Nuffield Department of
POPULATION HEALTH

UNIVERSITY OF OXFORD

Lower lipids, higher glucose?

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Disclosures

- None
- CTSU has a guideline to not accept any personal honoraria

Content

- Old data:
  - Niacin
  - Statins (trials + genes)
- Newer data:
  - Ezetimibe (trials + genes)
  - PCSK9i (trials + genes)
  - CETPi (trials + genes)
- Questions:
  - Is it only *LDL-c* or is *HDL-c* involved?
  - Are effects related to *specific drugs* or, rather, to effects of *any drug*?

Niacin

LDL-c	HDL-c	Total-c
↓	↑	↓

Trials / Meta-analyses	Number without DM	Effect on new-onset DM
HPS2-THRIVE	17,374	1.31 (95% CI 1.15-1.49)
10 trials	8,966	1.38 (95% CI 1.16-1.65)
10 trials + HPS2-THRIVE	26,340	1.34 (95% CI 1.21-1.49) NNH: treat 43 for 5yr

A strong effect on new-onset DM given the small change in lipids

HPS2-THRIVE Collaborative Group; NEJM 2014; 371: 203-12
Goldie et al; Heart 2016; 102: 198-203

JUPITER and the statin story

- Mixed data in older trials, most not analysed new-onset DM
- n=17,802, 1.9 years
- Rosuvastatin vs. placebo
- Pre-specified endpoint: new-onset DM

- Surprising result for new-onset DM: 25% increase
  - Rosuvastatin: 270/8901
  - Placebo: 216/8901

Ridker P et al, NEJM 2008; 359: 2195-2207

Statins and new-onset DM

LDL-c	HDL-c	Total-c
↓↓	↔	↓↓

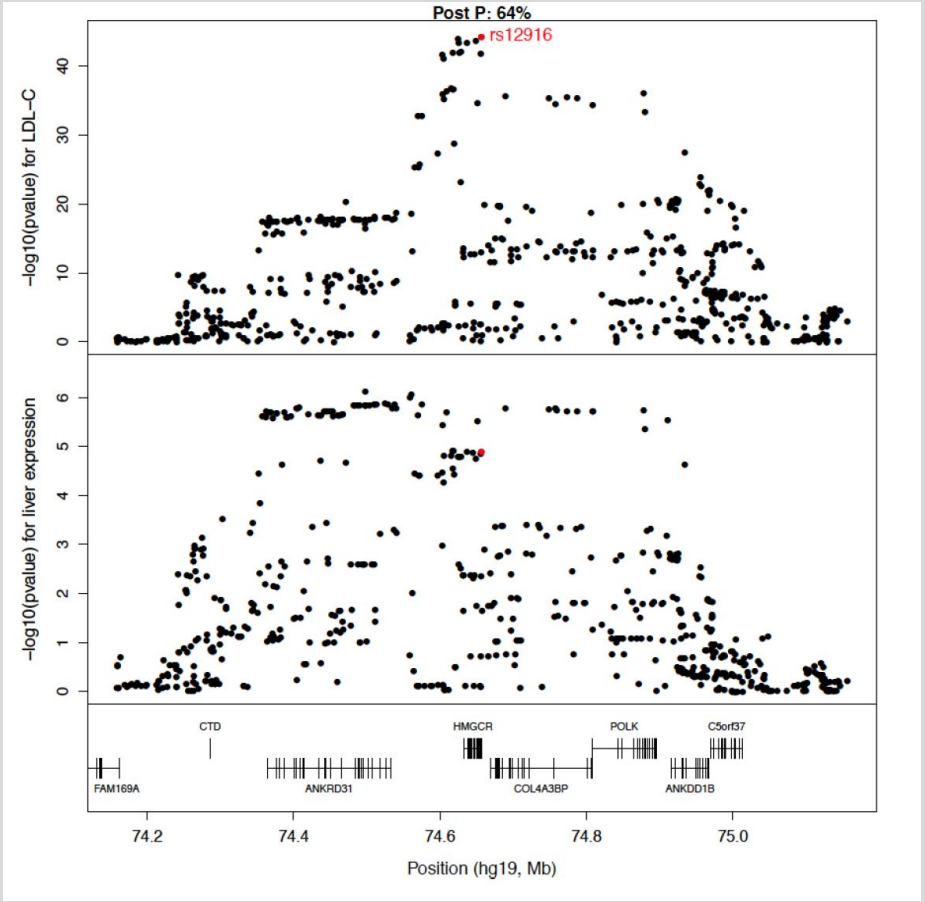
	Number of patients	LDL-c difference	Risk ratio
Statin vs. placebo or standard care (15 trials)	96,418	1.0 mmol/L	1.11
High dose vs. moderate dose statins (5 trials)	32,752	0.5 mmol/L	1.12
Combined (20 trials)	129,170		1.12

Sattar et al, Lancet 2010;375:735-42
Swerdlow et al, Lancet 2015;385:351-61
Preiss et al. JAMA 2011;305:2556-64

Study of *HMGCR* variants

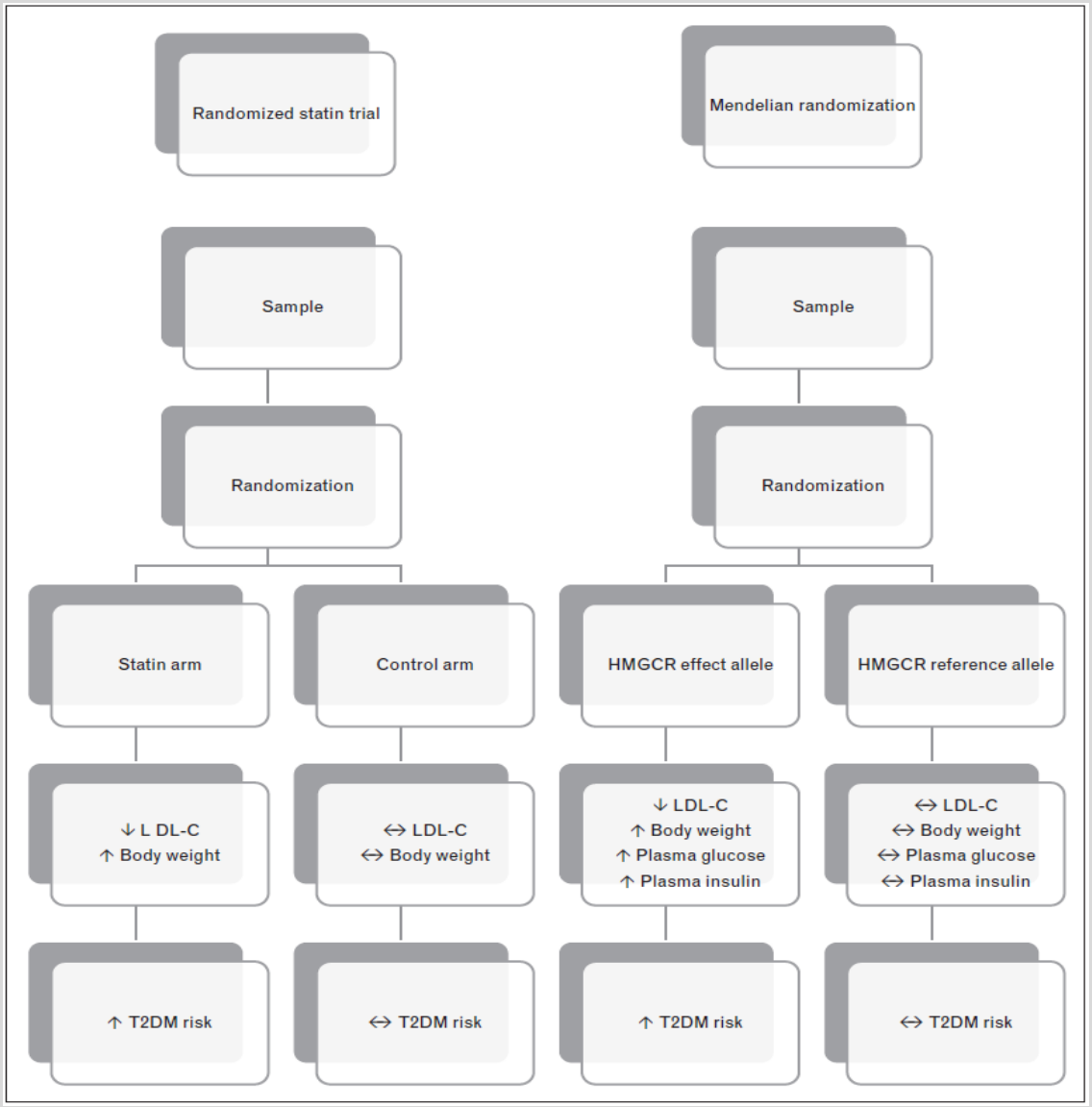
HMGCR SNPs rs17238484 and rs12916, chr5:

- Up to 220,000 individuals
- Incident + prevalent DM
- Glucose
- Insulin
- Weight
- Waist circumference



Swerdlow et al, Lancet 2015;385:351-61

Randomized Trials vs. Polymorphisms



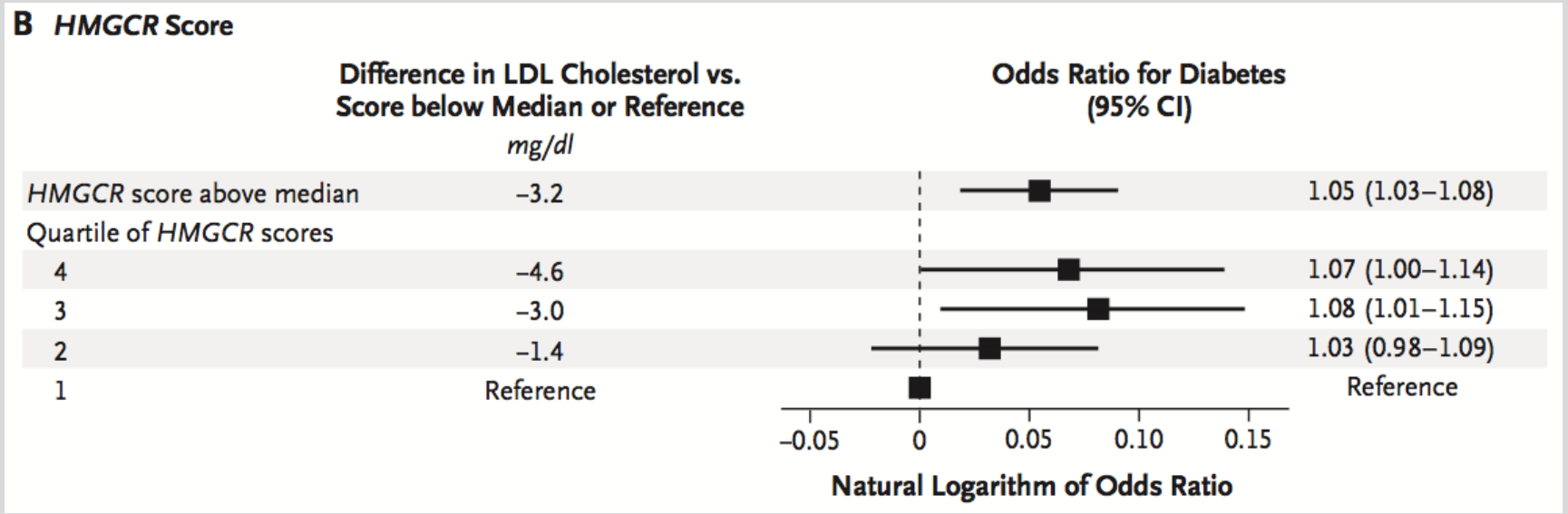
Statin vs. *HMGCR* genetic variants

	Per additional rs17238484 allele	Per additional rs12916 allele	Statin trial
LDL-c	↓ 0.06 mmol/L	↓ 0.08mmol/L	↓↓
CVD	↓	↓	↓↓
Weight	↑ 0.30 kg	↑ 0.20kg	↑0.25kg
Waist circ.	↑ 0.32 cm	↑ 0.30cm	-
Glucose / HbA1c	↑ 0.23%	0.13	↑
Insulin	↑ 1.62%	0.66%	-
T2DM	~ 1.02	↑ 1.06	↑1.1

- Effect likely to be true
- Effect likely to be on-target (at least in part)

Swerdlow et al, Lancet 2015;385:351-61

Further data for *HMGCR* genetic variants



Ference et al, NEJM 2016;375:2144-53

Summary

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		HDL-c	LDL-c	New-onset DM	Related traits
Niacin	Drug	↑	↓	↑	↑
	Related gene	-	-	-	-
Statin	Drug	↔	↓↓	↑	↑
	Related gene	↔	↓	↑	↑

✓

Questions

1. Is this modest ‘diabetogenic’ effect observed with other LDL-c lowering drugs?
2. Is LDL itself implicated in developing diabetes?
3. Are other lipids (e.g. HDL) involved?
4. Should we care?

Other targets? Ezetimibe and NPC1L1

LDL-c	HDL-c	Total-c
↓	↔	↓

- 50 775 individuals with type 2 diabetes and 270 269 controls
- NPC1L1, HMGCR, PCSK9, ABCG5/G8, LDLR

- NPC1L1 genotype data
  - DM: OR 2.4 for genetically predicted 1mmol/L lower LDL-c
- 'associations with type 2 diabetes were heterogeneous, indicating gene-specific associations with metabolic risk of LDL-C-lowering alleles…'

Lotta et al, JAMA 2016; 316:1383-91

Ezetimibe

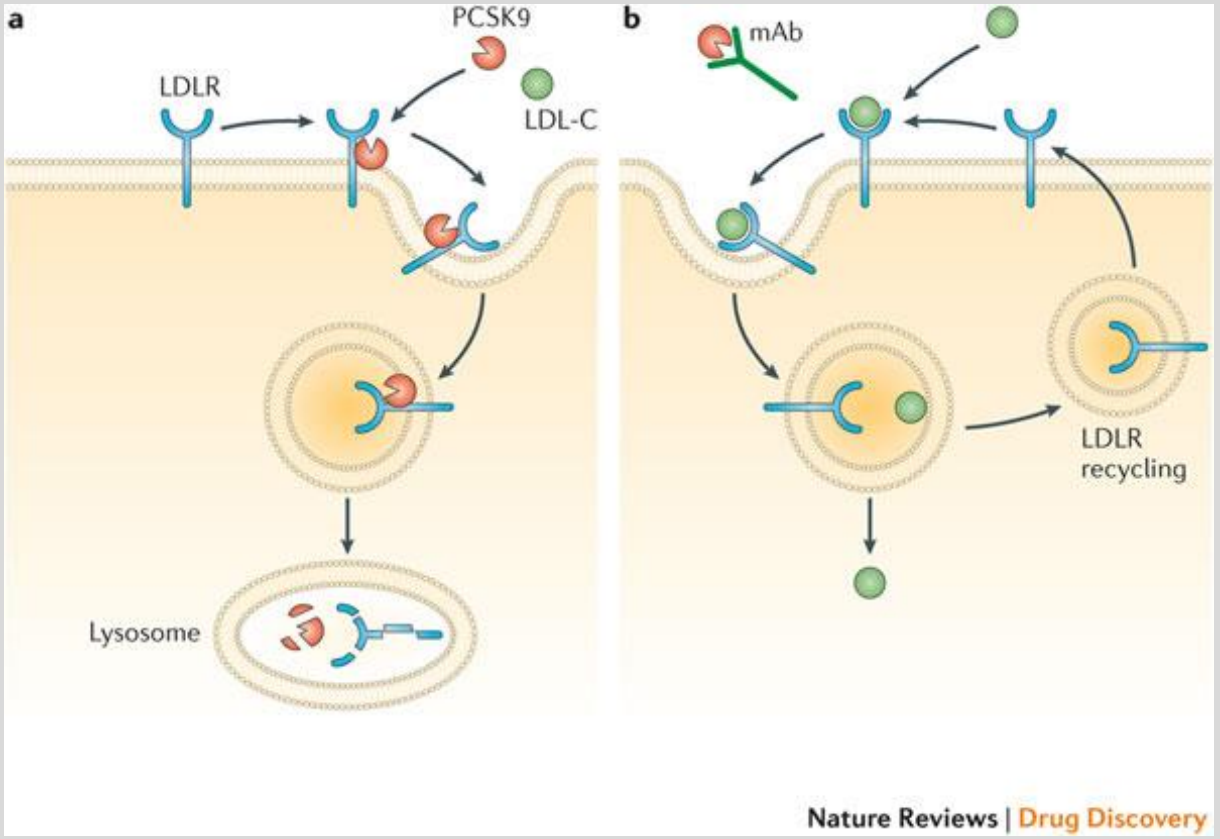
- IMPROVE-IT data
  - Ezetimibe or placebo added to simvastatin 40mg
  - N=18,144 (27% with DM), 7 years
  - LDL-C difference 0.4mmol/L
  - Cases of new-onset DM:
    - Ezetimibe = 720
    - Placebo = 694
  - HR 1.04 (0.94-1.15)

Cannon et al; NEJM 2015; 372:2387-2397
DM data presented

PCSK9 monoclonal antibodies

LDL-c	HDL-c	Total-c
↓↓	↔	↓↓

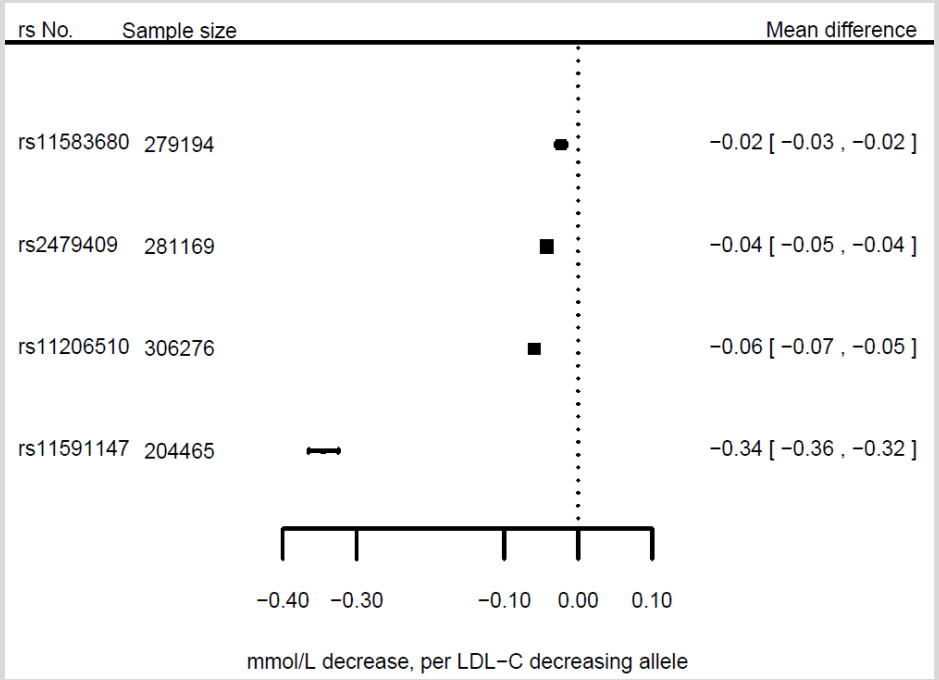
- Evolocumab
- Alirocumab
- Bococizumab



- Genetics
  - CHD: many analyses confirming low CHD
  - DM: recent data

PCSK9 polymorphisms

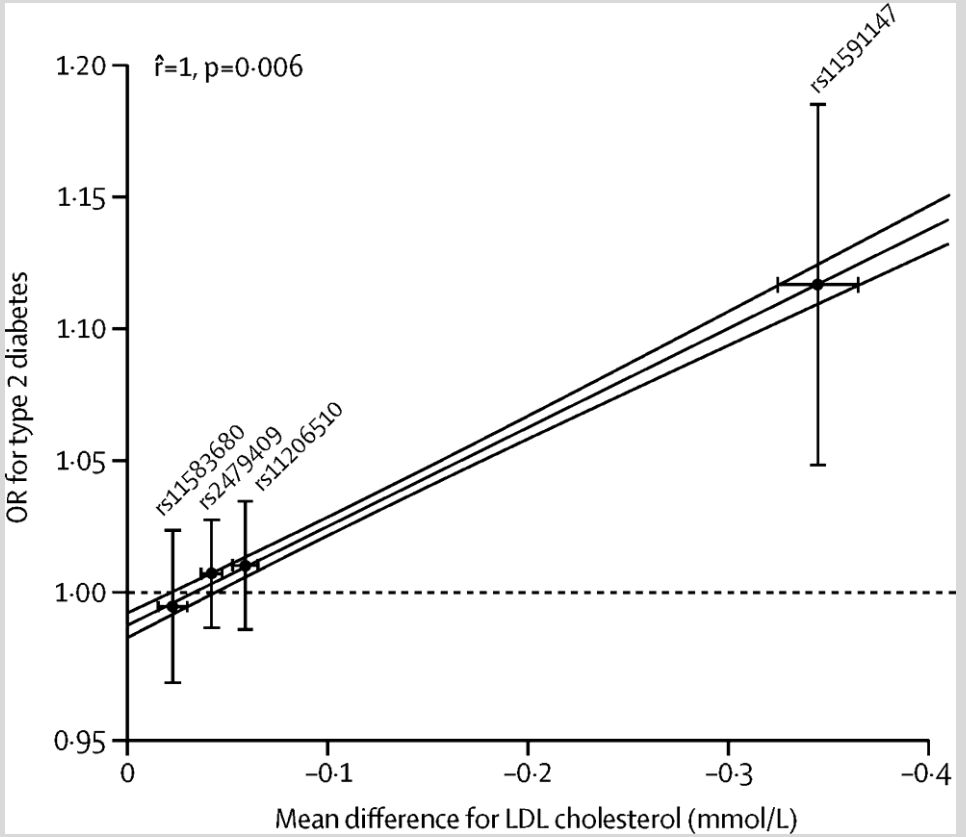
- Up to 50,000 cases and 500,000 controls
- SNPs:
  - rs11583680 and rs11591147 (in PCSK9 gene)
  - rs2479409 and rs11206510 (adjacent to gene)



Schmidt AF et al, Lancet DE, 2017; 5:97-105

PCSK9 polymorphisms: gene score

Trait	Mean difference (Fixed effect) Scaled to 1mmol/L lower LDL-c
Weight	↑ 1kg
Waist/hip ratio	↑
HbA1c	↔
Fasting glucose	↑ 0.1mmol/L
Fasting insulin	↔
New-onset DM	↑ 29%



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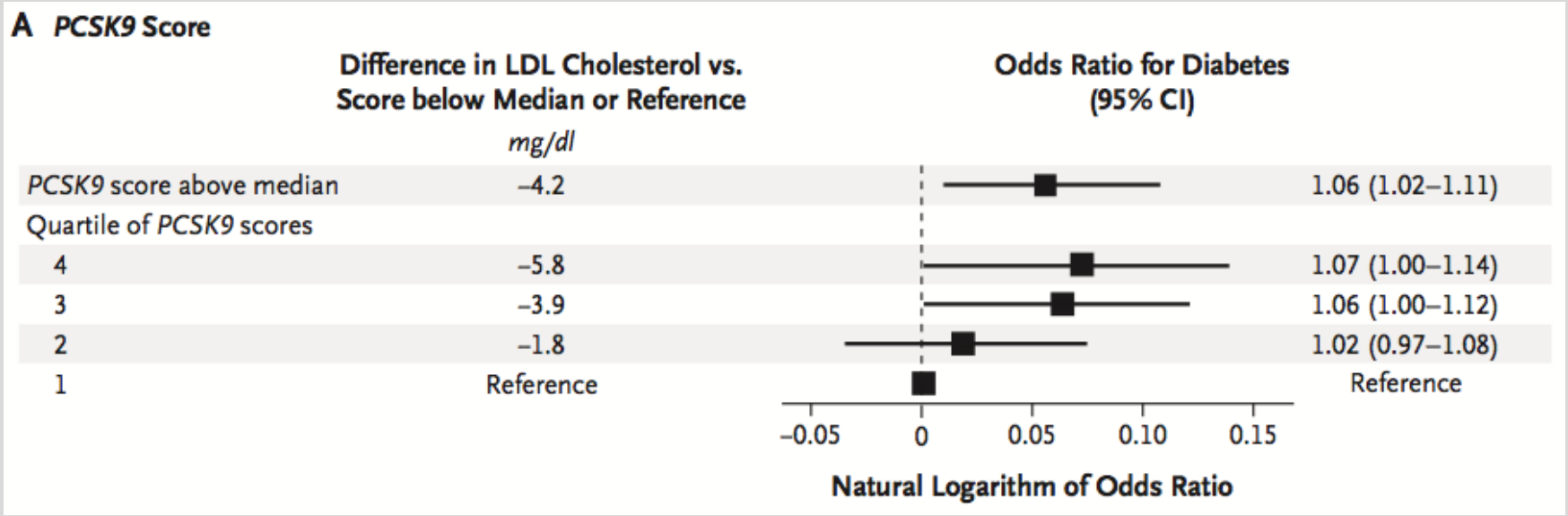
PCSK9 polymorphisms



Ference et al, NEJM 2016;375:2144-53

Evolocumab data

(IMAGE REMOVED)

FOURIER trial:

- non-significant 5% (677/8337 vs. 644/8339) increase[1]

OSLER trials

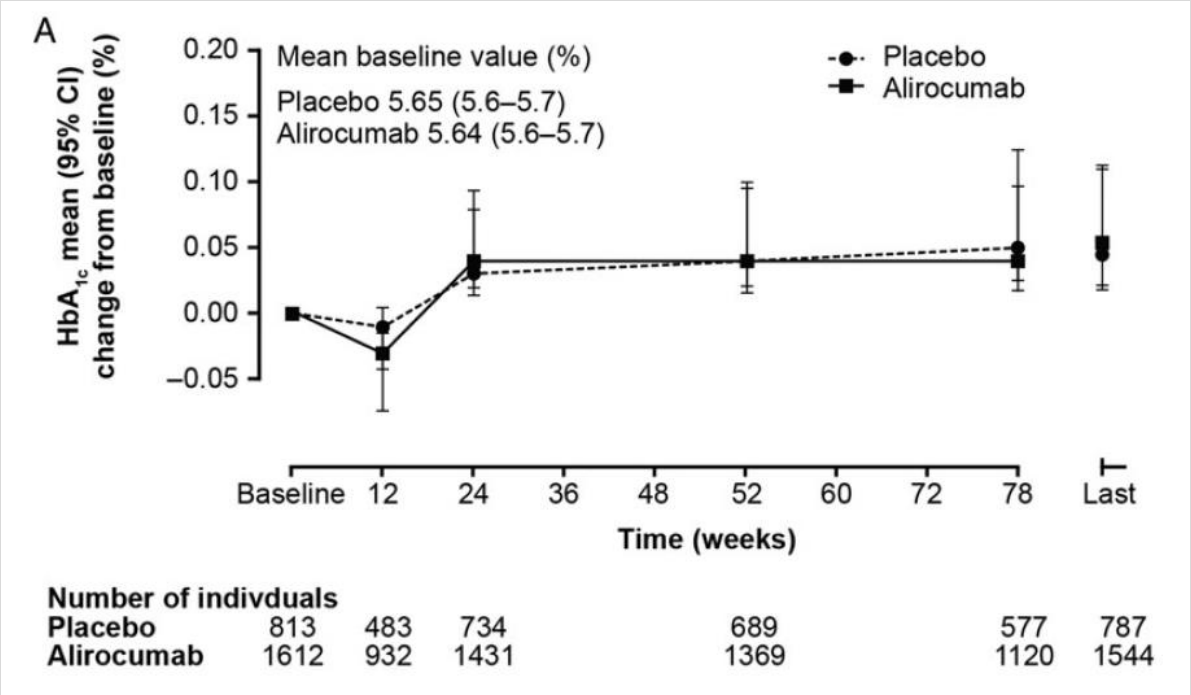
Sattar N et al, AJC (in press)
Sabatine et al, NEJM 2017; 376: 1713-22

Evolocumab: new-onset DM

- FOURIER trial: non-significant 5% (677/8337 vs. 644/8339) increase[1]

1. Sabatine et al, NEJM 2017; 376: 1713-22
2. Unpublished, in press AJC

Alirocumab: effects in non-DM



New-onset DM	Alirocumab	Placebo / Ezetimibe
Ten trials (24-104 weeks)	112 / 2202 (5.1%)	62 / 1246 (5.0%)

Colhoun et al; EHJ 2016; 37(39):2981-2989

Summary

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		HDL-c	LDL-c	New-onset DM	Related traits
Niacin	Drug	↑	↓	↑	↑
	Related gene	-	-	-	-
Statin	Drug	↔	↓↓	↑	↑
	Related gene	↔	↓	↑	↑
Ezetimibe	Drug	↔	↓	↔ (?)	-
	Related gene	-	↓	↑ (?)	-
PCSK9i	Drug	↔	↓↓↓	↔	↔
	Related gene	↔	↓	↑	↑↔

Questions

1. Is this modest ‘diabetogenic’ effect observed with other LDL-c lowering drugs?
2. Is LDL itself implicated in developing diabetes?
3. Are other lipids (e.g. HDL) involved?

The LDL-c argument: FH

LDL-c	HDL-c	Total-c
↑↑↑	↔	↑↑↑

Table 1. Demographic and Clinical Characteristics of All Participants

	Patients With Familial Hypercholesterolemia (n = 25 137)	Unaffected Relatives (n = 38 183)
Male sex, No. (%)	11 920 (47.4)	18 340 (48.0)
Age, mean (SD), y	38 (20.6)	43 (20.0)
Body mass index, mean (SD)[a]	23.5 (5.4)	24.4 (5.3)
Current smoker, No. (%)	4917 (19.8)	11 222 (29.4)
Statin use, No. (%)	7271 (28.9)	3431 (9.0)
Statin intensity categories, No. (%)[b]		
Low[b]	513 (2.0)	440 (1.2)
Moderate	4754 (18.9)	2657 (7.0)
High	2006 (8)	336 (0.9)
History of cardiovascular disease, No. (%)[d]	1864 (7.4)	1916 (5.0)
Cholesterol, mean (SD), mg/dL		
Low-density lipoprotein[d,e]	204 (76)	121 (43)

Besseling et al, JAMA 2015;313:1029-36

Self-reported T2DM at FH screening

	Unadjusted OR	Adjusted OR
FH	0.62	0.49
APO B (i.e. less severe)	-	0.65
LDLR (i.e. more severe)	-	0.45
Receptor defective	-	0.49
Receptor negative	-	0.38

Hypothesis: "…pancreatic beta cells and cellular cholesterol uptake…"

Or simply bias?

Besseling et al, JAMA 2015;313:1029-36

LDL gene score and DM risk (1)

- Malmo Diet and Cancer study
- 27,254 non-DM participants
- 15 years of follow-up
- 3,248 diagnosed with DM

- LDL gene score:
  - 1SD ↓ *genetically determined* LDL-c = 2X ↑ T2DM

ESC annual meeting 2014, poster 143

LDL gene score and DM risk (2)

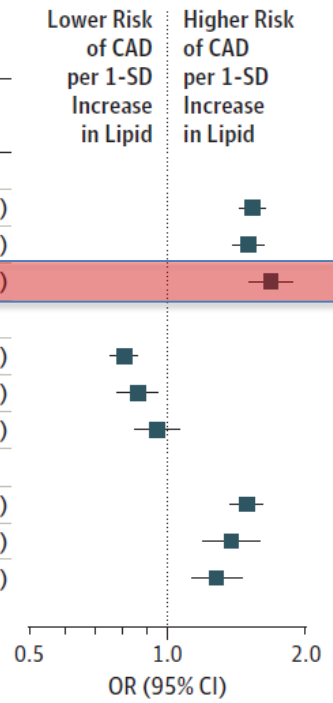
- 34,840 T2DM cases and 114,981 controls
  - 1SD ↑ *genetically determined* LDL-c:
    19% ↓ DM risk ($p = 5X10^{-6}$)
  - Mixed bag of results in sensitivity analyses
  - No strong evidence for HDL-c or triglycerides

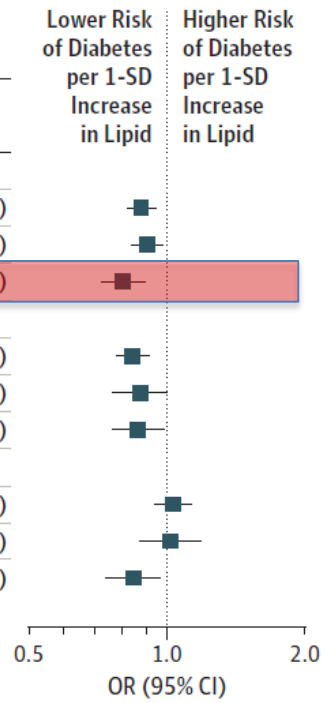
- Authors urged <u>cautious interpretation</u>

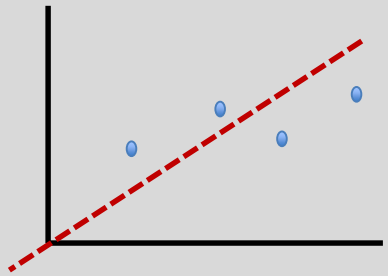
Fall et al, Diabetes 2015;64:2676-84

LDL gene score and DM risk (3)

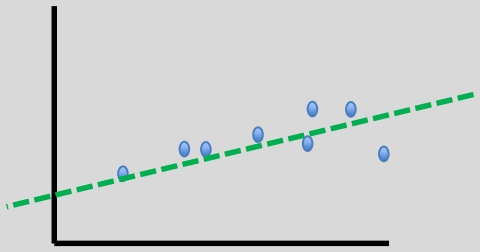
Lipid, MR Model	No. of SNPs	R^2	Coronary Artery Disease: Unbalanced Pleiotropy	Coronary Artery Disease: OR (95% CI)	Diabetes: Unbalanced Pleiotropy	Diabetes: OR (95% CI)
LDL-C (per 1-SD [38-mg/dL] increase)			Present		Present	
Conventional	130	0.08		1.53 (1.44-1.64)		0.86 (0.80-0.93)
MVMR	130	0.08		1.50 (1.39-1.63)		0.89 (0.82-0.96)
MR-Egger	130	0.08		1.68 (1.51-1.87)		0.79 (0.71-0.88)
HDL-C (per 1-SD [16-mg/dL] increase)			Present		Absent	
Conventional	140	0.07		0.80 (0.75-0.86)		0.83 (0.76-0.90)
MVMR	140	0.07		0.86 (0.78-0.96)		0.86 (0.74-0.98)
MR-Egger	140	0.07		0.95 (0.85-1.06)		0.85 (0.74-0.97)
TG (per 1-SD [89-mg/dL] increase)			Present		Present	
Conventional	140	0.06		1.49 (1.37-1.62)		1.01 (0.92-1.11)
MVMR	140	0.06		1.38 (1.19-1.59)		1.00 (0.86-1.16)
MR-Egger	140	0.06		1.28 (1.13-1.45)		0.83 (0.72-0.95)







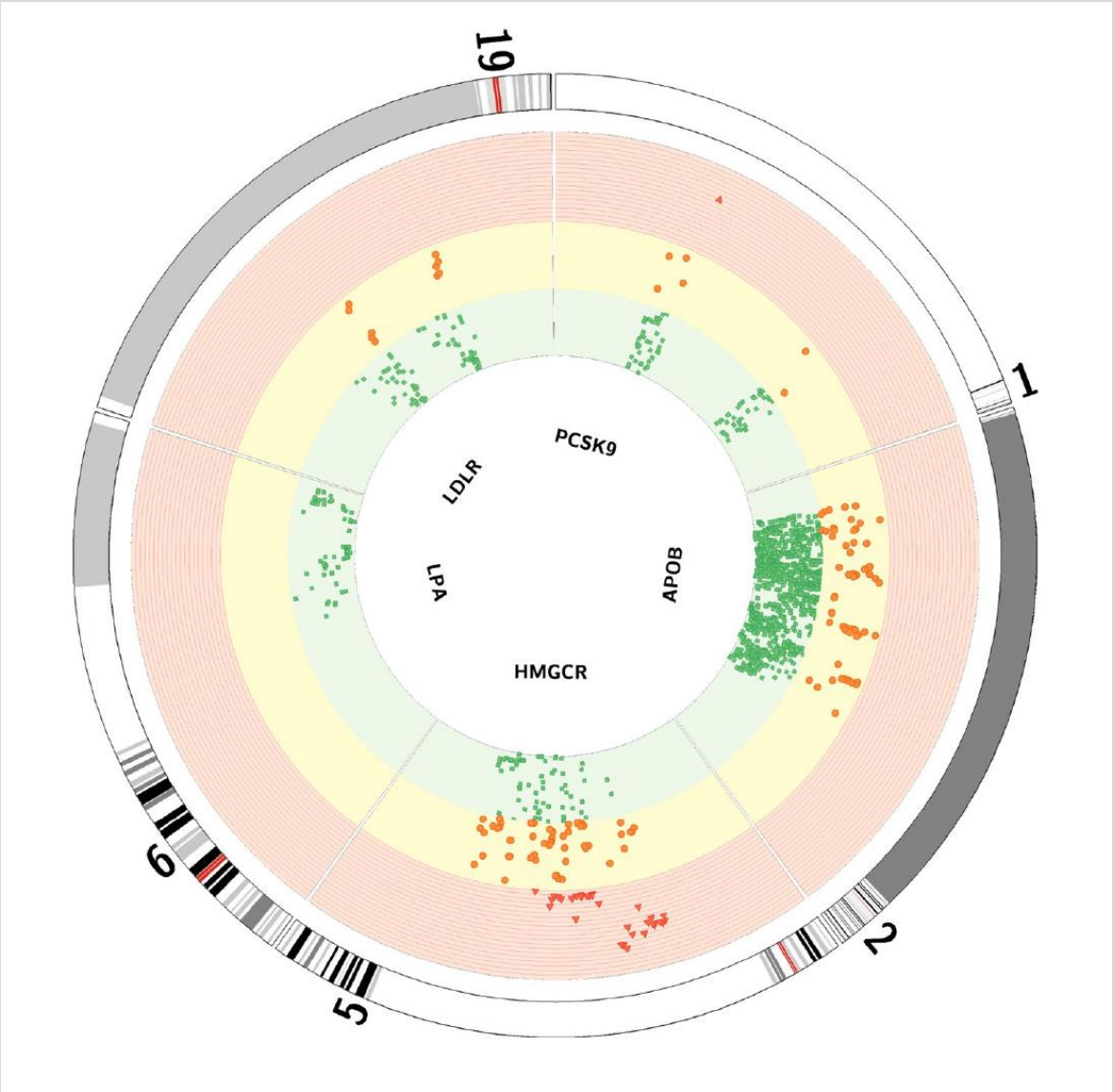
Conventional MR



MR Egger

White et al, JAMA Cardiol 2016 ;1:692-9

Specific LDL-c variants



Circos plot:

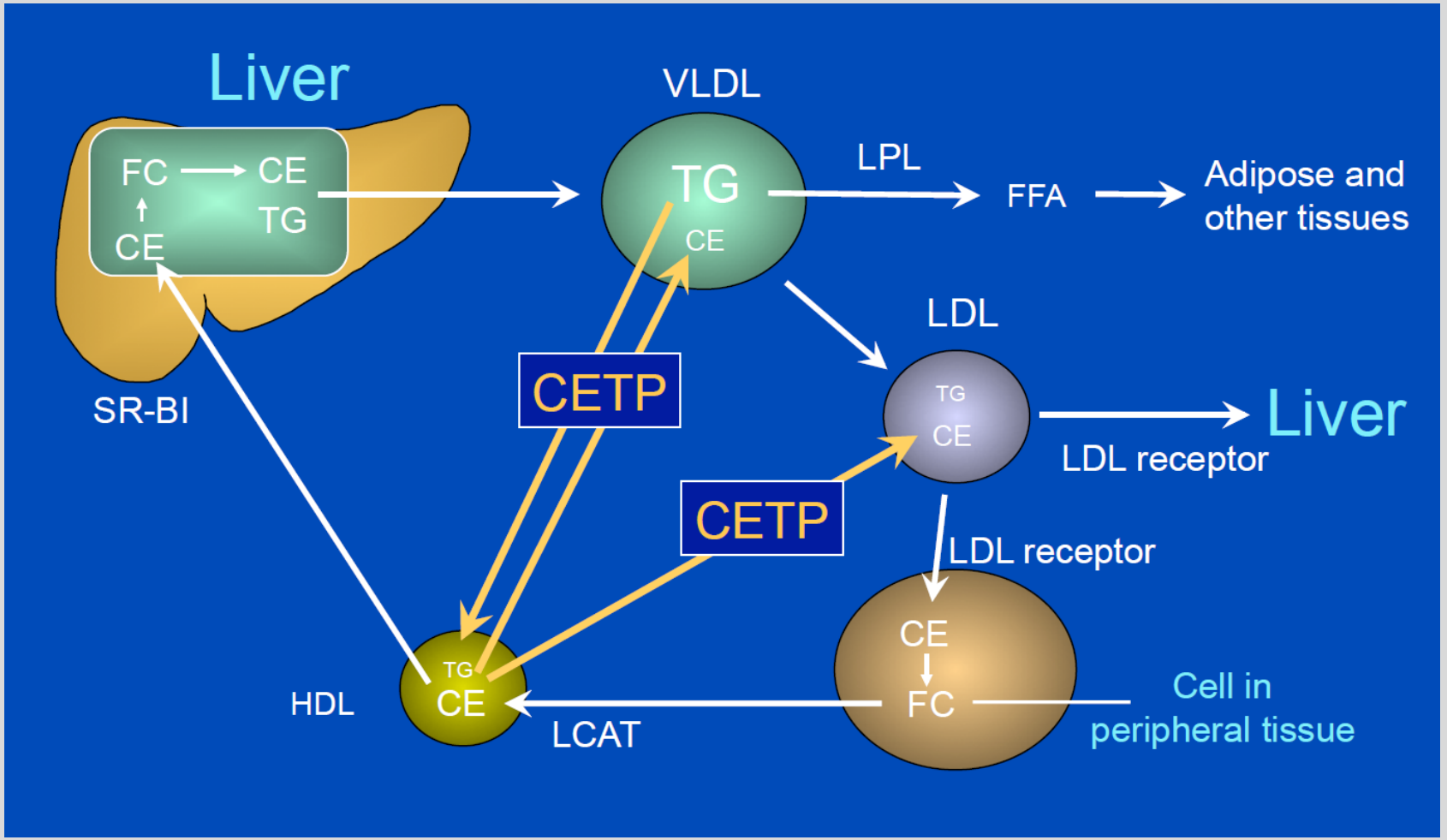
Green: P ≥0.05
Orange: P 0.001-0.049
Red: P <0.001

Tragante et al; Hum Genetics 2016; 135: 453-67

Questions

1. Is this modest ‘diabetogenic’ effect observed with other LDL-c lowering drugs?
2. Is LDL-c implicated in developing diabetes?
3. Are other lipids involved?

CETP inhibition



CETP inhibition

	HDL-c	LDL-c	Study	N	CVD	Off target effect?
CETP loci	↑	↓		-	↓	-
Torcetrapib	↑↑72%	**↓25%**	ILLUMINATE	15,067	↑	↑ aldo ↑BP
Dalcetrapib	↑30%	↔	DalOUTCOMES	15,871	↔	-
Anacetrapib	↑↑140%	**↓40%**	DEFINE (REVEAL)	30,000	↓	(BP)
Evacetrapib	↑↑130%	**↓37%**	ACCELERATE	12,000	↔	(BP)

DalOUTCOMES - dalcetrapib

	PLACEBO (n=7908)	DALCETRAPIB (n=7911)
HbA1c		
Month 6	+0.1%	0.0%
Month 24	+0.1%	0.0%
Glucose		
Month 6	0.0 mmol/L	0.0 mmol/L
Month 24	+0.2 mmol/L	+0.2 mmol/L

Schwartz et al, NEJM 2012:367:2089-99

REVEAL - anacetrapib

	Placebo (n=9560)	Anacetrapib (n=9571)	Effect
New-onset DM	6.0%	5.3%	↓11%

HPS3/TIMI55-REVEAL, NEJM 2017 (online)

ILLUMINATE - Torcetrapib

	Visit	Torcetrapib – Placebo
DIABETES (N=6,661)		
Glucose	3 months	-0.34mmol/L
HbA1c	3 months	-0.33%
Insulin	3 months	-11.7uU/mL
NO DIABETES (N=8,406)		
Glucose	3 months	-0.09mmol/L
HbA1c	3 months	-0.22%
Insulin	3 months	-6.6uU/mL

Barter et al, Circulation 2011:124:555-62

ILLUMINATE - Torcetrapib

- Table removed – confidential data

  - Clear glucose-lowering (anti diabetogenic) effect
  - ‘Despite’ increase in aldosterone etc.?

Barter et al, Circulation 2011:124:555-62
+ unpublished data

ACCELERATE: evacetrapib

	Evacetrapib (N = ~2000)	Placebo (N = ~2000)	Risk ratio (approximate)
New-onset DM	149 (2.5%)	183 (3.0%)	↓20% P=0.06

Taken together:

- Weak CETP inhibitor: no effect on diabetes
- Strong CETP inhibitors: clearly anti-diabetogenic

ACC 2016 presentation

Summary

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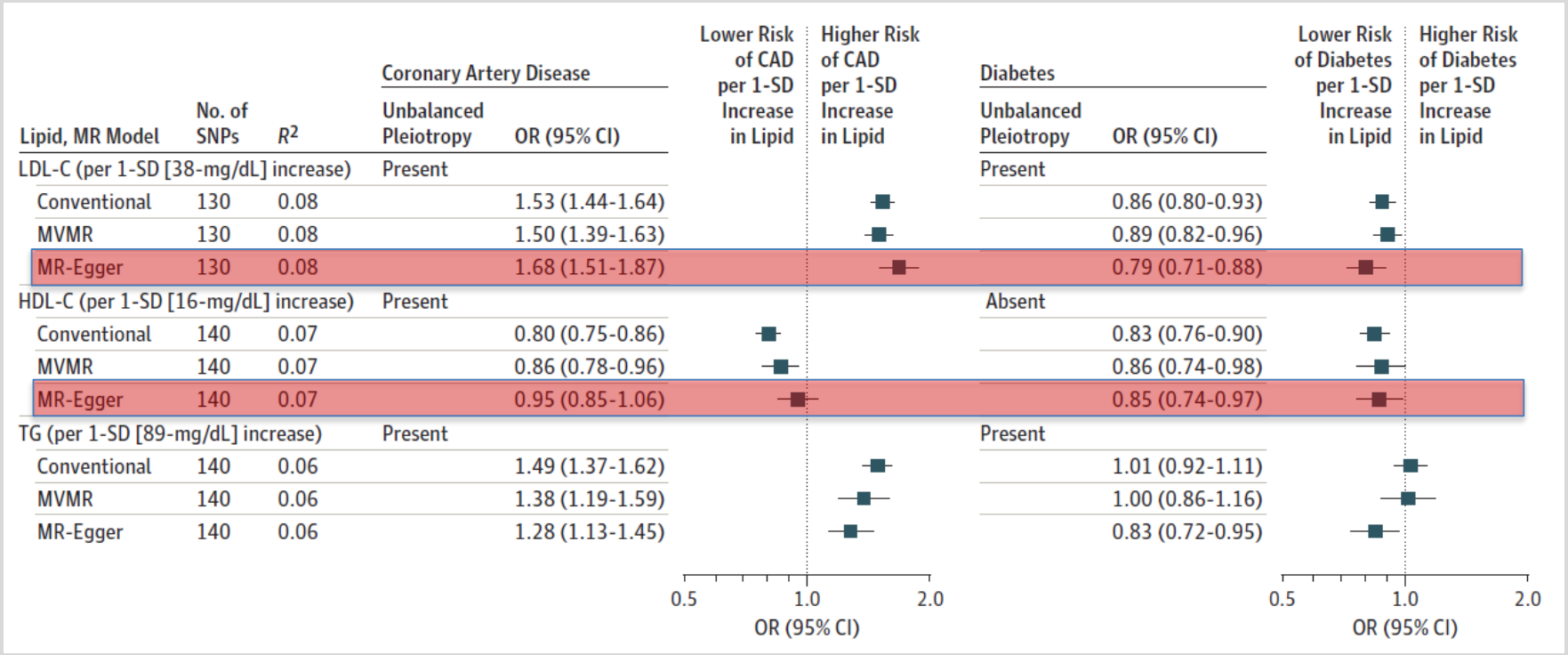
		HDL-c	LDL-c	New-onset DM	Related traits	CVD
Niacin	Drug	↑	↓	↑	↑	↔
	Related gene	-	-	-	-	-
Statin	Drug	↔	↓↓	↑	↑	↓↓
	Related gene	↔	↓	↑	↑	↓
Ezetimibe	Drug	↔	↓	↔ (?)	-	↓
	Related gene	-	↓	↑ (?)	-	↓
PCSK9i	Drug	↔	↓↓↓	↔ (?)	↔ (?)	↓ (?)
	Related gene	↔	↓	↑	↑ ↔	↓
CETPi	Drug (weak)	↑	↔	↔	↔	↔
	Drug (strong)	↑↑	↓↓	↓	↓	?
	Related gene	ongoing				

What about HDL-cholesterol?



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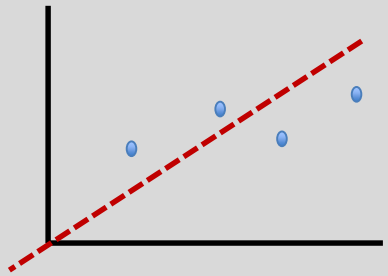
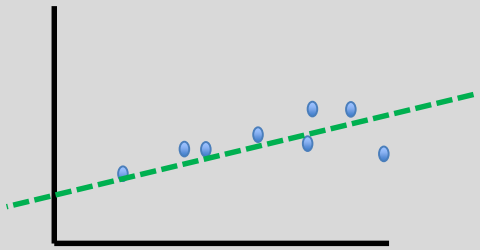


Conventional MR



MR Egger

White et al, JAMA Cardiol 2016 ;1:692-9

Summary: a lipid-centric view

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- Lipids are involved in glucose metabolism
- The relationship is complex and lipids are only one element
- Conflicting evidence (drug vs. drug; gene vs. drug)

Combined effect of: LDL-c + HDL-c	Combined effect of: LDL-c + HDL-c
Familial Hypercholesterolaemia	Niacin (trials)
CETP inhibitors (trials)	Statins (trials + genetics)
	Ezetimibe (genetics)
	PCSK9i (genetics)

↓ diabetes

↑ diabetes

But what about bile acid sequestrants?

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