[41], Christopher A. Haiman[12], Loïc Le Marchand[42], Lynne R. Wilkens[42], Joshua C. Bis[43], Hampton Leonard[44,45], Botong Shen[46], Leslie A. Lange[47,48,49], Ayush Giri[50,51], Ozan Dikilitas[52], Iftikhar J. Kullo[52], Ian B. Stanaway[53], Gail P. Jarvik[54,55], Adam S. Gordon[56], Scott Hebbring[57], Bahram Namjou[58,59], Kenneth M. Kaufman[58], Kaoru Ito[17], Kazuyoshi Ishigaki[60], Yoichiro Kamatani[60,61], Shefali S. Verma[62,63], Marylyn D. Ritchie[62,63], Rachel L. Kember[20,64], Aris Baras[65], Luca A. Lotta[65], Regeneron Genetics Center*, CARDIoGRAMplusC4D Consortium*, Biobank Japan*, Million Veteran Program*, Sekar Kathiresan[23,66,67,68], Elizabeth R. Hauser[69,70], Donald R. Miller[71,72], Jennifer S. Lee[1,73], Danish Saleheen[20,74], Peter D. Reaven[75,76], Kelly Cho[18,33], J. Michael Gaziano[18,33], Pradeep Natarajan[23,67,77], Jennifer E. Huffman[18], Benjamin F. Voight[20,62,78,79], Daniel J. Rader[21], Kyong-Mi Chang[20,21], Julie A. Lynch[80,81], Scott M. Damrauer[14,20,62], Peter W. F. Wilson[82,83], Hua Tang[11], Yan V. Sun[84,85,89], Philip S. Tsao[1,73,86,89], Christopher J. O'Donnell[18,33,89] and Themistocles L. Assimes[1,2,86,87,89] ✉

We report a genome-wide association study (GWAS) of coronary artery disease (CAD) incorporating nearly a quarter of a million cases, in which existing studies are integrated with data from cohorts of white, Black and Hispanic individuals from the Million Veteran Program. We document near equivalent heritability of CAD across multiple ancestral groups, identify 95 novel loci, including nine on the X chromosome, detect eight loci of genome-wide significance in Black and Hispanic individuals, and demonstrate that two common haplotypes at the 9p21 locus are responsible for risk stratification in all populations except those of African origin, in which these haplotypes are virtually absent. Moreover, in the largest GWAS for angiographically derived coronary atherosclerosis performed to date, we find 15 loci of genome-wide significance that robustly overlap with established loci for clinical CAD. Phenome-wide association analyses of novel loci and polygenic risk scores (PRSs) augment signals related to insulin resistance, extend pleiotropic associations of these loci to include smoking and family history, and precisely document the markedly reduced transferability of existing PRSs to Black individuals. Downstream integrative analyses reinforce the critical roles of vascular endothelial, fibroblast, and smooth muscle cells in CAD susceptibility, but also point to a shared biology between atherosclerosis and oncogenesis. This study highlights the value of diverse populations in further characterizing the genetic architecture of CAD.

Remarkable progress in the prevention and treatment of coronary artery disease (CAD) has been made over the last half century. However, the rate of decrease in the age-adjusted prevalence of CAD has slowed substantially in the last decade, and CAD remains the leading cause of death worldwide[1]. Sizeable differences in the age-adjusted fatality rates of CAD persist between men and women and among the major populations in the United States, with non-Hispanic Black men persistently having the highest risk

ΓΙΣ

GWAS Loci Account for ~25-30% of MI/CHD Heritability

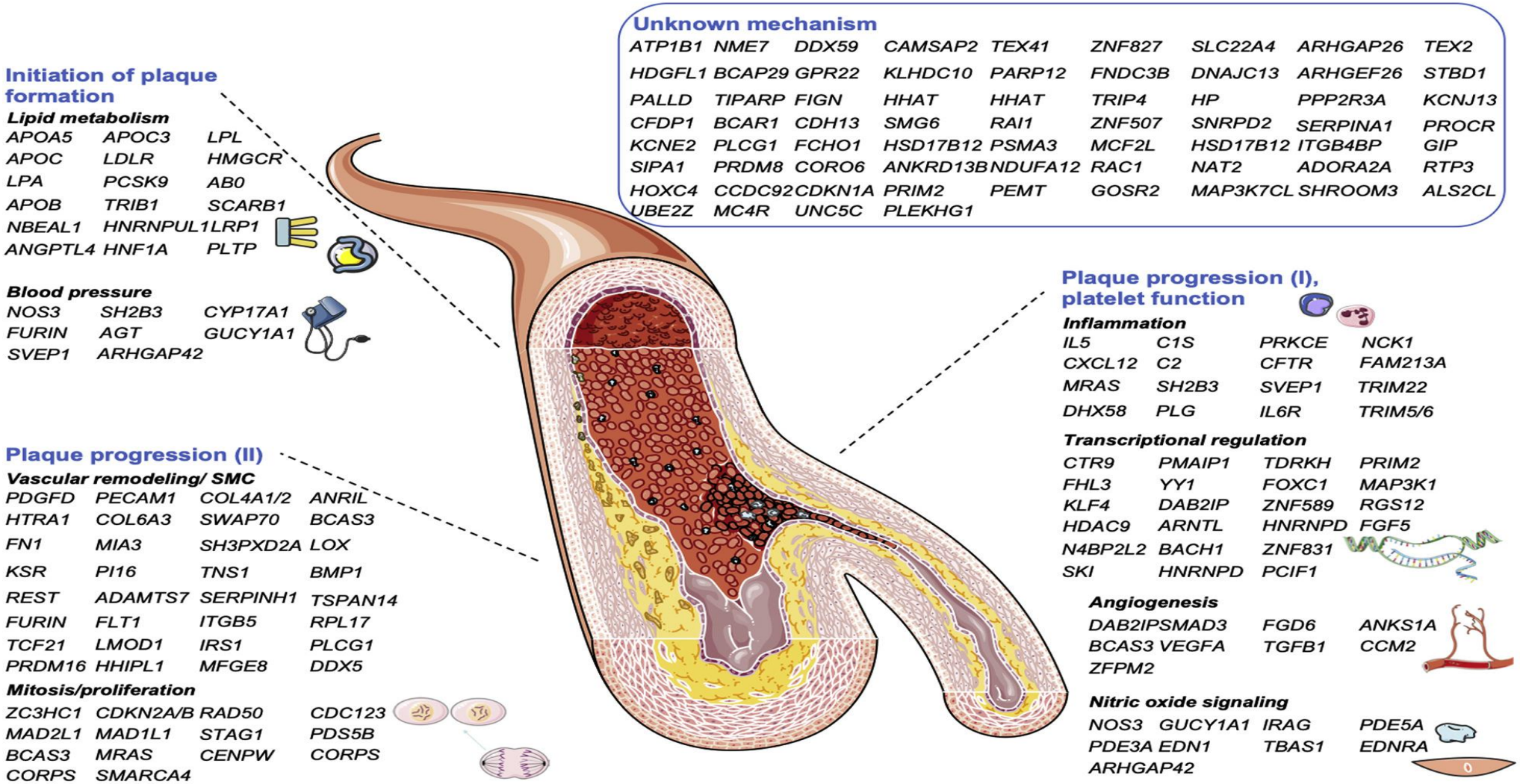
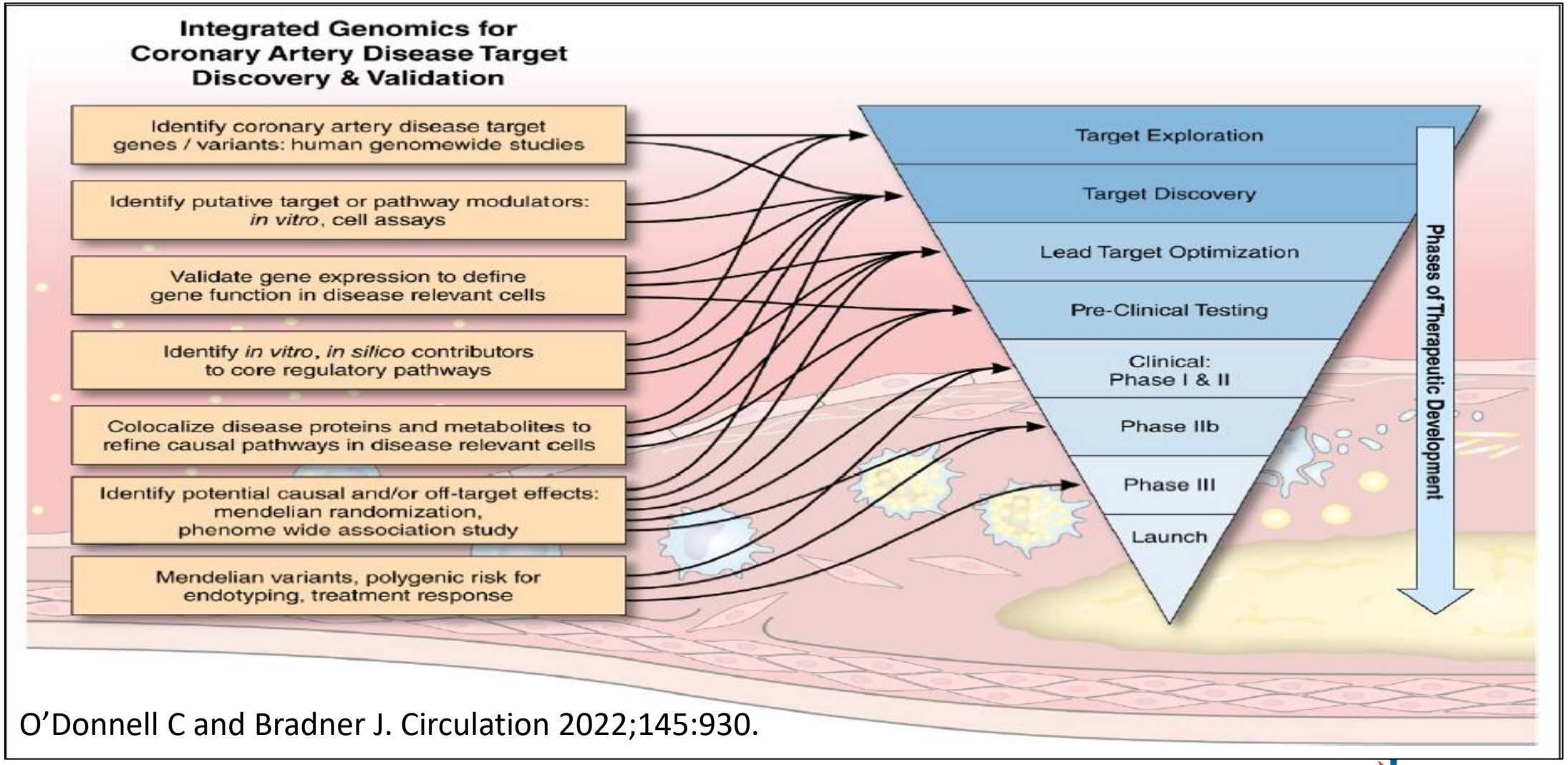


Figure 1. Kessler and Schunkert. JACC: Basic to Translational Science Vol 6, No 7, 2021

Harnessing Genomics for Translational Therapeutic Development for ASCVD



O'Donnell C and Bradner J. Circulation 2022;145:930.

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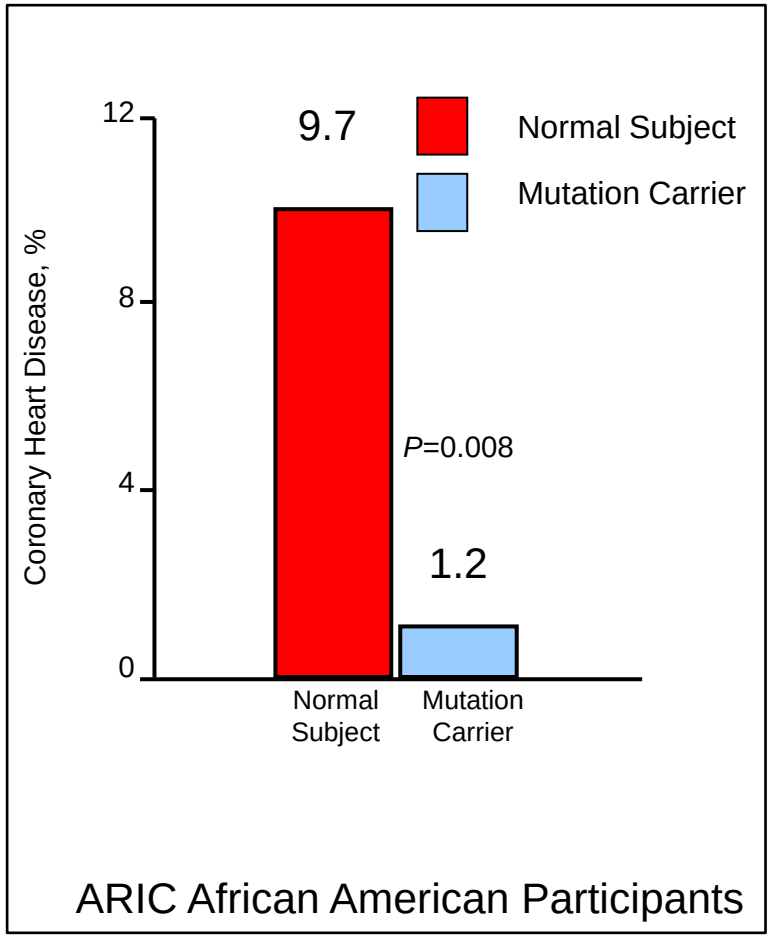
Reduced CHD from Lifelong Low LDL-C from Mutations in PCSK9 & Other Genes

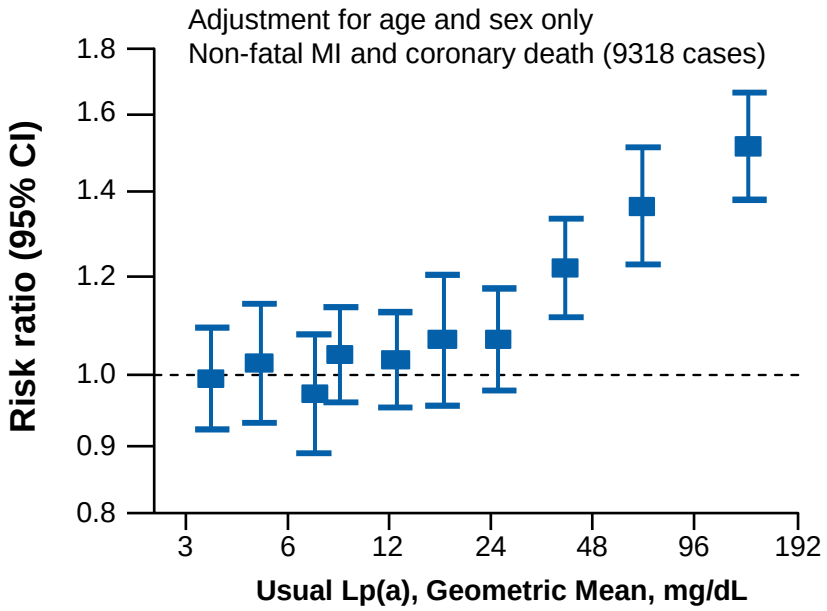


Cohen JC et al. *NEJM* 2006;354(12):1264–1272

PCSK9 Timeline:
From Discovery to RCTs:
Human Genetic Studies
2003 NEJM GOF mutation
2006 NEJM LOF mutation
Monoclonal Ab
2006-09 Preclinical Studies
2010-14 Phase I-II
2014 Phase III
2015 FDA Approve
2017 FOURIER (NEJM)
siRNA
2017 Inclisiran Phase I
2022 FDA Approve
ORION, VICTORIAN Trials Underway
Gene Editing
2021 Preclinical Rx
2023 Verve Phase Ib

Elevated Lp(a) Increases CVD Risk ~2X, a Level Similar to LDL-C

Lp(a) is an independent, genetic and causal risk factor for MI, stroke and PAD[1,2,3]



Erquo S et al. JAMA 2009;302:412.

1 in 5 people worldwide have elevated Lp(a)*[1,2]

1.4 billion people have elevated Lp(a)*, increasing their ASCVD risk[1,2]

Lp(a) is both the **most common monogenic CVD risk factor** and one of the strongest genetic CVD risk factors[2–5]

Polygenic risk score (PRS) reasonably accurately predicts level of Lp(a), Lp(a) levels remain reasonably stable over lifetime, modestly decrease with statins

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Options for Genetically Supported Therapy: Range of Approaches to Lower PCSK9

Therapeutic Approach (***Nucleotide-based)	Opportunities	Limitations	2º Prevention or High Risk?	1º Prevention?
Monoclonal Antibodies	Benefit in CVOT Efficacy, safety to date FDA and EMA Approved	Injections q1-2 months Long-term safety pending	+++	TBD
siRNA* **(miRNA→not in clinic)**	**2x per year SQ injection** **Efficacy, safety to date** **FDA and EMA Approved**	**CVOT pending** **Available safety excellent** **Long-term safety pending**	**+++**	**TBD**
Small Molecule Oral	Ease for patient	Phase 1-2 AEs, Compliance	+++	TBD
ASO* **	**SQ injection**	**Phase 1-2** **AEs, Compliance**	**+++**	**TBD**
Vaccine	Yearly injection	Phase 1 Safety, efficacy pending	+++	TBD
CRISPR Gene Editing***	Single injection	Phase 1 Safety, efficacy, ethics pending	+++	TBD
AAV Gene Therapy***	Single injection	No active trials	NA	NA

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Evolution of ASO and siRNA Therapy

- Discovery of the molecular structure of DNA by Watson and Crick In 1953 (1962 Nobel Prize, +Wilkins)
- A novel and selective drug platform that has the potential to target all RNA in cells
- Selectivity and specificity: the antisense-RNA must exactly and selectively match the mRNA of interest

ASO Therapy (a single strand RNA)

- 1978: ASO approach proposed: birth of the antisense concept
- 1998: First ASO therapy, Fomivisen approved, not a commercial success
- 2013: First systemically administered ASO therapy, Mipomersen, approved by FDA
- 2020: First liver-targeted ASO, pelacarsen, entered into Phase 3 trial

siRNA Therapy (a double strand RNA)

- 1998: Discovery of RNAi mechanism by Fire and Mello (2006 Nobel Prize)
- 2018: First siRNA therapy, Patisiran, approved (lipid nanoparticle formulation, iv infusion)
- 2020: First liver-targeted siRNA therapy, Inclisiran, for chronic use in large patient population approved by EMA, approved by FDA in 2021

≥15 oligonucleotide therapies have received regulatory approval, 9 ASO- and 6 siRNA therapies

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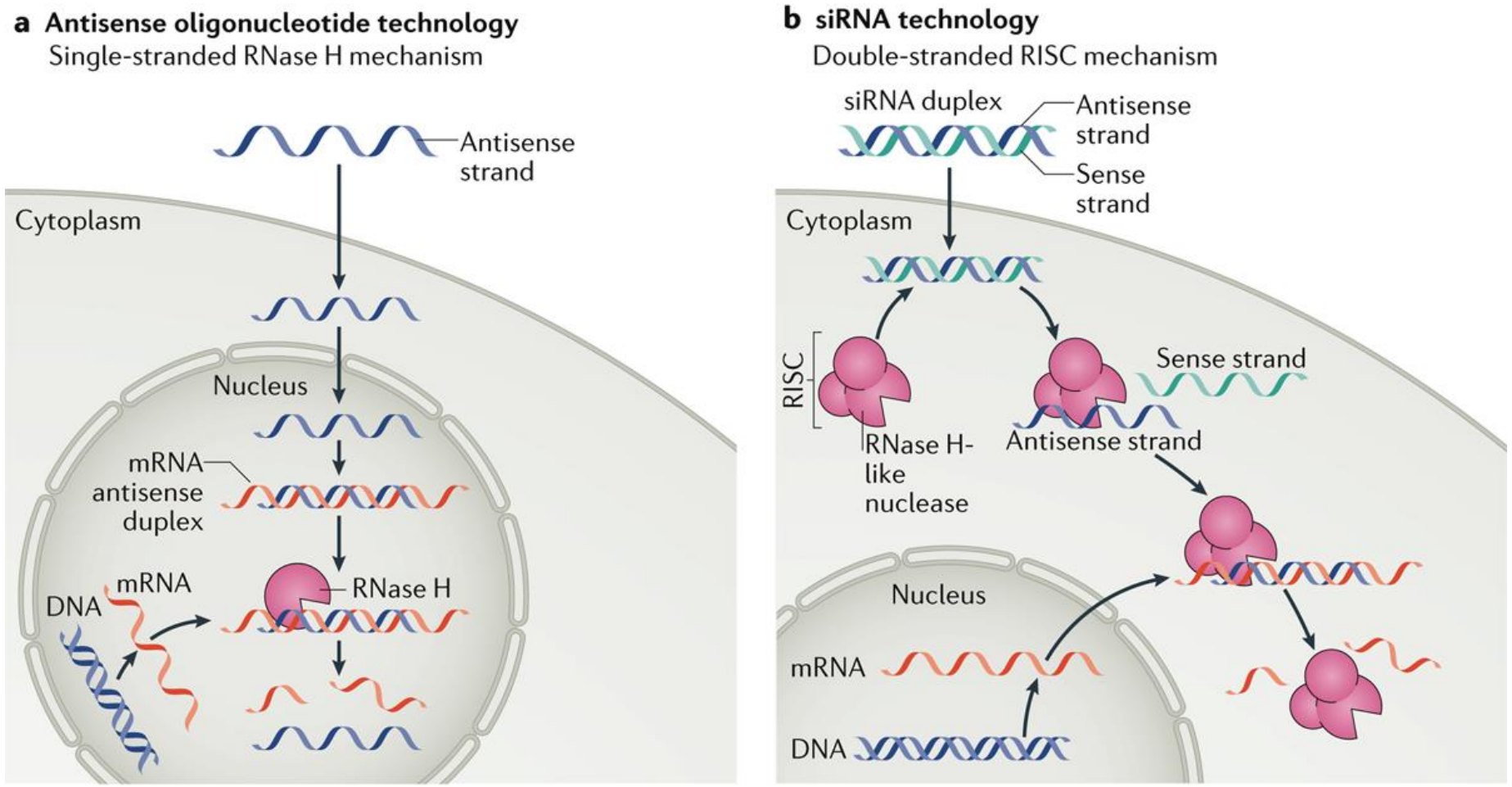
Some Important Differences in ASO-Based versus siRNA-Based Approaches



Nordestgaard et al. 2018 Nat Rev Cardiol

Nature Reviews | Cardiology

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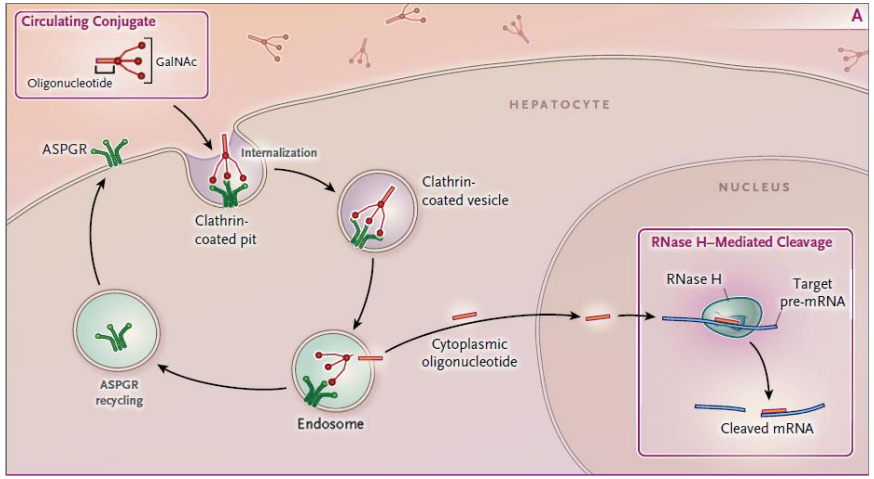
Early Development Challenges to Delivering ASO and siRNA Therapies to Patients

- **Stability of oligonucleotides** (ASO or siRNA)
- **Chemical modifications**
- **Delivery systems to target organs/tissues**
  - **GalNAc-conjugates (liver-targeting)**
  - Lipid nanoparticles
  - Liposomes



- **Potential toxicity and safety** associated with ASO and siRNA therapy
  - Safety/tolerability profiles lead to main focus on rare and life-threatening diseases
  - Inclisiran is the first nucleic acid therapy, including both ASO and siRNA modalities, aimed at larger patient populations for chronic use: i.e. hypercholesterolemia
  - Many other siRNA therapies are now under early or clinical development for larger patient populations for chronic use
- **Delivery and/or targeting to organs beyond liver**

Levin 2017 NEJM

Late Development and Commercial Risks, Benefits & Tradeoffs of Nucleotide Rx (ASO, siRNA, Gene Editing)

1. **Safety, Safety, Safety**:
   - Absence of off-target effects (e.g., avoid off-target siRNA or ASO motifs)
   - Injection site, target organ/tissue, other organ/tissue, reproductive toxicity
2. **Efficacy** relative to available generic therapy; what is the *target patient profile?*
3. **Tissue specificity and efficacy** of tissue-specific delivery
   - Extrahepatic ("***de-livering***") platforms and targets (e.g, myocardial, endothelial, adipose, renal)
   - For expanded use in other unmet cardiometabolic disease indications
4. **Dose frequency, duration of effect**
5. **Ease** of administration, **patient acceptance and compliance**
6. **Accessibility** to target population
   - Rare, uncommon, common diseases
   - Diverse and/or underserved populations
7. **Cost** (includes ancillary monitoring, COGs)
8. **Prevention**: Applications to secondary, primary, primordial prevention
9. **Overall level of risk/PoS/cost** for orphan versus rare/Mendelian CVD versus common CVD

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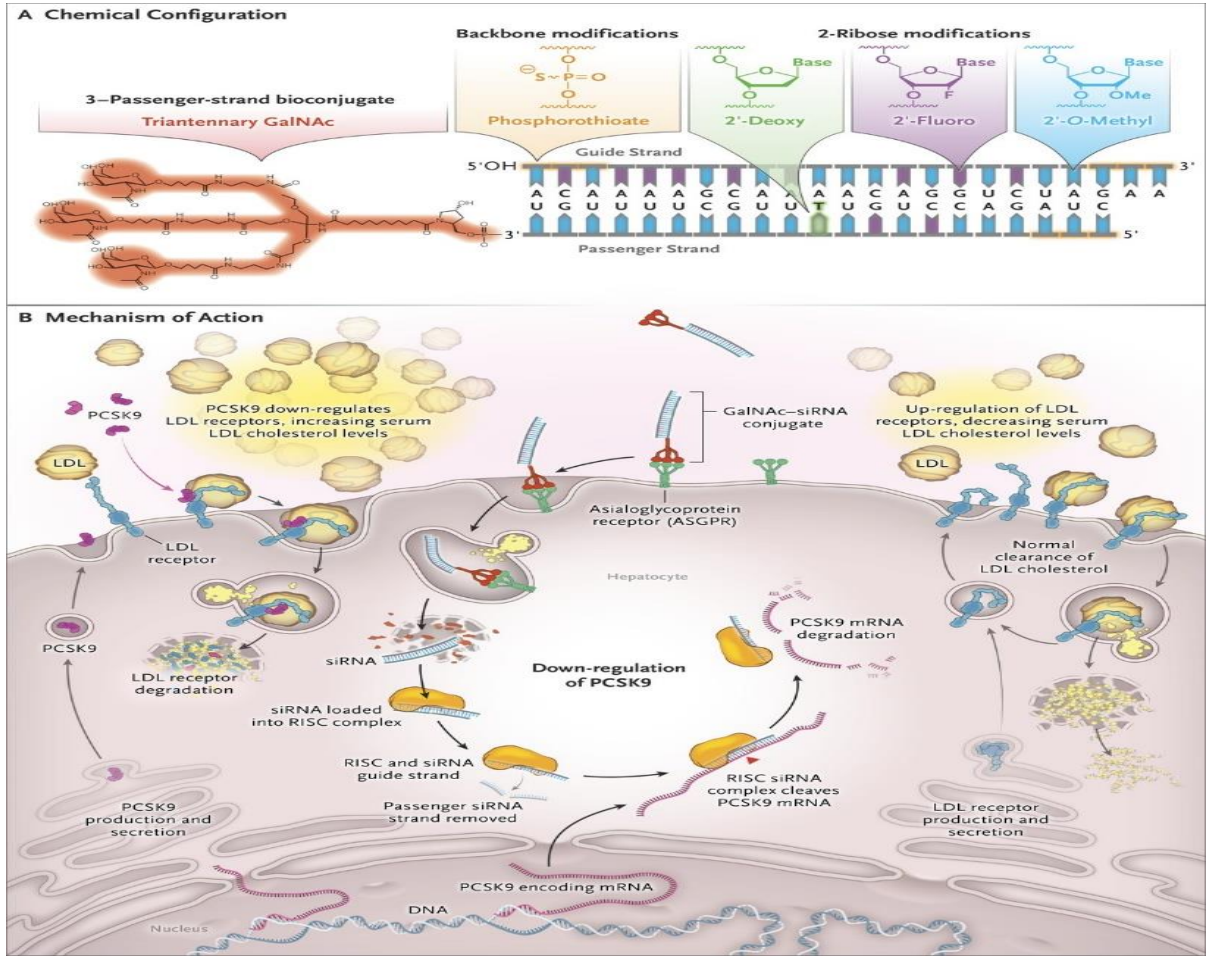
siRNA Therapy for Lifelong Use in Large Patient Populations: Inclisiran



- Inclisiran, a double-stranded siRNA, causes degradation of PCSK9 mRNA, leading to the reduced translation and production of the PCSK9 protein.
- PCSK9, predominantly expressed by the liver, is critical for the regulation (down) of LDLR on hepatocytes
- Reduced PCSK9 protein leads to higher levels of LDLR on hepatocytes, leading to reduced LDL-C in the circulation
- Inclisiran is covalently linked to a ligand, N-acetylgalactosamine (GalNAc), which enables specific uptake by the hepatocytes through the asialoglycoprotein receptors (ASGPR)
    - ASGPR: primarily expressed in the liver

Khvorova, 2017 NEJM

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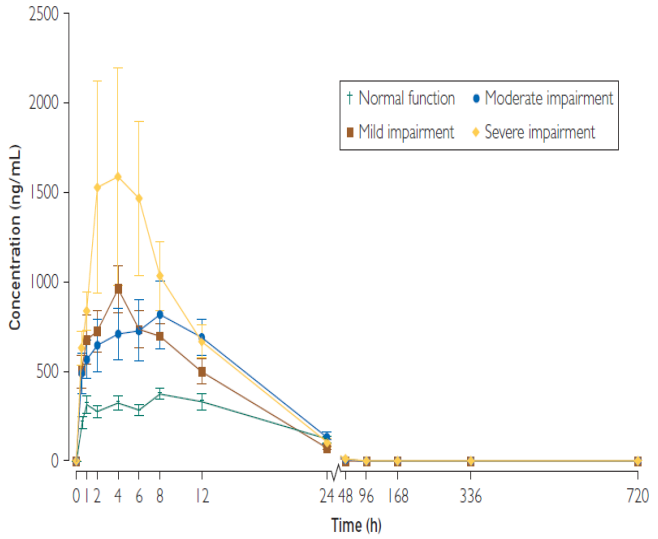
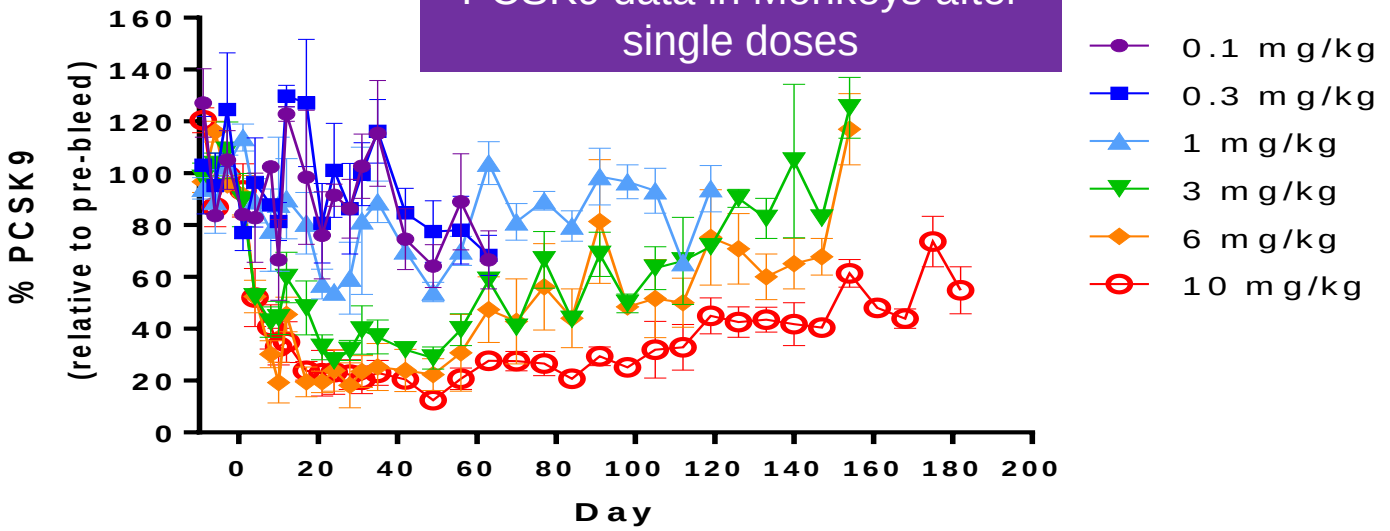
Duration of Action (PCSK9) in Monkey vs Human: Inclisiran

Human PK exposure of Inclisiran only detectable over 24-hours, while the PD effects sustain for >6 months

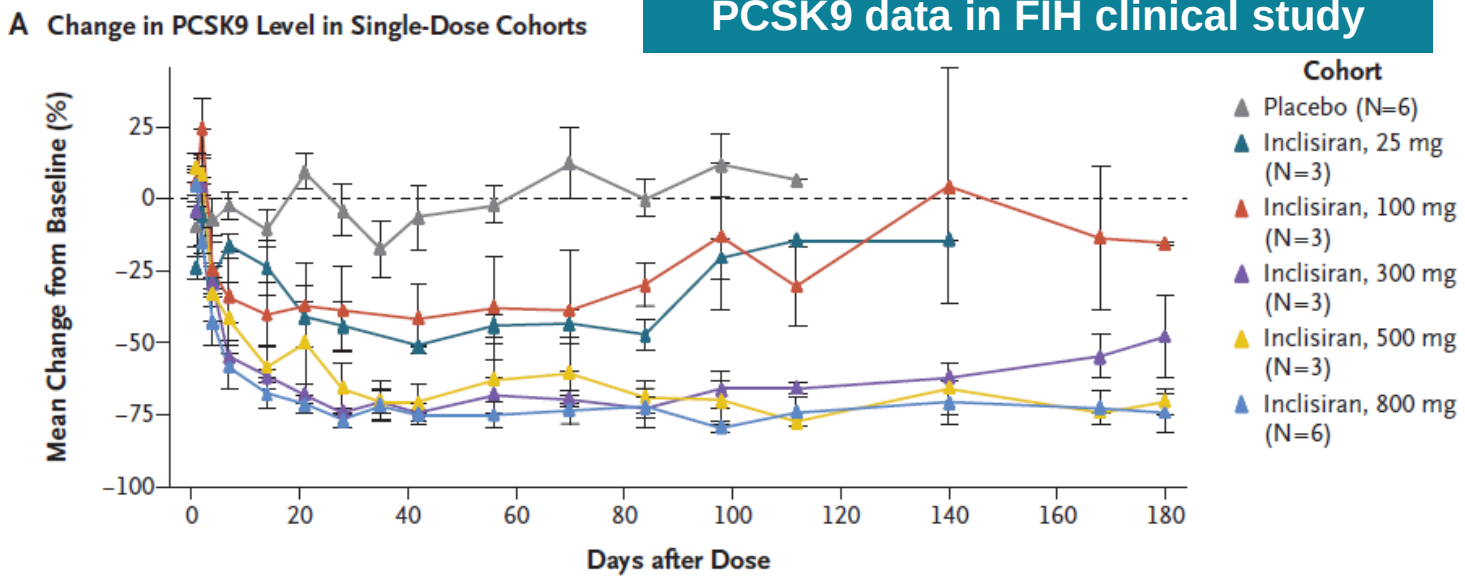


Fitzgerald et al. 2016 NEJM

PCSK9 data in Monkeys after single doses



PCSK9 data in FIH clinical study



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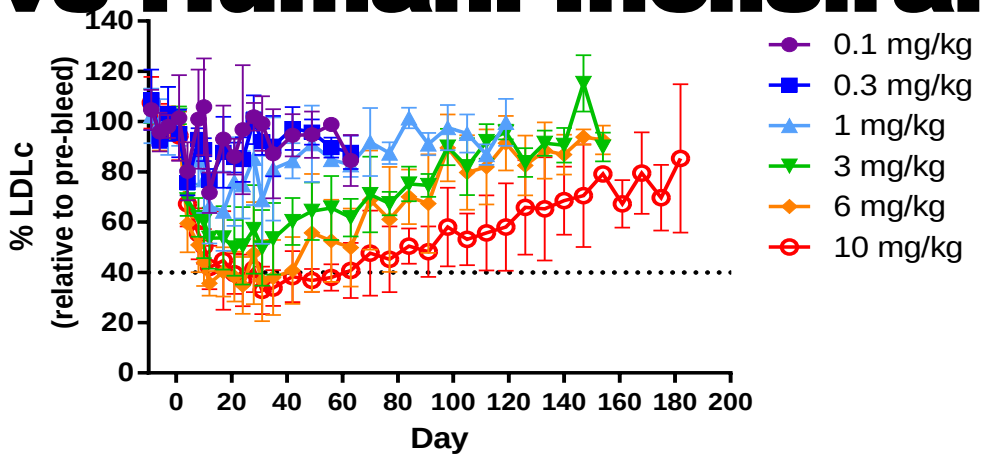
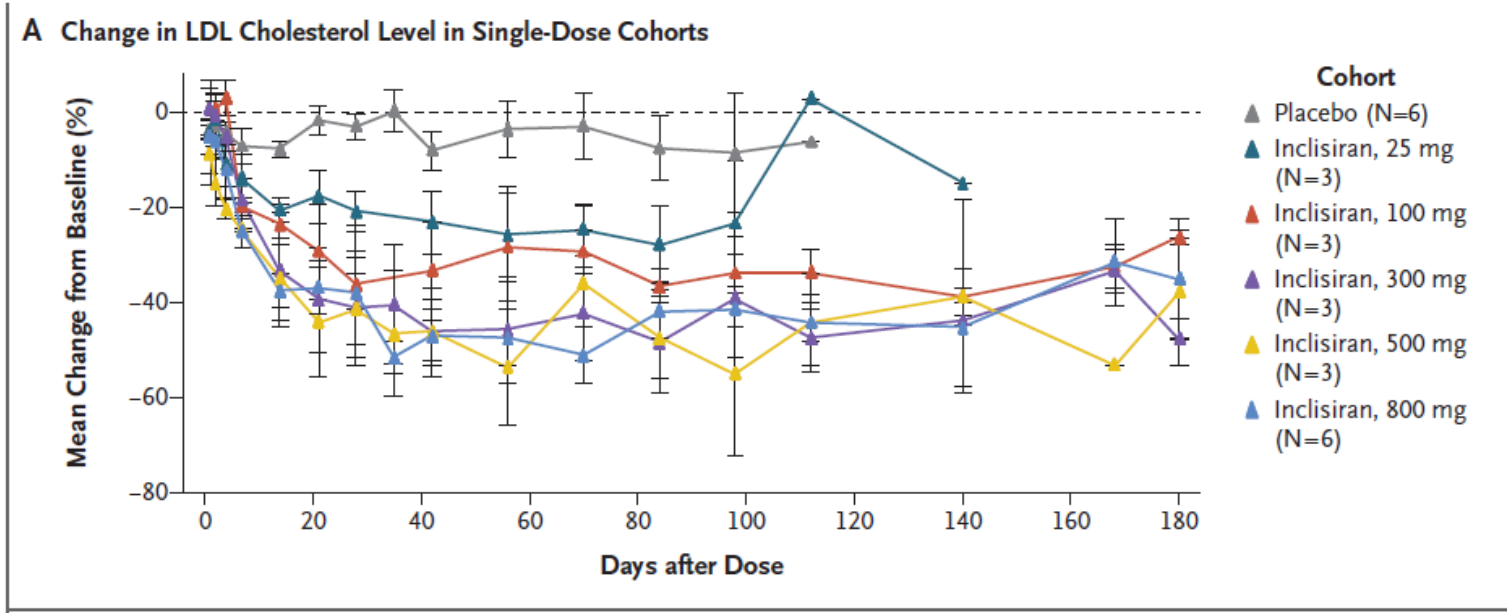
Duration of Action (LDL-C) in Monkey vs Human: Inclisiran

Efficacy (LDL-C) data in Monkeys after single doses



Efficacy (LDL-C) data in FIH clinical study after single doses



Fitzgerald et al. 2016 NEJM

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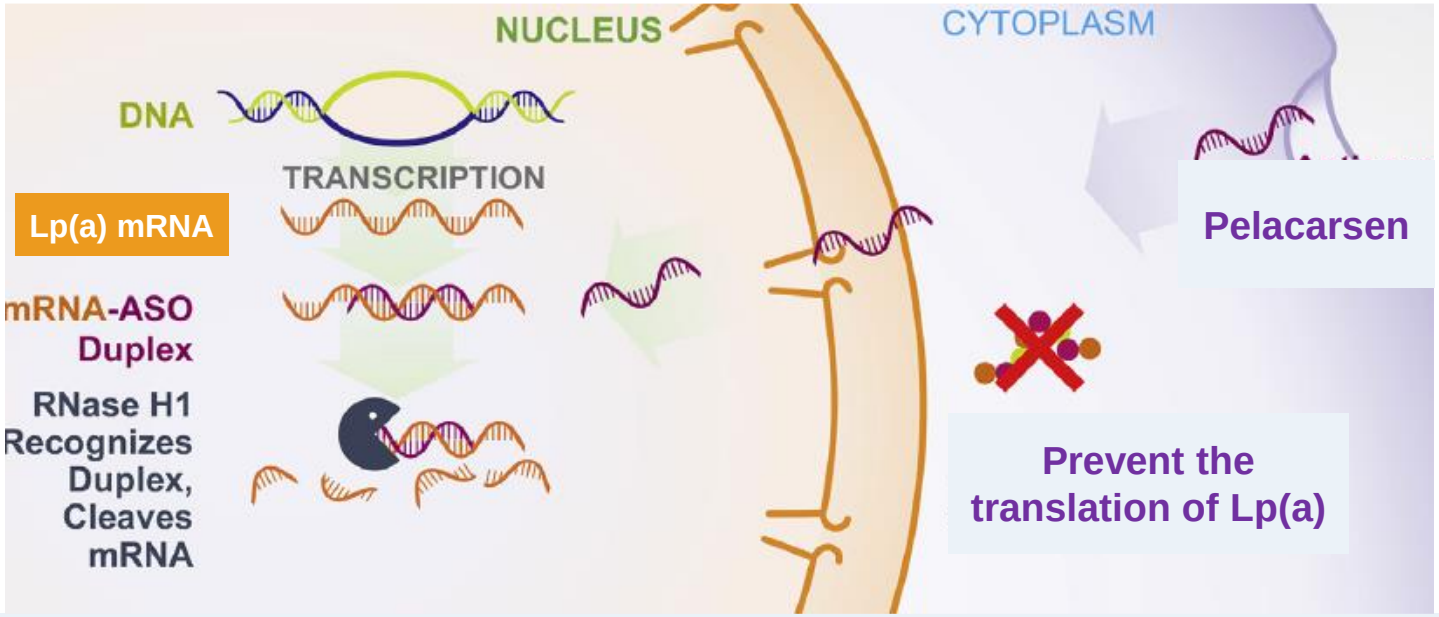
Pelacarsen, GalNAc-Conj. ASO Targeting Lp(a)

ASO therapy intended for a larger patient population (ASCVD)



- Lp(a) identified in 1963, elevated levels associated with atherosclerotic CVD and aortic stenosis etc.
- Lp(a) is primarily synthesized by the liver, levels are <u>exclusively determined by genetics</u>
  - lifestyle modification does not impact on Lp(a) levels
- No approved therapy for reducing Lp(a), irrespective of its discovery >50 years ago
  - Difficulty in targeting hepatic production of apo(a) with either small molecule or mAb
- Oligonucleotide therapeutics: ideal modalities to reduce Lp(a) production in the liver

Tsimikas et al. 2021 JACC

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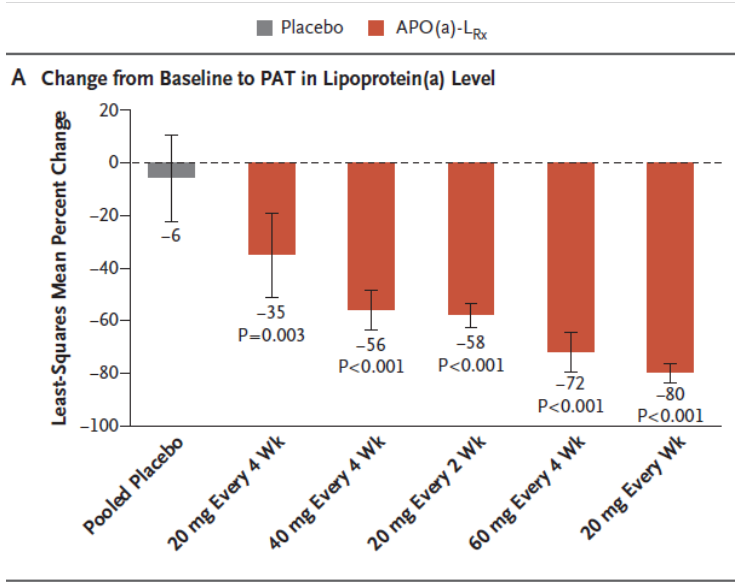
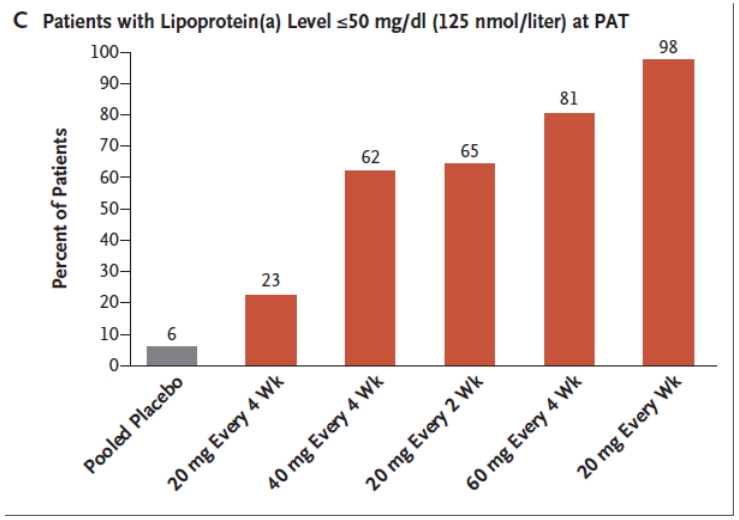
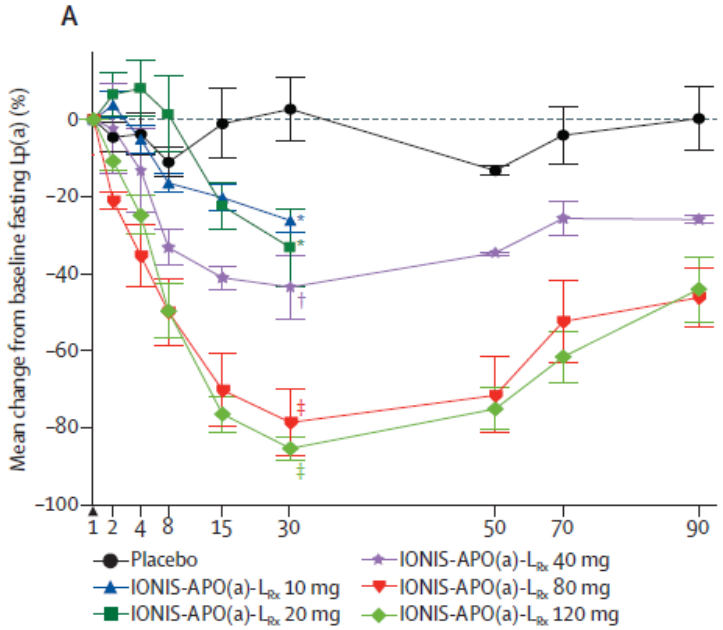
Pelacarsen: Ph3 dosing regimen (80 mg Q4W) could be predicted from the FIH clinical study

PoC/Ph2DRF study in patients; Dosing regimens tested: 20mg (QW Q2W Q4W); 40mg Q4W; 60mg Q4W

FIH clinical study (SAD) 80 mg: Max efficacy for 30 days







Ph2 clinical data is only critical for assessing and establishing clinical safety in patient population to support larger and longer Ph3 trial(s)

Tsimikas et al. 2020 NEJM; Viney et al. 2016 Lancet

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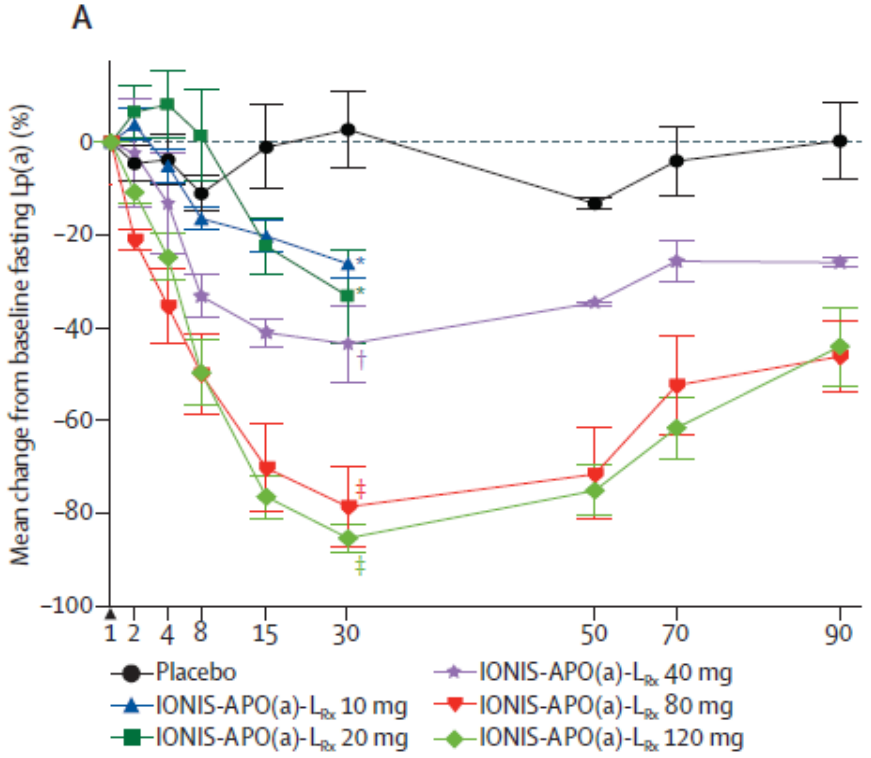
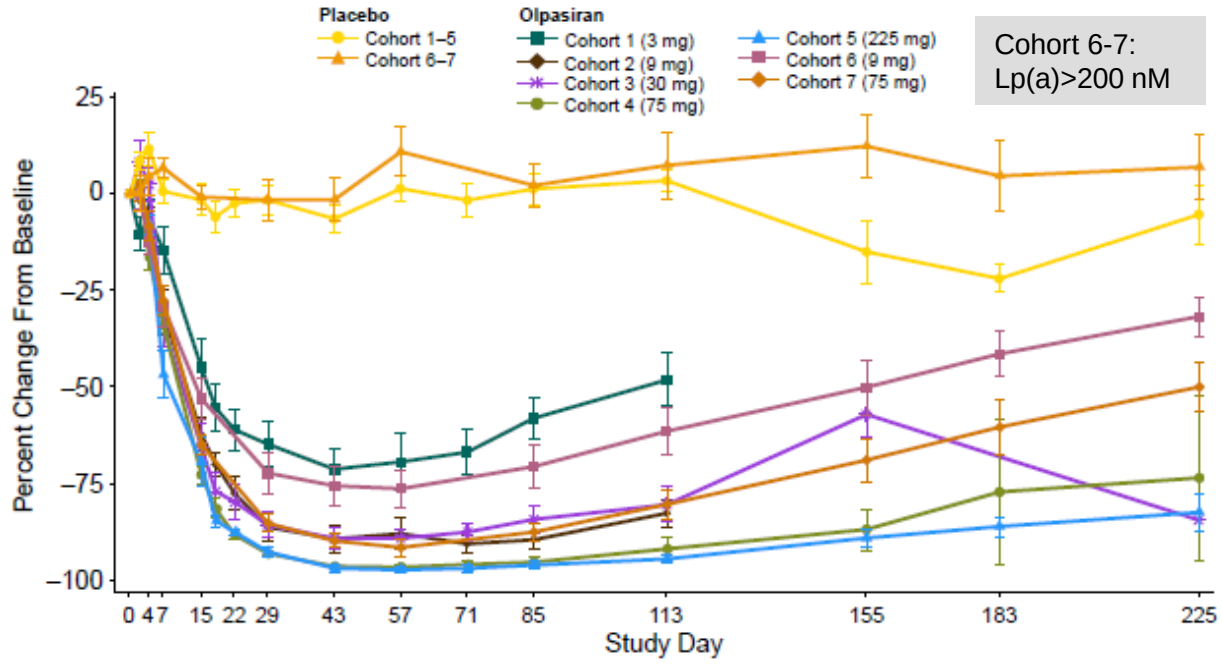
GalNAc-Conj. ASO versus siRNA Targeting Lp(a)

GalNAc-conjugated ASO
Pelacarsen: single dose sc injection
N=3 or 6 per cohort



GalNAc-conjugated siRNA
Olipasiran: single dose sc injection
N=6:2 cohort 1-5; N=9:3 cohort 6-7



Viney et al. 2016 Lancet; Koren et al. 2022 Nat Med

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Designing FIH and PoC Clinical Trials for Oligonucleotide Therapy

FIH/PoC Clinical Study
Single dose only may be sufficient

- **Unconventional FIH/PoC study design is critical →PoM/PoC**
  - **Single dose data is critical**, may not need MAD in FIH unless PoC is combined
- Measurement of **PD/efficacy endpoints** should be carefully designed →PoM/PoC
  - Sufficiently long duration
- **Safety and PK**
  - PK exposure does not predict the duration of effects

Combined PoC/Ph2b Study
Clinical safety data to support Ph3

- **PoC Trial in patients may be combined with Ph2b DRF study**
  - Due to longer duration of action
  - Especially for liver-targeted siRNA/ASO
- **Thoroughly interrogate FIH PD/efficacy data to optimize the PoC/Ph2b design**
  - Aim for fewer dosing regimens

➢ **Seamless handoff between PoC and Ph2b DRF is the key to accelerate**

Ph3 Clinical Study(ies)

- **Ph3 clinical trials can be initiated quickly**
- Proactive analysis of the clinical efficacy data from well designed FIH/PoC/Ph2b clinical studies can precisely inform Ph3 clinical development
- Initiate Ph3 trial when confidence is built for the dosing regimen and the targeted effect size and duration
- May not need to wait for Ph2b completion

Consider adaptive design when possible; skip Ph2b if willing to invest at risk with confidence in clinical safety and dosing regimen. The most aggressive strategy: FIH SAD → Ph3 trial

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Summary and Future Implications

- Largescale human genetics / genomics has advanced our understanding of the etiology of risk factors and disease and identified a growing range of tractable cardio-metabolic disease targets plus leads for patient strata and biomarkers.
- The first wave nucleic acid-based Rx for disease prevention and treatment have focused on liver-based targets for inhibition of target gene expression that markedly reduces pharmacodynamic risk biomarkers [eg, LDL-C, Lp(a)]
- Novel nucleic acid Rx approaches optimized for maximal safety, efficacy and long duration of action are transforming cardiovascular therapeutics. Early phase trials of ASO & siRNA Rx (targeted at liver) define PoM/PoC/dosing.
- Future studies addressing risks & challenges promise to enable the full potential of an expanded armamentarium of nucleic acid Rx to treat, possibly cure and ultimately prevent the epidemic of cardiometabolic disease.