ARO-ANG3 KOL Webinar

November 19, 2020

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Welcome and Introductions

Vince Anzalone, CFA

Safe Harbor Statement

This presentation contains forward-looking statements within the meaning of the "safe harbor" provisions of the Private Securities Litigation Reform Act of 1995. These statements are based upon our current expectations and speak only as of the date hereof. Our actual results may differ materially and adversely from those expressed in any forward-looking statements as a result of various factors and uncertainties, including, without limitation, our developmental stage and limited operating history, our ability to successfully and timely develop products, enter into collaborations and achieve other projected milestones, rapid technological change in our markets, demand for our future products, legislative, regulatory and competitive developments and general economic conditions. Our Annual Report on Form 10-K and other SEC filings discuss some of the important risk factors that may affect our ability to achieve the anticipated results, as well as our business, results of operations and financial condition. Readers are cautioned not to place undue reliance on these forward-looking statements. Additionally, Arrowhead disclaims any intent to update these forward-looking statements to reflect subsequent developments.

Panelists

New York University Grossman School of Medicine

Dr. Ira Goldberg, M.D..
Clarissa And Edgar Bronfman Professor
Director, Division of Endocrinology, Diabetes and Metabolism

Arrowhead Pharmaceuticals

Chris Anzalone, Ph.D
President & Chief Executive Officer

Vince Anzalone, CFA
Vice President, Investor Relations

Javier San Martin, M.D.
Chief Medical Officer

Jim Hassard
Chief Commercial Officer

Agenda

- Welcome and Introductions – Vince Anzalone
- Market Opportunity – Jim Hassard
- ANGPTL3 as a Therapeutic Target in Mixed hyperlipidemia – Dr. Ira Goldberg
- ARO-ANG3 Clinical Development – Dr. Javier San Martin
- Wrap up – Dr. Christopher Anzalone
- Q & A – Panel

Broad Pipeline

THERAPEUTIC AREA		PRE-CLINICAL	PHASE 1	PHASE 2	PHASE 3	Product Rights
Cardiometabolic	**ARO-APOC3** FCS, sHTG					
	ARO ANG Dyslipidemia					
	AMG 890 CVD					AMGEN
Pulmonary	**ARO-ENAC** Cystic fibrosis					
	ARO-Lung2 COPD					
Liver	**ARO-HSD** NASH					
	ARO-AAT AATD					Takeda
	JNJ 3989 HBV					janssen
Oncology	**ARO-HIF2** RCC					
Undisclosed	**JNJ1**					janssen
	JNJ2					janssen
	JNJ3					janssen

Tissue Targets

Liver Lung Tumor

Market Opportunity

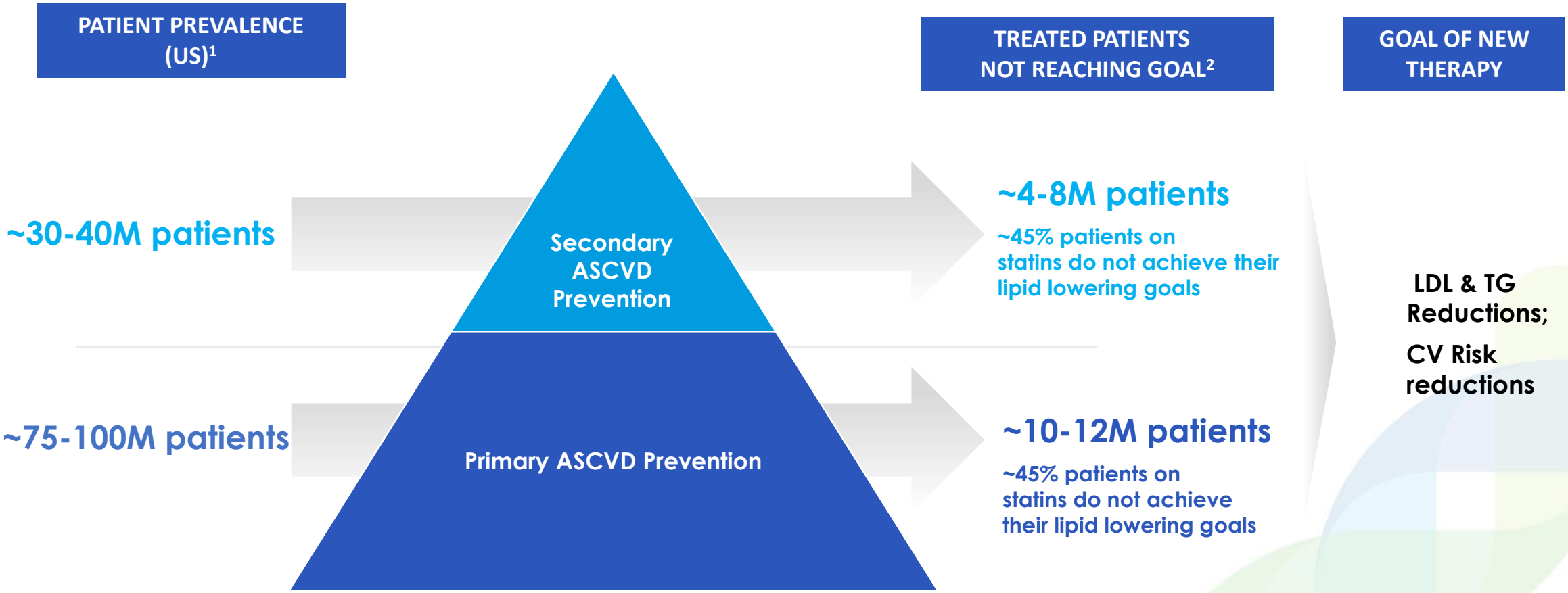
Jim Hassard

Residual CV risk remains despite LDL-lowering drugs

CVD accounts for:	Avg annual cost of CVD in US:	Residual risk despite LDL lowering drugs[3]
1 of every 3 deaths globally[1] **600,000 deaths per year in the US[2]**	**>$350Bn in 2015[3]** **Projected >$1.1 Tn in 2035[3]**	**Statins reduce risk of CV death by ~20-40%[4]** **26% ↑ rate of major CVE in patients with CVD on statins if TG ≥150 mg/dL[5]**

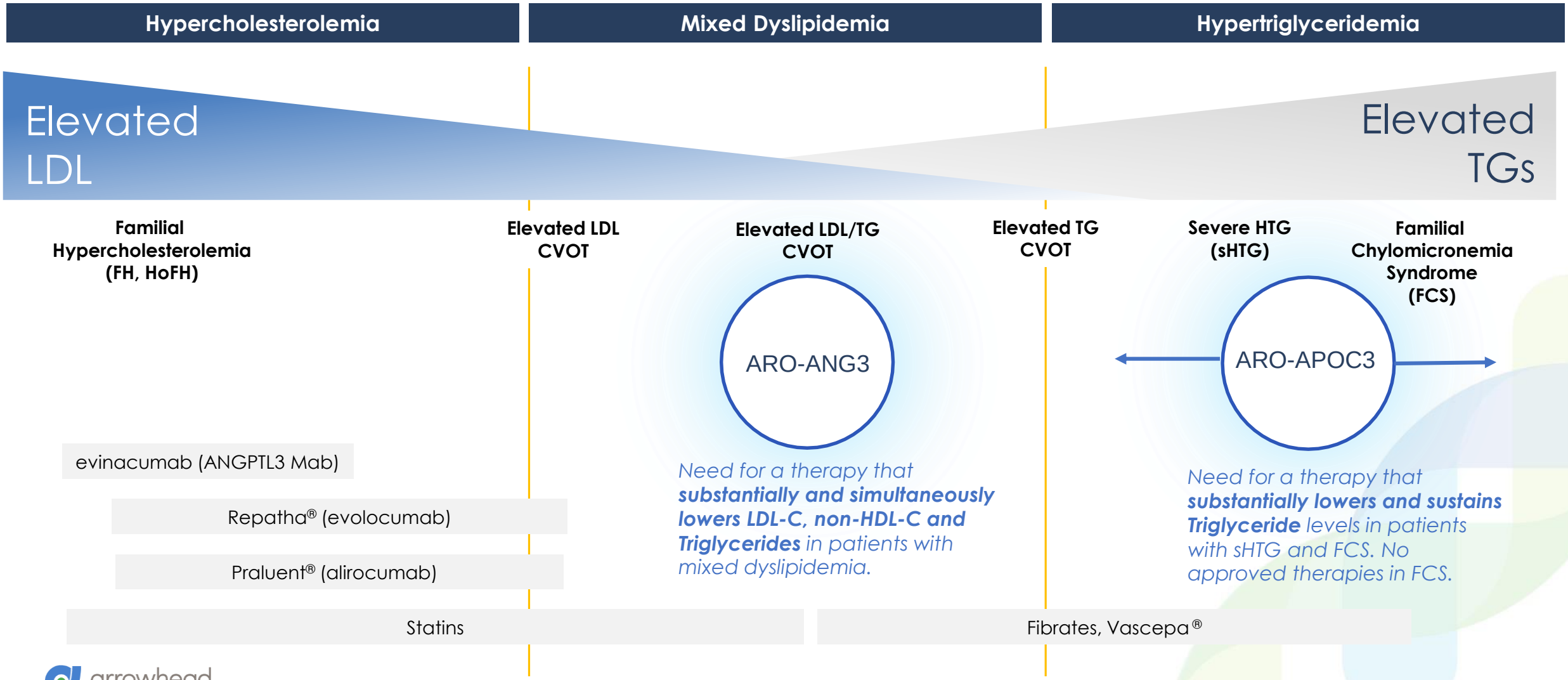
1. World Heart Federation. 2. CDC Heart Disease Facts.. 3. AHA Heart Disease and Stroke Statistics-2019 At-a-Glance. 4. Cholesterol Treatment Trialists Collaboration. 2010. 6. Toth 2019.

ARO-ANG3 has the potential to serve primary and secondary prevention ASCVD populations



1. NHANES 2015-16 2. Fan et al Cardiology Journal (2019) 26(5): 604-606

ARO-ANG3 and ARO-APOC3 serve key unmet patient needs



ANGPTL3 as a Therapeutic Target in Mixed Dyslipidemia

Ira Goldberg, M.D.

NYU Langone Health

Division of Endocrinology, Diabetes and Metabolism

ANGPTL3 AS A TARGET FOR MIXED HYPERLIPIDEMIA

Ira J. Goldberg

Clarissa And Edgar Bronfman Professor

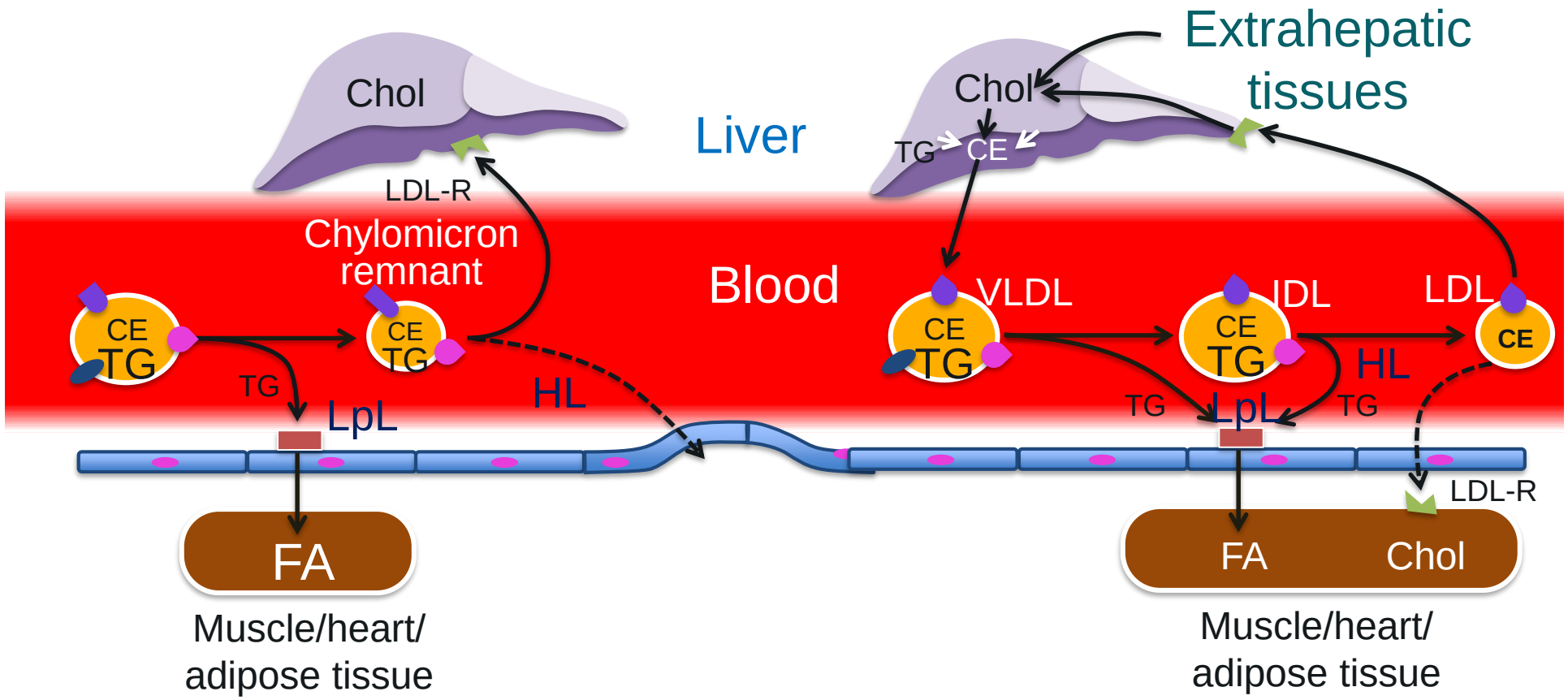
Director, Division Of Endocrinology, Diabetes And Metabolism

New York University Grossman School Of Medicine

Outline

- Introduction to lipoprotein disorders
- Atherogenic lipoproteins – LDL and beyond
- ANGPTL3, and comparison ApoC3
- HDL- its controversy
- Typical patient with combined hyperlipidemia

Chylomicrons and VLDL compete for LpL.



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Too much fat in the blood

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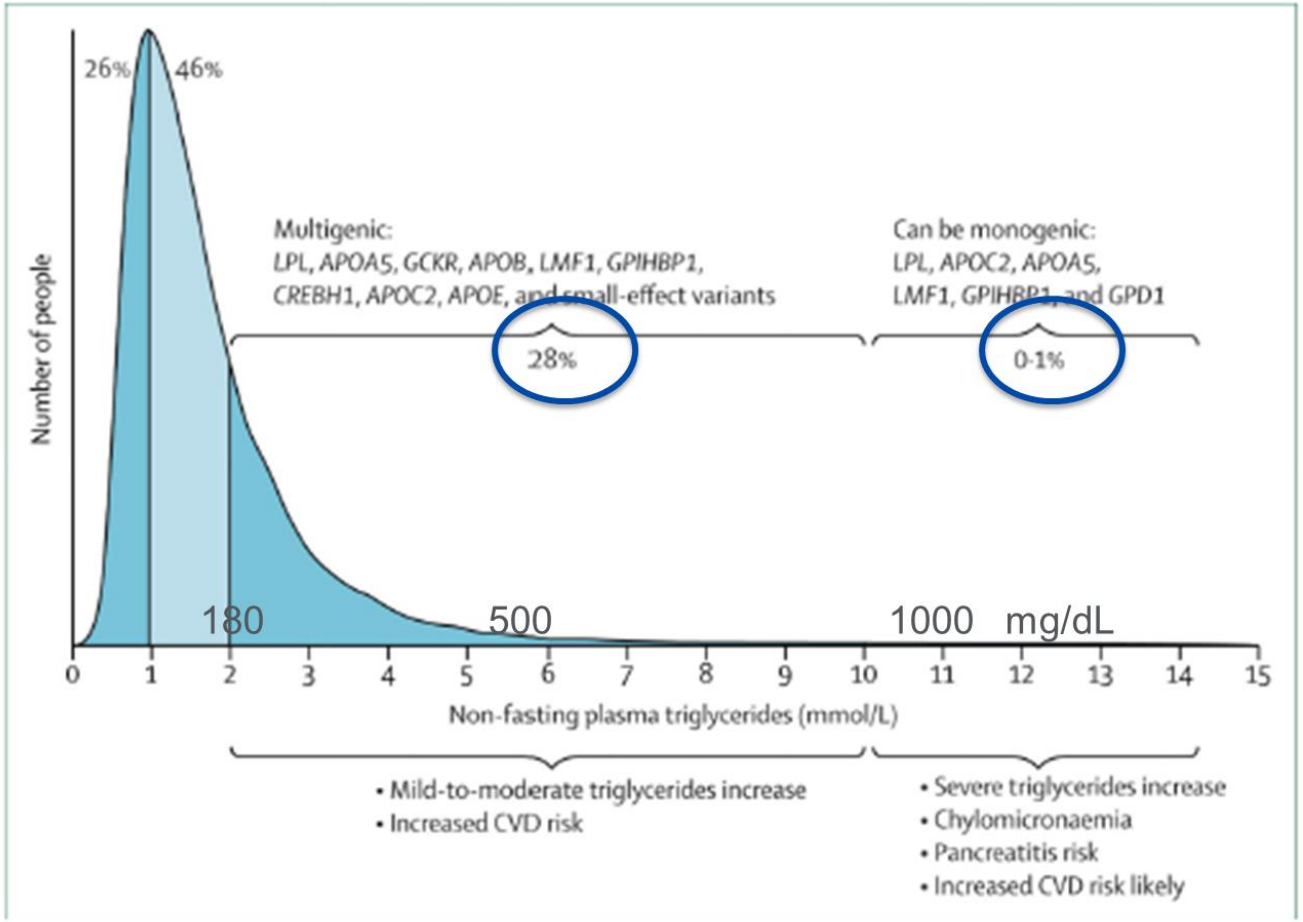
Triglyceride levels above 2 mM (~165 mg/dL) occur in 28% of the population.



Hegele et al. Lancet Diabetes Endocrinol. 2014 Aug;2(8):655-66.

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Hyperlipidemia in Coronary Heart Disease

I. LIPID LEVELS IN 500 SURVIVORS OF MYOCARDIAL INFARCTION

JOSEPH L. GOLDSTEIN, WILLIAM R. HAZZARD, HELMUT G. SCHROTT, EDWIN L. BIERMAN, and ARNO G. MOTULSKY with the assistance of MARY JO LEVINSKI and ELLEN D. CAMPBELL

From the Departments of Medicine (Division of Medical Genetics, University Hospital, and Division of Metabolism and Gerontology, Veterans Administration Hospital) and Genetics, University of Washington, Seattle, Washington 98195

"These results raise the possibility that hypertriglyceridemia may be as an important a risk factor for coronary atherosclerosis as hypercholesterolemia."

J Clin Invest 1973 Jul;52(7):1533-43.

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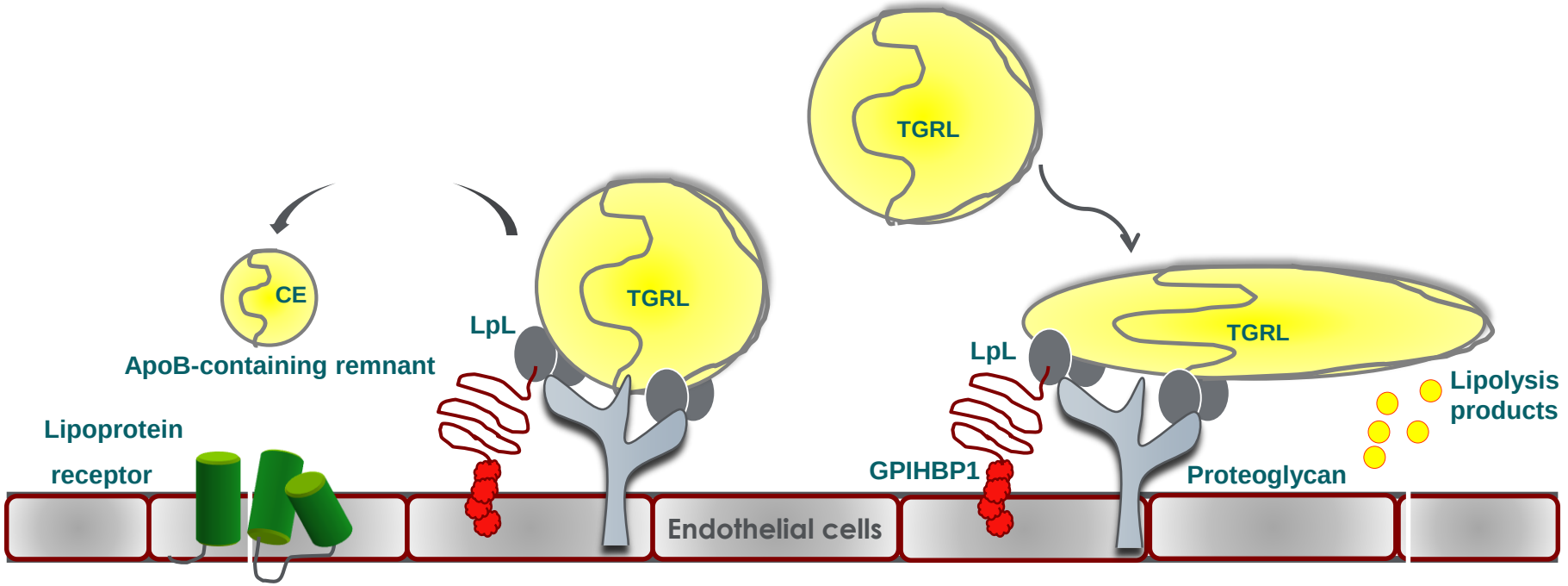
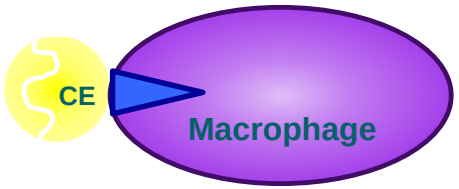
Atherogenicity of Triglyceride-Rich Lipoproteins (TGRL)





Remnant hypothesis

Increased inflammation, adhesion, and coagulation

Lipolytic toxin hypothesis

Triglycerides and heart disease, still a hypothesis?
Goldberg, McPherson, Eckel, ATVB 2011, 31:1716-25

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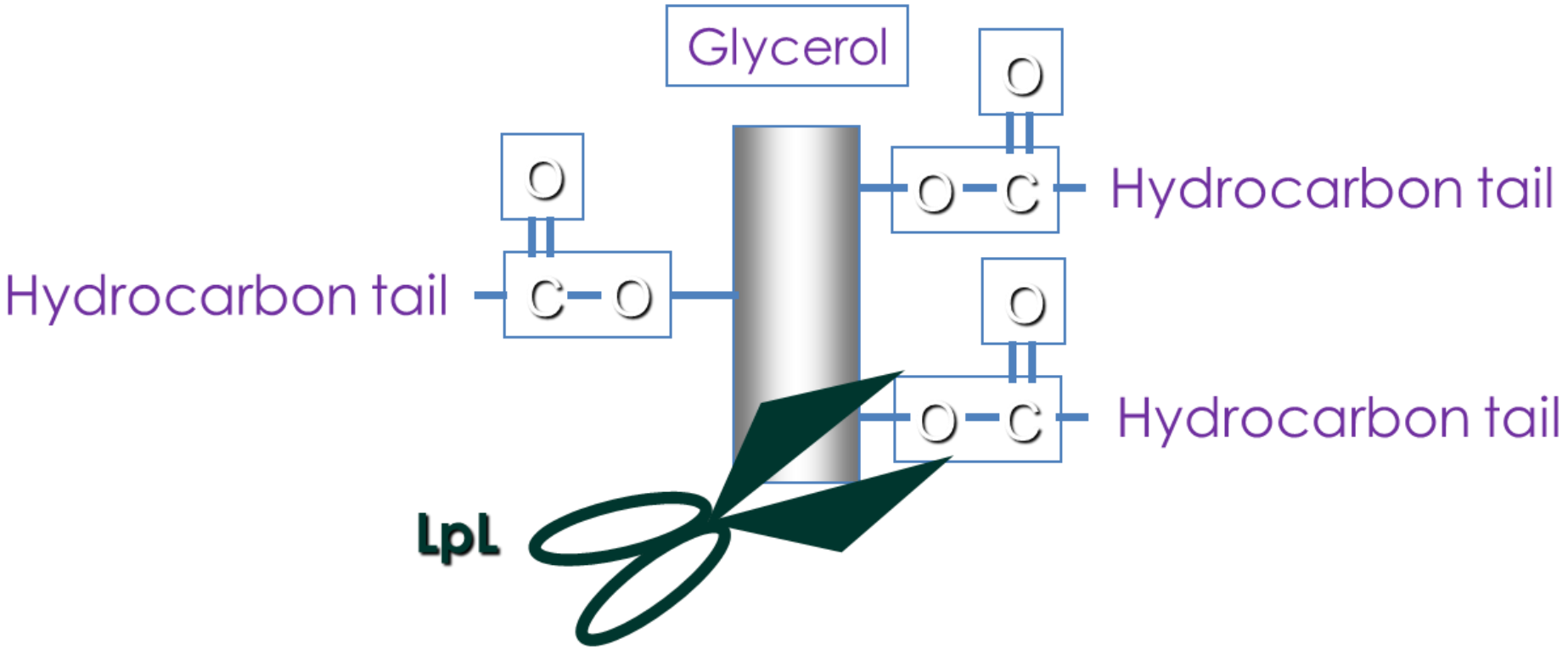
Triglyceride (TG) and Lipoprotein Lipase (LpL)



What regulates lipolysis?

Activators

- ApoC-II (activator)
- GPIHBP1 (endothelial cell binding site)
- Lipase maturation factor (LMF, intracellular production)
- ApoA-V (increases binding to endothelial cells

Inhibitors

- ApoC-III
- Angiopoietin-like proteins 3,4,8

A genetic mutation leading to hypolipidemia but no fatty liver disease

The NEW ENGLAND JOURNAL of MEDICINE

BRIEF REPORT

Exome Sequencing, *ANGPTL3* Mutations, and Familial Combined Hypolipidemia

Kiran Musunuru, M.D., Ph.D., M.P.H., James P. Pirruccello, B.S., Ron Do, M.S., Gina M. Peloso, M.S., Candace Guiducci, B.S., Carrie Sougnez, B.S., Kiran V. Garimella, M.S., Sheila Fisher, M.L.A., Justin Abreu, M.S., Andrew J. Barry, B.S., Tim Fennell, B.S., Eric Banks, Ph.D., Lauren Ambrogio, B.S., Kristian Cibulskis, B.S., Andrew Kernytsky, Ph.D., Elena Gonzalez, B.S., Nicholas Rudzicz, M.S., James C. Engert, Ph.D., Mark A. DePristo, Ph.D., Mark J. Daly, Ph.D., Jonathan C. Cohen, Ph.D., Helen H. Hobbs, M.D., David Altshuler, M.D., Ph.D., Gustav Schonfeld, M.D., Stacey B. Gabriel, Ph.D., Pin Yue, Ph.D., and Sekar Kathiresan, M.D.

SUMMARY

We sequenced all protein-coding regions of the genome (the "exome") in two family members with combined hypolipidemia, marked by extremely low plasma levels of low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides. These two participants were compound heterozygotes for

N Engl J Med 2010;363:2220-7.

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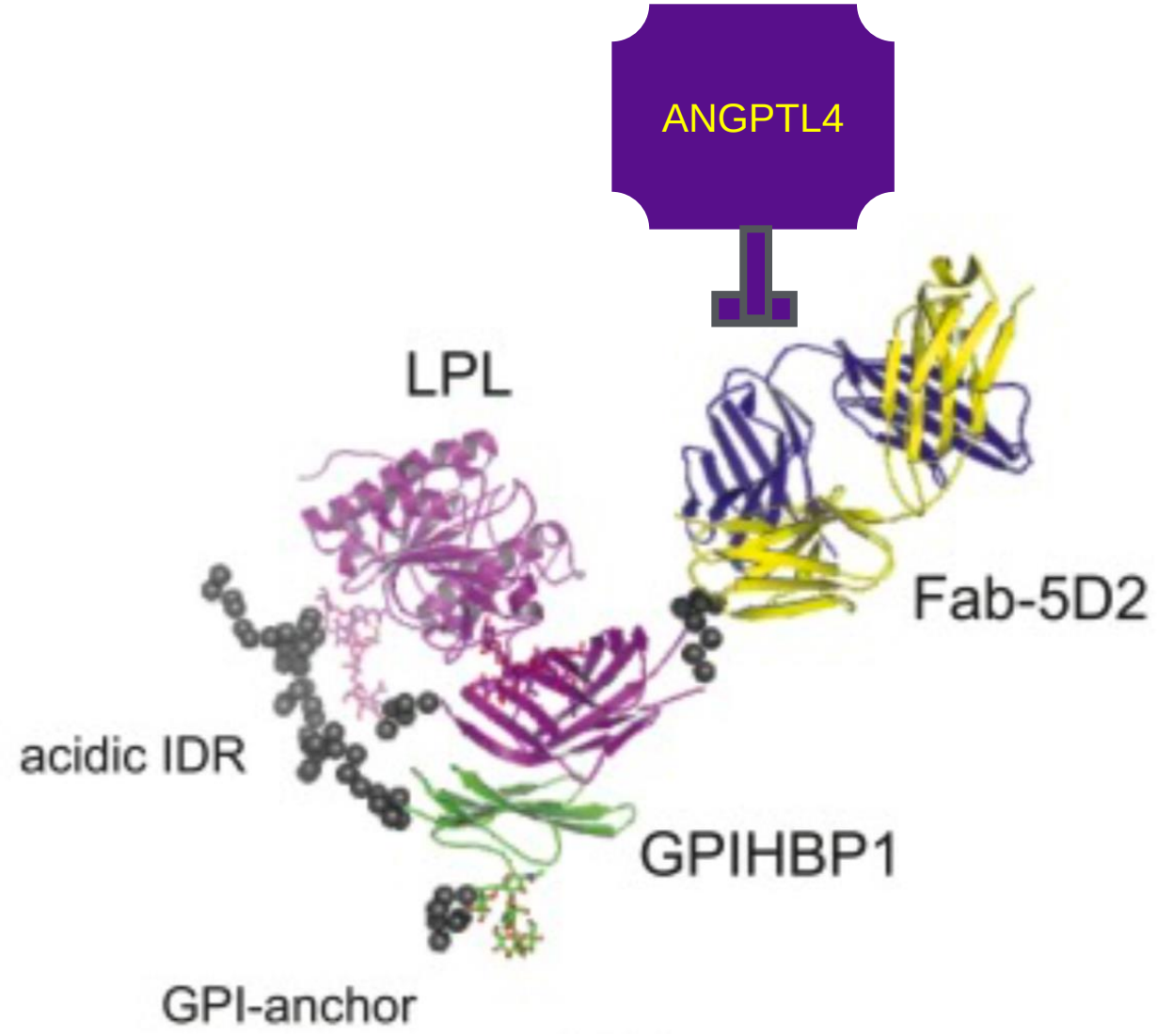
Angptl4 inactivates LpL.



PNAS 2020; 117, 4337-4346

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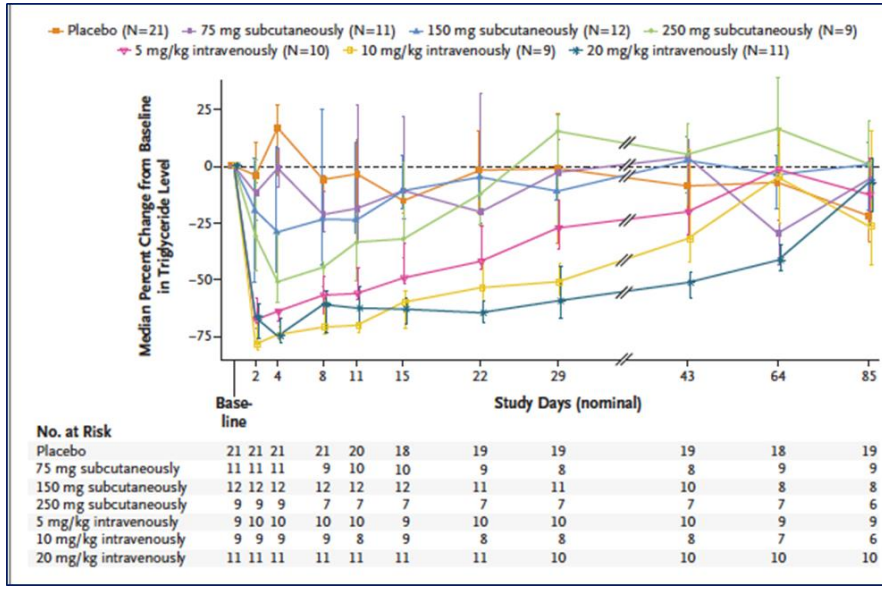
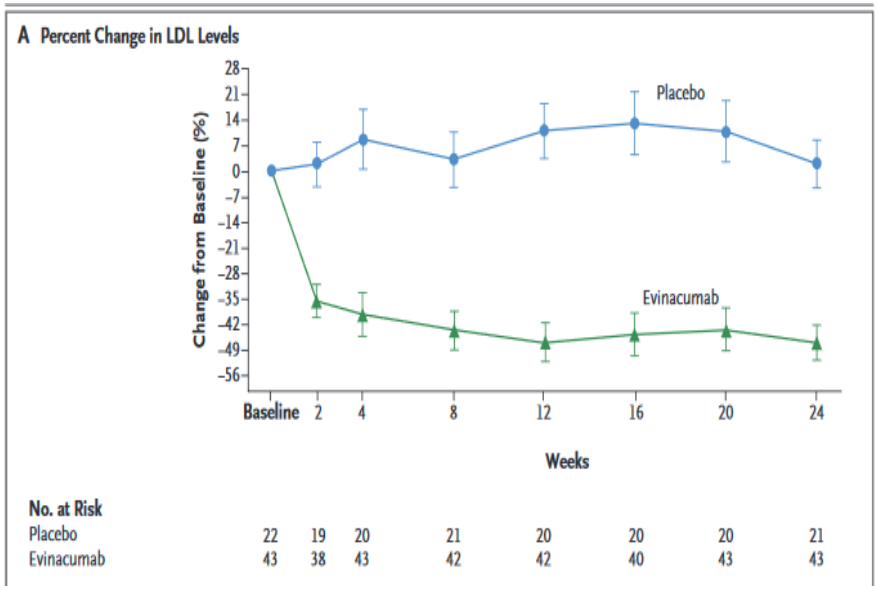
Inhibition of ANGPTL3 with a monoclonal antibody (or ASO) Lowers TG and LDL >50%

Triglyceride*



LDL** ~260mg/dL;~150mg/dL



* Graham NEJM 2017, 222-232; Dewey NEJM 2017 377:211 ** NEJM 2020; 383:711-720; **NEJM 2020, Nov 15.**

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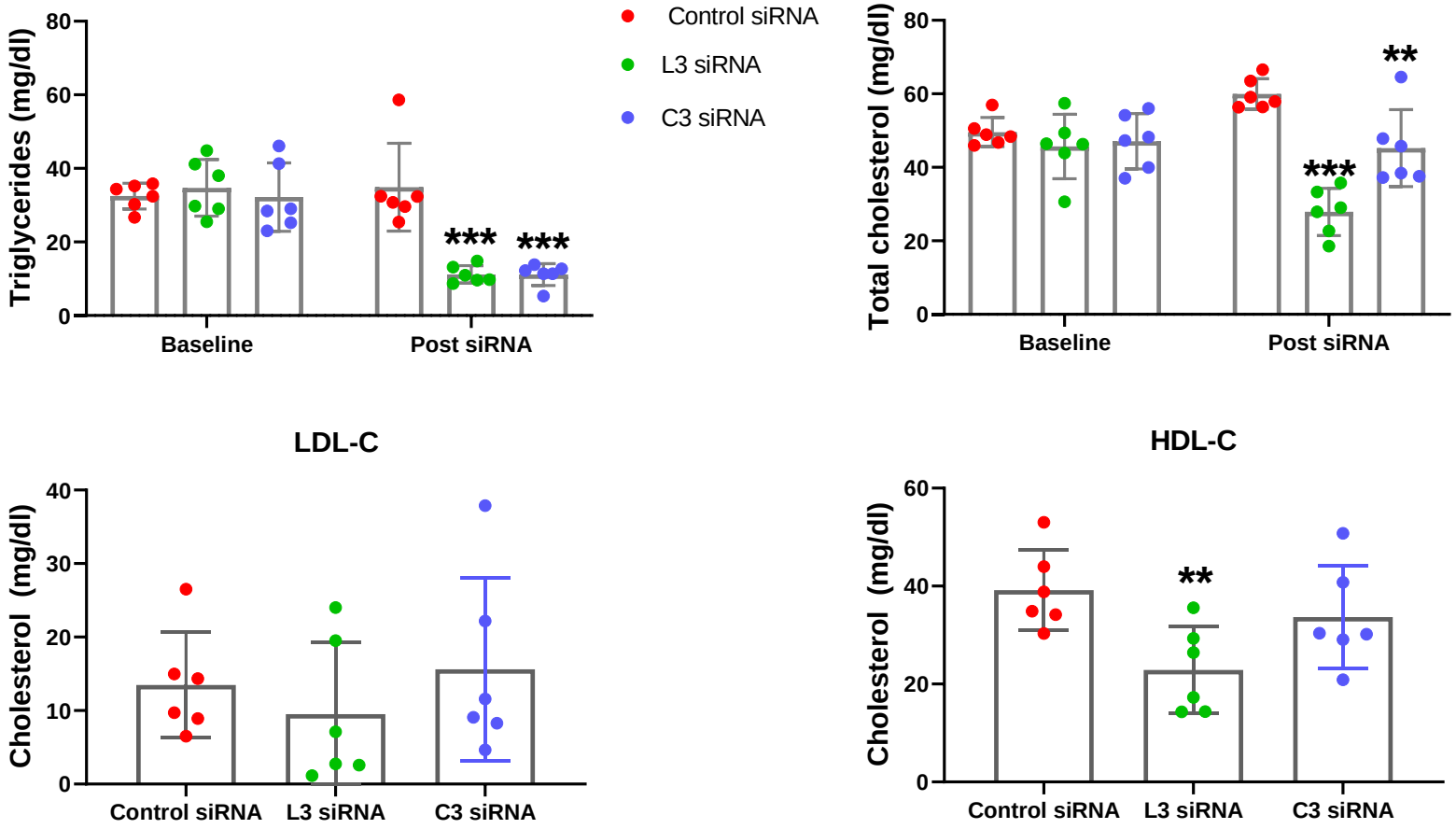
Mouse direct comparison between ANGPTL3 siRNA (green) and apoC3 siRNA (blue)- both reduced TG ~55% in chow-fed mice. Only ANGPLT3 siRNA reduced LDL (trend) and HDL.



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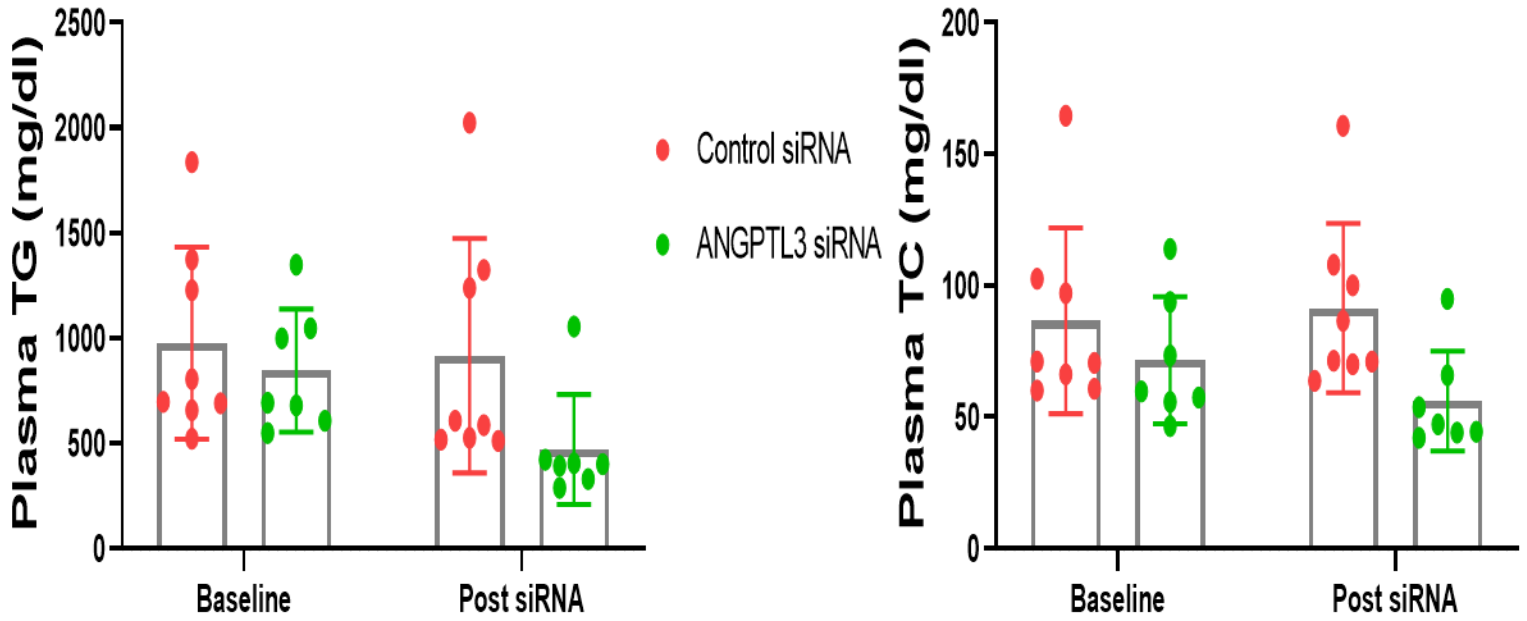
ANGPTL3 siRNA lowers plasma TG and TC in male *iLpl-/-* mice, similarly to published data using ApoC3 ASO.



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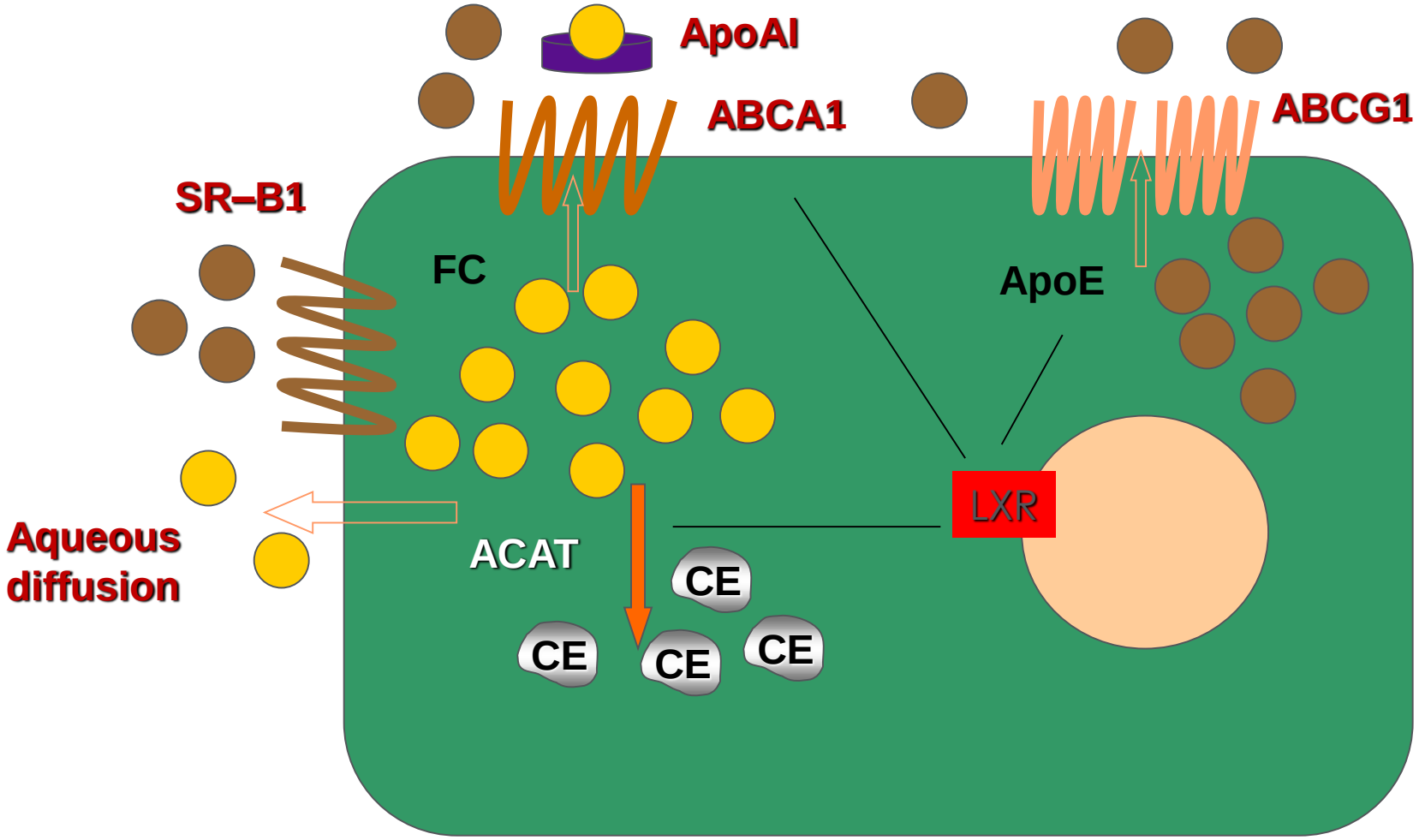
Macrophage cholesterol efflux pathways



Lessons from rare genetic HDL Deficiency States-1 (low in blue, high in red)

1. ApoA-I Deficiency - ++ premature CHD. ↓ RCT
2. ABCA1 Deficiency (Tangier Disease) - + premature CHD. ↓RCT
3. LCAT (alpha and beta) Deficiency – likely no CHD risk. ↓RCT
4. LPL Deficiency - No increased CHD risk. ↑RCT.
5. HL Deficiency - premature CHD increased remnants. ?RCT
6. CETP Deficiency - ?decreased RTC, little effect on CHD

In large GWAS, neither endothelial lipase nor CETP track with CVD risk.

Diabetes with moderate hypertriglyceridemia and CVD(??)

- 60 yr old man
- Post-MI x 3 yrs
- Hypertension- treated
- **BMI 33**
- HbA1c 7.5%
- **TC 270**
- **LDL 185**
- **TG 250**
- **HDL 35**
- Non HDL 225

What do you do after statin therapy? More LDL reduction? Ezetimibe TG reduction?

ANGPTL3 inhibition can lower both TG and LDL

- HbA1c 7.5%
- TC 270
- **LDL 185**
- **TG 250**
- HDL 35
- Non HDL 225

On 40 mg rosuvastatin

- HbA1c 7.5%
- TC 170
- **LDL 85**
- **TG 250**
- HDL 35
- Non HDL 125

Take Home Messages

- Hypertriglyceridemia occurs in >25% of the population, esp. with diabetes and obesity
- ANGPTL3 and ApoC3 inhibition leads to similar TG reduction
- Angptl3 also reduces LDL (and HDL)
- Human genetics suggest that loss of ANGPTL3 leads to a non-atherogenic profile without liver steatosis
- HDL changes are not likely to be clinical important

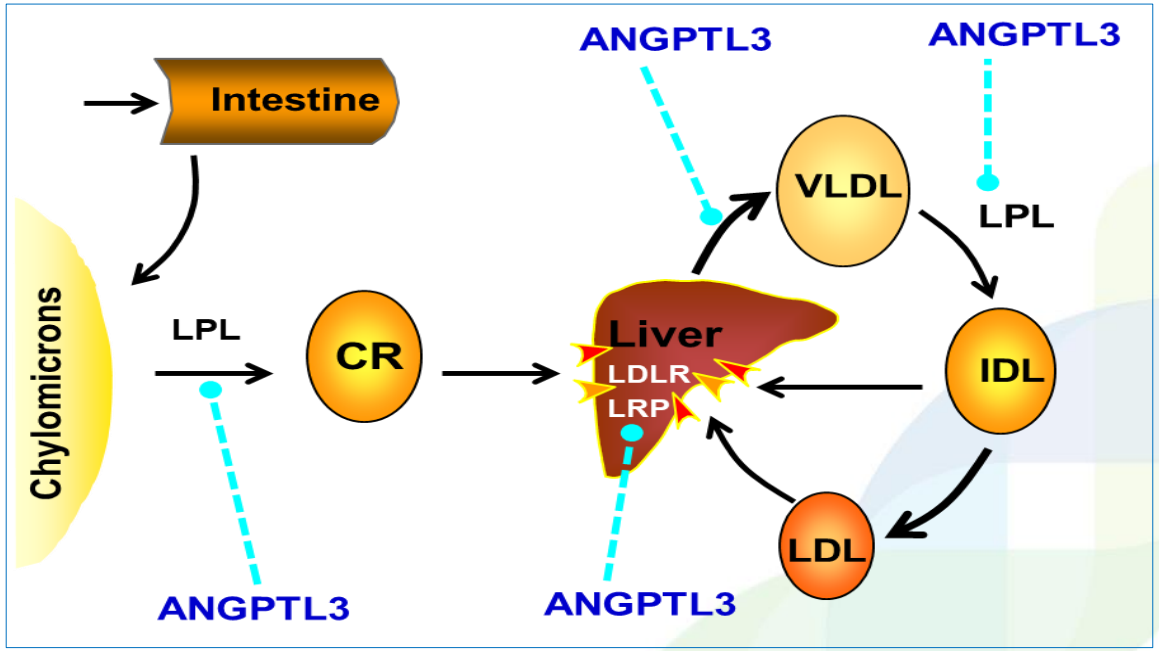
ARO-ANG3 Clinical Development

Javier San Martin, M.D.

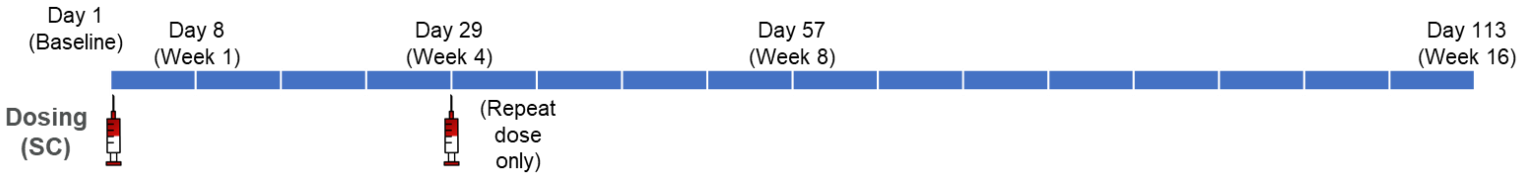
ANGPTL3 as a Target to Treat Dyslipidemia

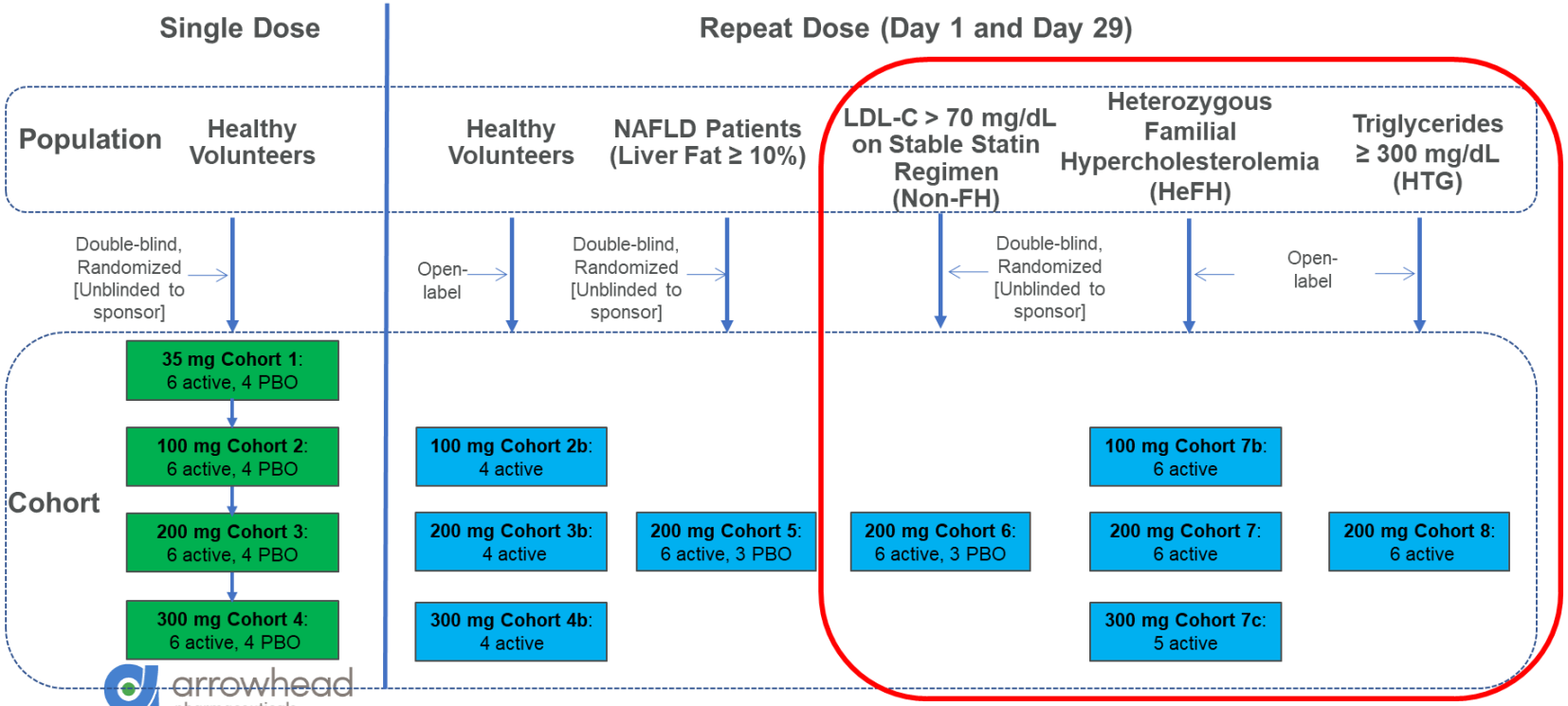
- **Dyslipidemia** is a major risk factor for cardiovascular disease (CVD), and **residual risk of CVD persists** even with current standard of care (including PCSK9 inhibitors)
- **ANGPTL3** is a **key regulator of lipid and lipoprotein metabolism** with multiple potential nodes of action, including inhibition of Lipoprotein Lipase (LPL) and Endothelial Lipase (EL)
- Loss-of-function mutations in *ANGPTL3* lead to enhanced LPL and EL activity, resulting in:
  - Low TG, LDL-C, VLDL-C, and HDL-C
  - Reduced risk of CVD, and
  - No known adverse phenotype associated with genetic deficiency in *ANGPTL3*
- **ARO-ANG3** is an investigational synthetic, double-stranded, hepatocyte-targeted RNA interference (RNAi) trigger designed to specifically silence *ANGPTL3* mRNA expression in the liver

Potential Regulatory Nodes of Action of ANGPTL3



Phase 1 Study to evaluate the effect of ARO-ANG3 in dyslipidemic patients





Study Endpoints

Safety (Primary):

- Incidence and frequency of adverse events

Key Pharmacodynamic and Lipid Parameters:

- Change from baseline over time in ANGPTL3
- Change from baseline over time in the following parameters: fasting Triglycerides, LDL-C, non-HDL-C, and HDL-C

Patient Populations

- **HeFH** - Heterozygous Familial Hypercholesterolemia (HeFH) patients – genetically confirmed or Dutch lipid clinic network score ≥ 6
- **Non-FH** – Patients on stable statin regimen that are not at LDL-C goal (LDL-C > 70 mg/dL)
- **HTG** - Hypertriglyceridemia patients with TG >300 mg/dL at screening

Data cutoff: 30 Apr 2020

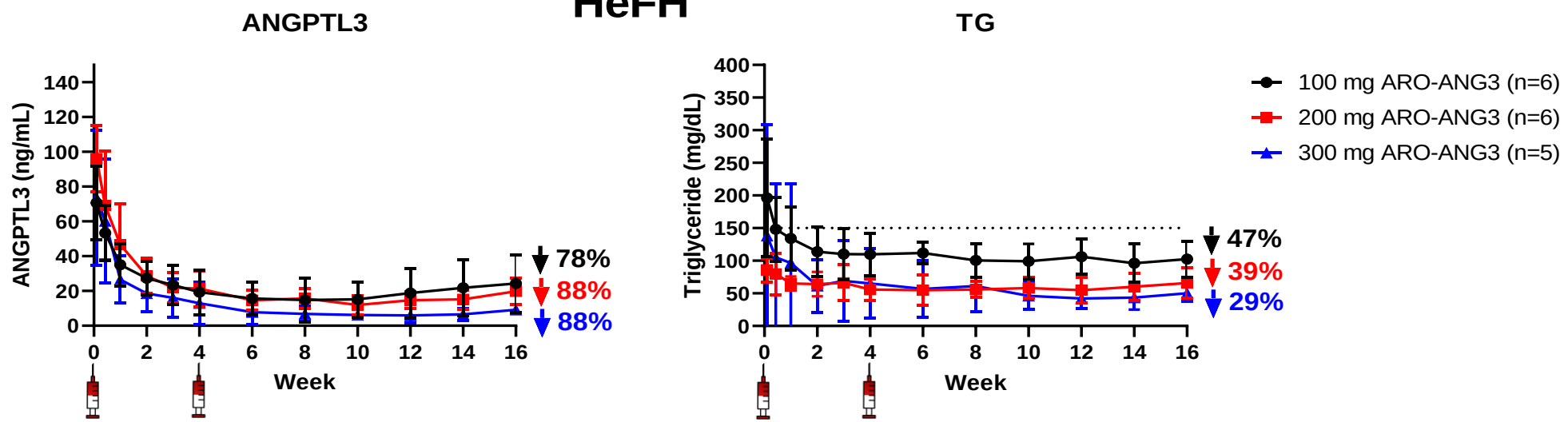
Baseline characteristics of HeFH, Non-FH and HTG patient cohorts

	HeFH Patients			Non-FH Patients		HTG Patients
Mean (range) Fasting values	100 mg ARO-ANG3 (n=6)	200 mg ARO-ANG3 (n=6)	300 mg ARO-ANG3 (n = 5)	Placebo (n=3)	200 mg ARO-ANG3 (n=6)	200 mg ARO-ANG3 (n=6)
Age (years)	43.5 (19-61)	49.3 (25-65)	45.2 (20-70)	58.7 (51-63)	51.7 (31-62)	62.8 (51-69)
Male (%)	50	50	60	67	83	67
BMI (kg/m^2)	29.9 (25.1-35.0)	28.0 (21.0-36.9)	25.6 (19.4-29.8)	28.8 (28.0-29.5)	26.8 (21.5-36.4)	31.2 (27.8-36.9)
ANGPTL3 (ng/mL)	71 (45-91)	96 (76-127)	74 (36-134)	91 (69-131)	87 (59-112)	107 (68-161)
Triglycerides (mg/dL)	196 (94-360)	86 (66-118)	138 (38-441)	198 (121-271)	87 (68-130)	973 (189-2743)
LDL-C (mg/dL) (direct assay)	129 (95-191)	146 (91-171)	126 (96-174)	98 (56-132)	96 (68-198)	79 (13-179)
Non-HDL-C (mg/dL)	171 (121-229)	168 (109-207)	163 (105-230)	131 (83-180)	112 (84-217)	236 (141-385)
HDL-C (mg/dL)	45 (32-59)	60 (46-86)	44 (30-57)	57 (54-61)	43 (34-53)	37 (10-75)
ApoB (mg/dL)	132 (88-202)	106 (73-138)	100 (75-135)	87 (60-124)	78 (64-133)	106 (71-149)

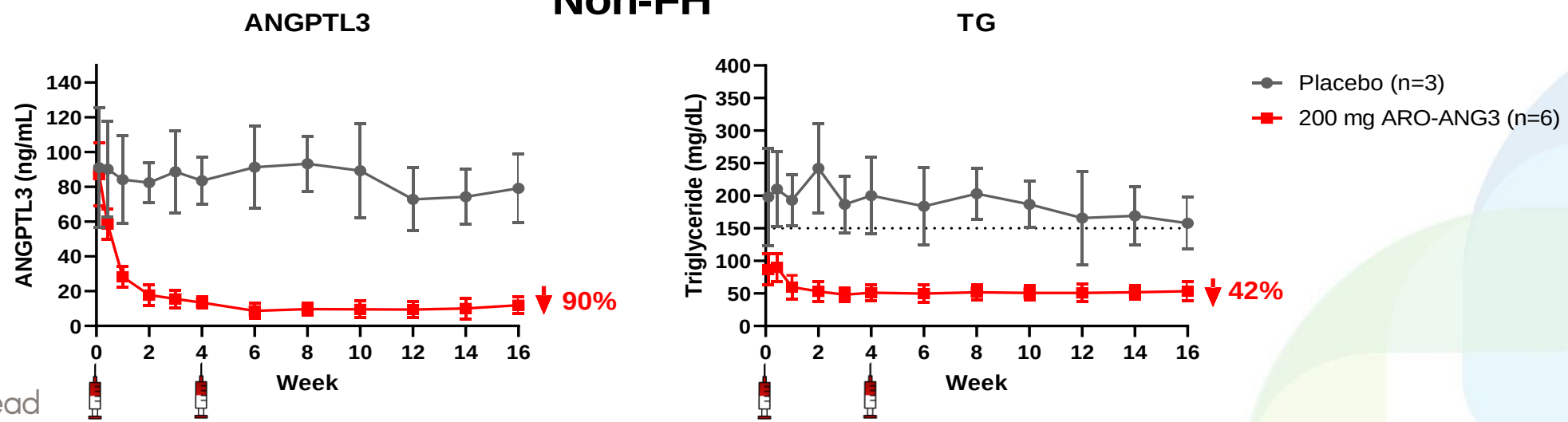
Data cutoff: 30 Apr 2020

ARO-ANG3 substantially reduces ANGPTL3 and TG in HeFH and non-FH patients

HeFH



Non-FH



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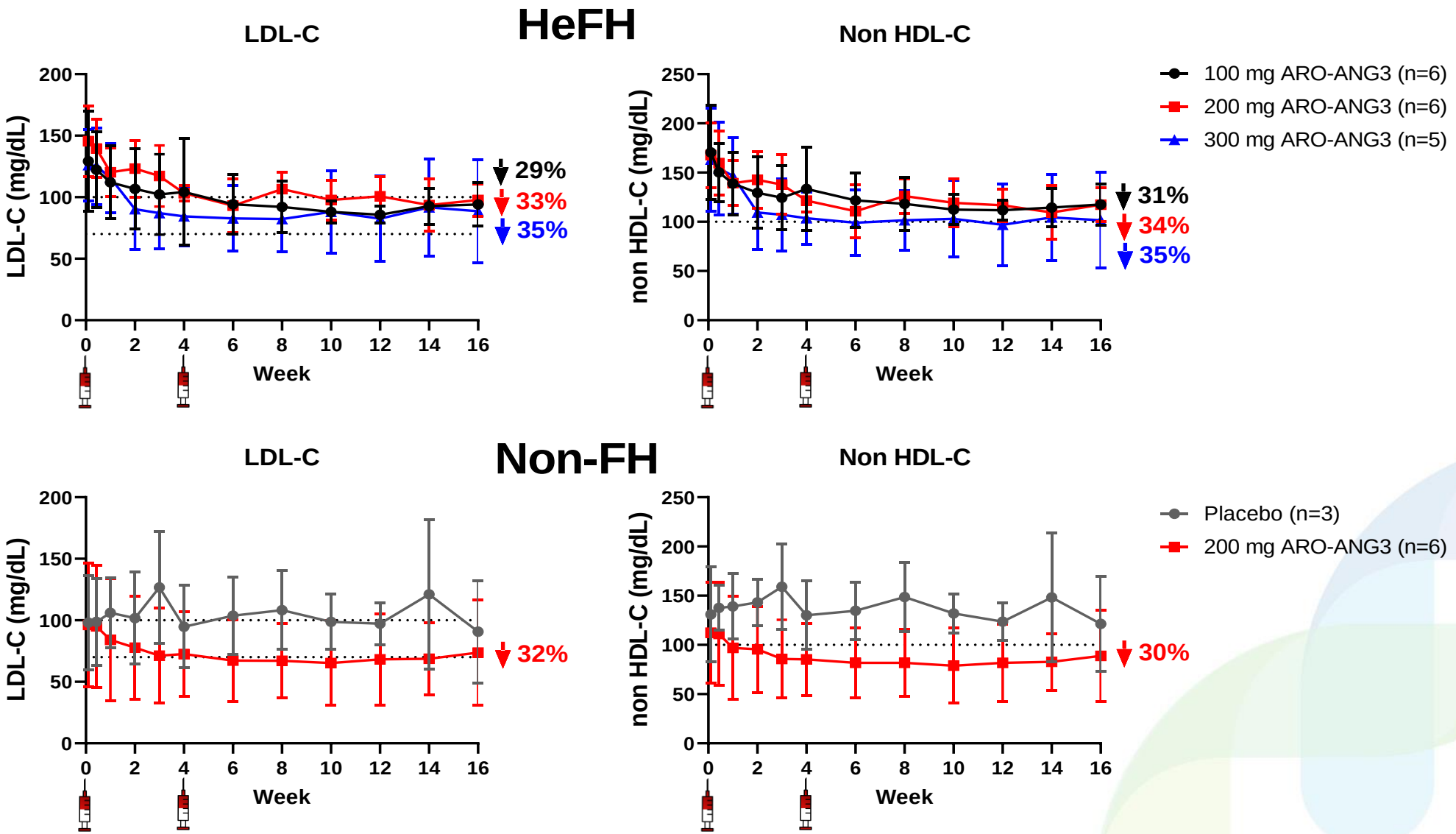
Mean values +/- SD are plotted for each cohort ;% values are maximum mean reductions for each cohort (n>1 subject at a visit date)

Data cutoff: 30 Apr 2020

ARO-ANG3 substantially reduces LDL-C and non-HDL-C in HeFH and non-FH patients



Mean values +/- SD are plotted for each cohort ;% values are maximum mean reductions for each cohort (n>1 subject at a visit date)

Data cutoff: 30 Apr 2020

Summary of interim safety data

	HeFH	HTG	Non-FH		
TEAEs Reported in > 2 subjects, AE Term (MedDRA Preferred Term)	**HeFH All Doses n = 17**	**200 mg n=6**	**200 mg Active n=6**	**Placebo n=3**	**Total Active n = 29**
Headache	4 (23.5%)	1 (17%)	0	1 (33%)	5 (17%)
Contusion	4 (23.5%)	0	0	0	4 (14%)
Oropharyngeal pain	3 (18%)	1 (17%)	0	0	4 (14%)
Vascular access site bruising/hematoma	2 (12%)	1 (17%)	1 (17%)	0	4 (14%)
Injection site erythema, bruising, pain, swelling	3 (18%)	0	0	1 (33%)	3 (10%)
Dizziness	2 (12%)	0	1 (17%)	1 (33%)	3 (10%)
Muscle spasm	1 (6%)	2 (33%)	0	0	3 (10%)
Presyncope, Syncope	3 (18%)	0	0	0	3 (10%)
Upper respiratory tract infection, Respiratory tract infection	1 (6%)	0	2 (33%)	1 (33%)	3 (10%)

- Two subjects reported SAEs (1 case of ketosis related to dapaglifozin and dehydration, 1 case of syncope with fibula fracture), both cases not related to ARO-ANG3.
- Two AEs of ALT elevation were reported. One case was asymptomatic (baseline 34 U/L, peak 91 U/L). The other (baseline 30 U/L, peak 238 U/L Day 29, 68 U/L Day 43 and 34 U/L at Day 113/EOS) was transient and associated with gastroenteritis. Neither associated with clinically significant elevations in total bilirubin.
- No clinically significant adverse changes in platelets
- No drug discontinuations
- Contusion AEs (n=4)
  - 2 events related to mechanical fall
  - 1 event related to NSAID treatment

Safety Data cut-off 11Sept 2020

ARO-ANG3, an investigational RNAi therapeutic targeting *ANGPTL3* mRNA transcripts results in sustained favorable lipid changes

- In **HeFH and Non-FH patients**,100 mg, 200 mg or 300 mg ARO-ANG3 SC resulted in mean reductions of:
  - -78% to -90% for ANGPTL3
  - -29% to -47% for TG
  - -29% to -35% for LDL-C
  - -31% to -35% for non-HDL-C
- In **HTG patients**, 200 mg of ARO-ANG3 SC resulted in mean reductions of:
  - -83% for ANGPTL3
  - -75% for TG
  - +5% for LDL-C
  - -56% for non-HDL-C
- ARO-ANG3 maintained reductions in these lipid parameters for **>12 weeks post second dose**, regardless of patient population
- ARO-ANG3 had a **favorable safety and tolerability** profile

ARO-ANG3 produces a substantial and prolonged reduction of LDL-C, non-HDL-C and TGs, and may prove useful as a therapeutic option in patients with dyslipidemia

Proposed Developmental Plan for ARO-ANG3

Est. Initiation Date
1H 2021

Phase 2 Dose Finding (TG>150mg/dl)

- N=180
- Prim EP: TG/dose
- Second EP: HDL-C, non-HDL-C, ANGPTL3, LDL-C, ApoB, Safety

Est. Initiation Date
2H 2023

Phase 3 Mixed Dyslipidemia

- N=1500
- Prim EP: LDL, TG, Non-HDL-C
- Second EP: HDL-C, ANGPTL3, ApoB, Safety

Phase 3 CV Outcomes

- N=15,000
- Prim EP: 3 point MACE clinical events
- Second EP: HDL-C, non-HDL-C, ANGPTL3, LDL-C, ApoB, Safety

Wrap Up

Chris Anzalone, Ph.D

ARO-ANG3: A Compelling Market Opportunity

- **Dyslipidemia is a major CVD risk factor**
  - Residual risk persists even with standard of care (including PCSK9 inhibitors)
- **ANGPTL3 is a validated target for mixed dyslipidemia**
- **Competitive landscape is attractive**
  - ARO-ANG3 is the *only* RNAi candidate currently in clinical development against ANGPTL3
  - ASOs and mAbs are the primary competition at this point
    - ARO-ANG3 is expected to have more favorable dosing schedule: sc injection every 3-6 months
      - ASOs expected to be monthly sc dosing
      - mAbs expected to be monthly iv dosing; weekly sc dosing being studied
    - We don't expect to see the ASO-related safety issues, such as thrombocytopenia

Clinical and Commercial Plans

- **Begin next clinical steps in 1h 2021**
  - Plan on P2b in triglyceridemic patients not meeting LDL-c goal
  - Enable a CVOT P3
- **Large commercial opportunity in mixed dyslipidemic patients**
  - Where ARO-ANG3 is positioned in treatment options is yet to be determined
    - Secondary prevention, downstream of PCSK9: large opportunity
    - Primary prevention, upstream of PCSK9: very large opportunity

Wherever ARO-ANG3 gets positioned, many patients could have powerful new options to decrease cardiovascular risk

Q&A Session
Panel