Role of PCSK9 Inhibitors in Diabetes: Indications for Use and Avoiding Misuse

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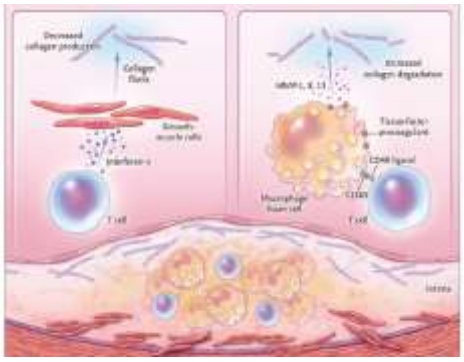
Overview Talk

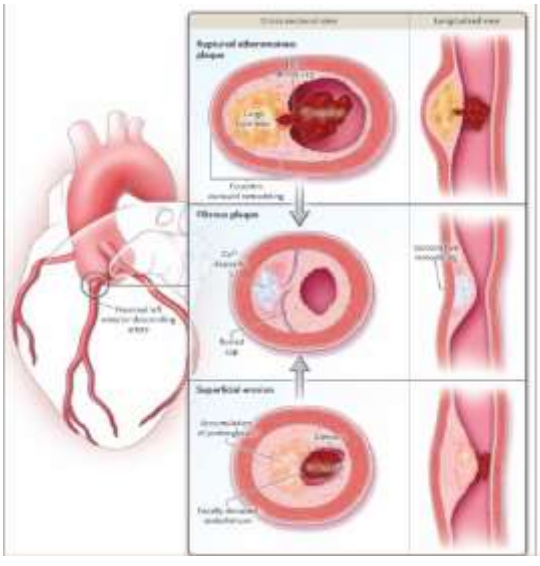
- Review of pathogenesis of atherosclerosis and residual risk
- In patients with diabetes need to go beyond LDL biomarker and assess non-HDL cholesterol
- Review of PCSK9 Inhibitors and their role in reducing LDL in patients with diabetes
- Impact of PCSK9 inhibitors on glucose levels in diabetics
- Avoiding misuse of PCSK9 inhibitors

Pathogenesis of Atherosclerosis

- **Atherosclerosis is a DIFFUSE DISEASE driven by inflammation, atherogenic lipoproteins and in the acute phase platelet aggregation.**
- Serial angiographic studies reveal culprit lesion of a future acute MI often does not cause significant stenosis.
- A multi biomarker strategy is needed for better risk factor stratification.



Libby, NEJM 2013



Libby, NEJM 2013

Plaque can cause outward expansion of the artery wall which accommodates the growth of the plaque and minimizes luminal narrowing

Luminal stenosis occurs late in the process of atherosclerosis

Angiography is an assessment of luminal narrowing

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Medical Management = PCI

- Landmark clinical trials such as COURAGE show that medical treatment of chronic angiographically defined CAD has the same outcome as percutaneous coronary intervention
- The cornerstone of medical management of CAD is treatment of dyslipidemia.

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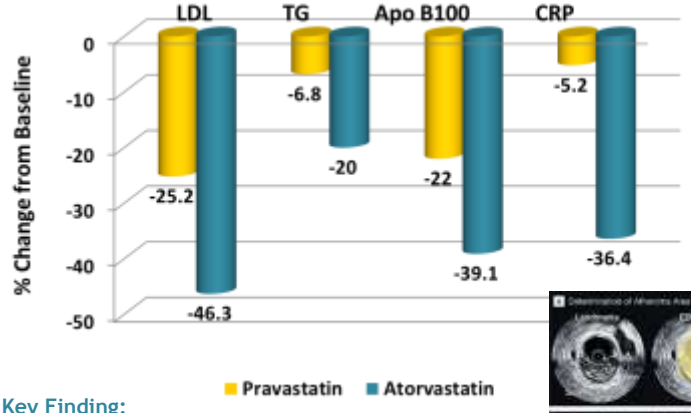
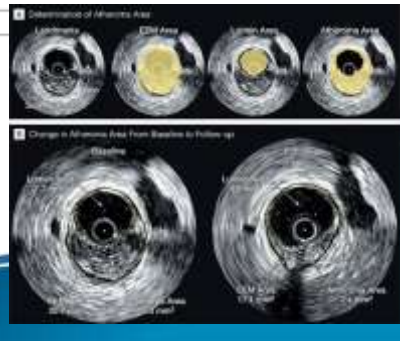
REVERSAL Study: Plaque Regression Associated with Decrease in Biomarkers



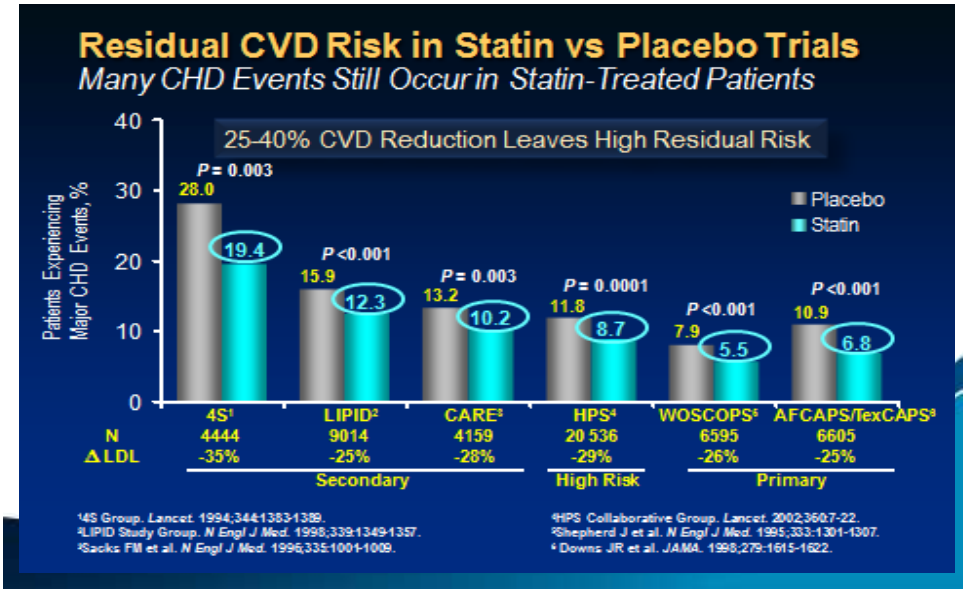


Key Finding:

- Intensive lipid-lowering treatment with atorvastatin for 18 months reduced progression of coronary atherosclerosis compared with pravastatin in CAD patients

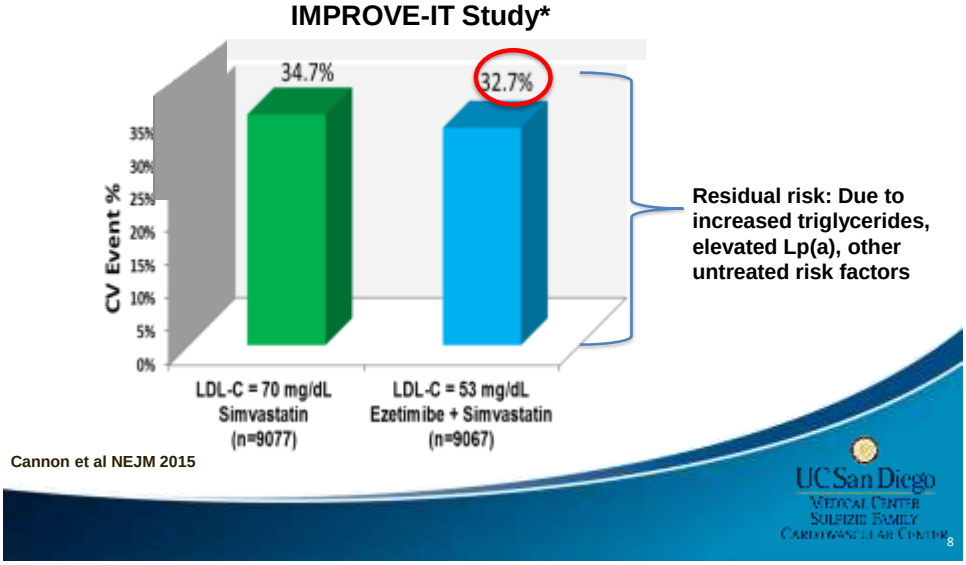
Nissen SE et al. JAMA 2004;291:1071-1080.

Better Biomarkers are needed to address Residual Risk



Aggressive LDL-C Lowering Therapy Does Not Eliminate CVD Risk

Significant Residual Risk Remains Untreated

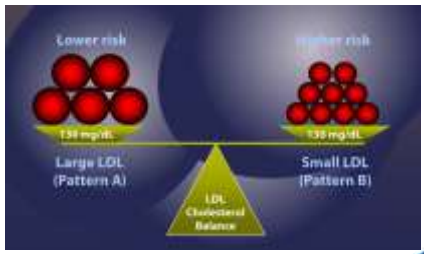


The Lipid Profile Is Different In Patients With Diabetes

Increase in triglycerides

Decrease in HDL cholesterol

Predominance of small dense LDL particles and increased number of particles



Krauss RM. Diabetes Care. 2004 Jun;27(6);1496-504
From Sanofi LPS Investigator meeting Slides.

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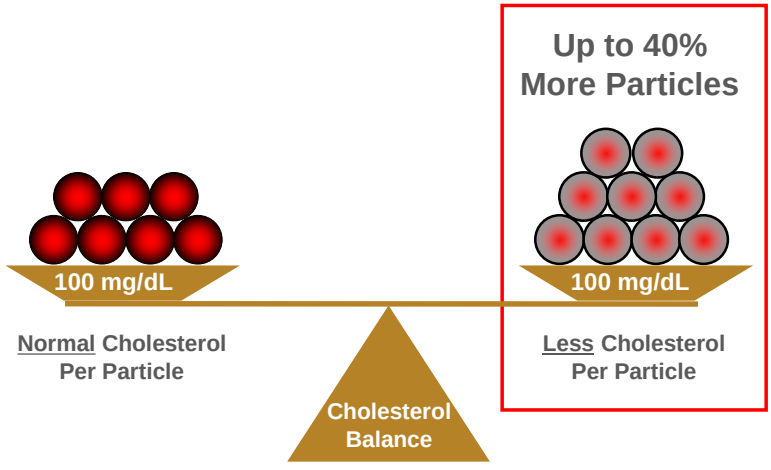
Even LDL Particles of the Same Size can Differ in Cholesterol Content

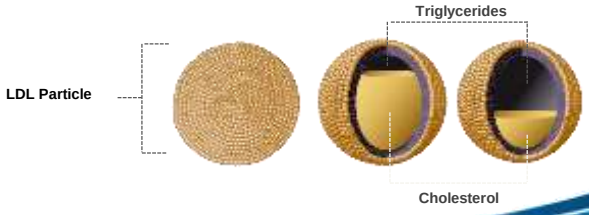


Adapted from Otvos JD, Jayarajah E, Cromwell, WC. AJC 2002;90(8A):22i-29i

LIPOSCIENCE

Beyond LDL Cholesterol in Diabetics

- LDL-C: amount of cholesterol in LDL particles
- LDL-P: number of LDL particles
- Apo-B: reflection of number of atherogenic particles
- Non-HDL: (Total cholesterol- HDL) amount of cholesterol in atherogenic particles
- Low HDL and high TG are associated with higher LDL-P
  - If triglycerides are high there will be less space for cholesterol and it may take more LDL particles to carry a given amount of cholesterol



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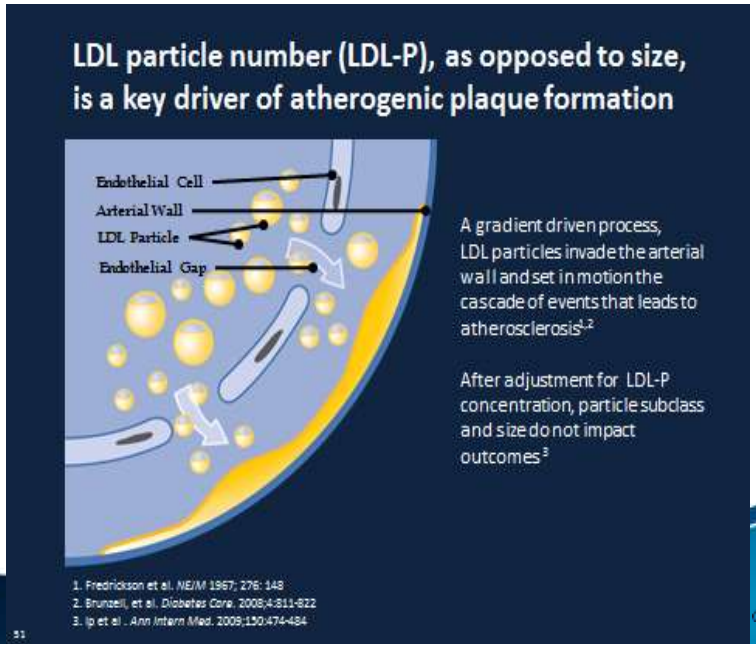
Atherosclerosis is a Gradient Driven Process



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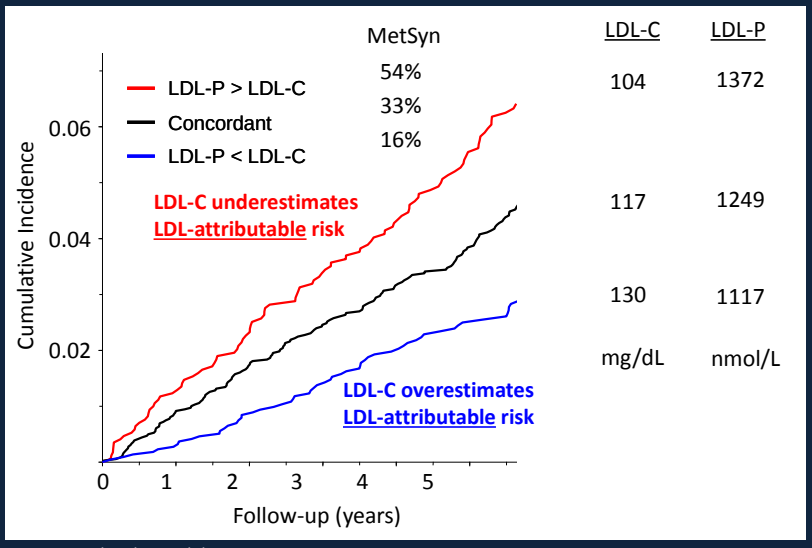
MESA: LDL-P and LDL-C Discordance Relations with Incident CVD Events (n=319)



Otvos et al. J Clin Lipidol 2011;5:105-13

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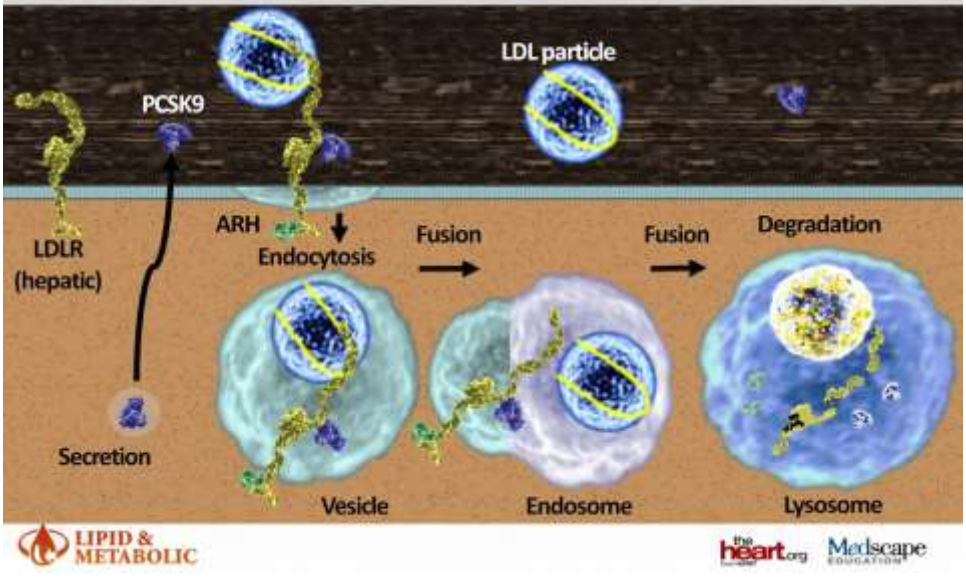
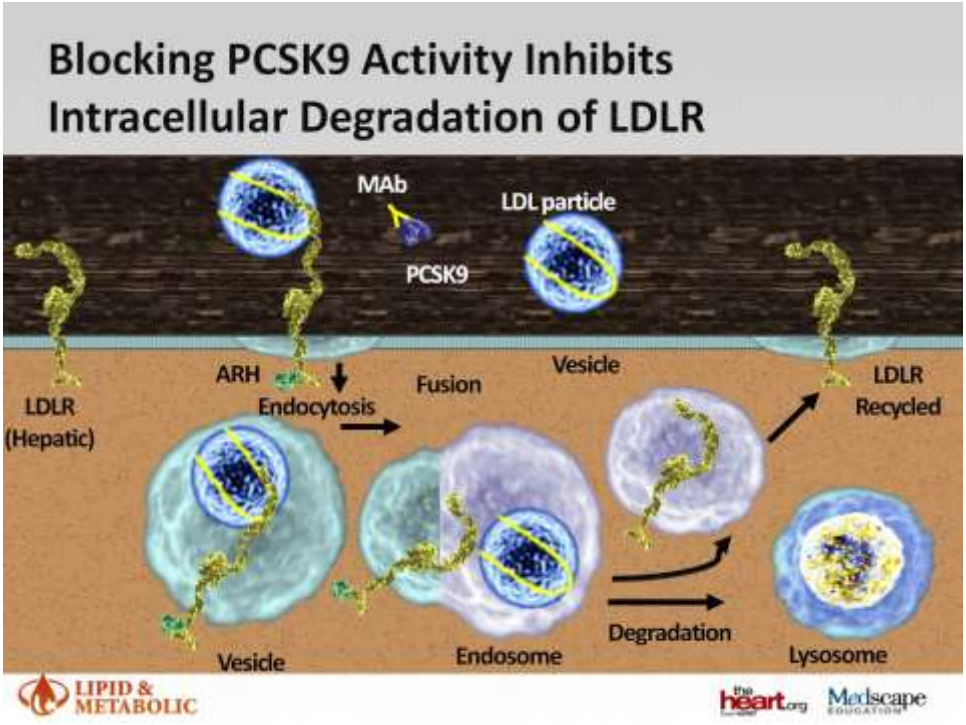
PCSK9 Regulates LDLR Turnover Through Increased Intracellular Degradation





Odyssey Trial Results

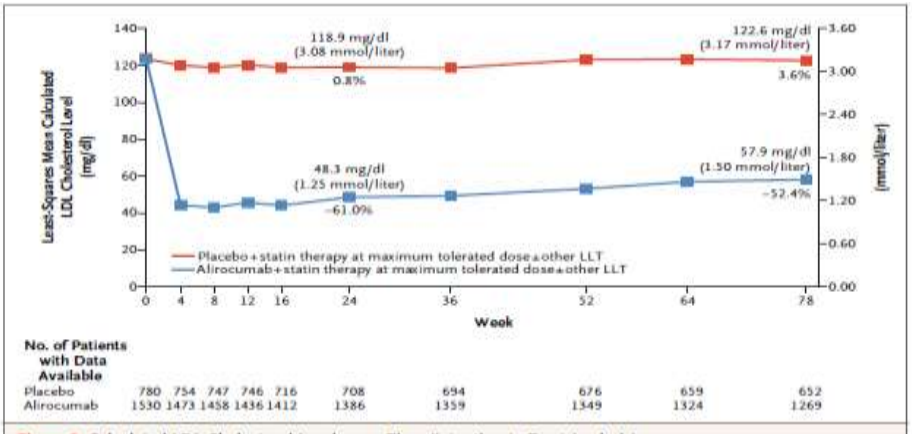
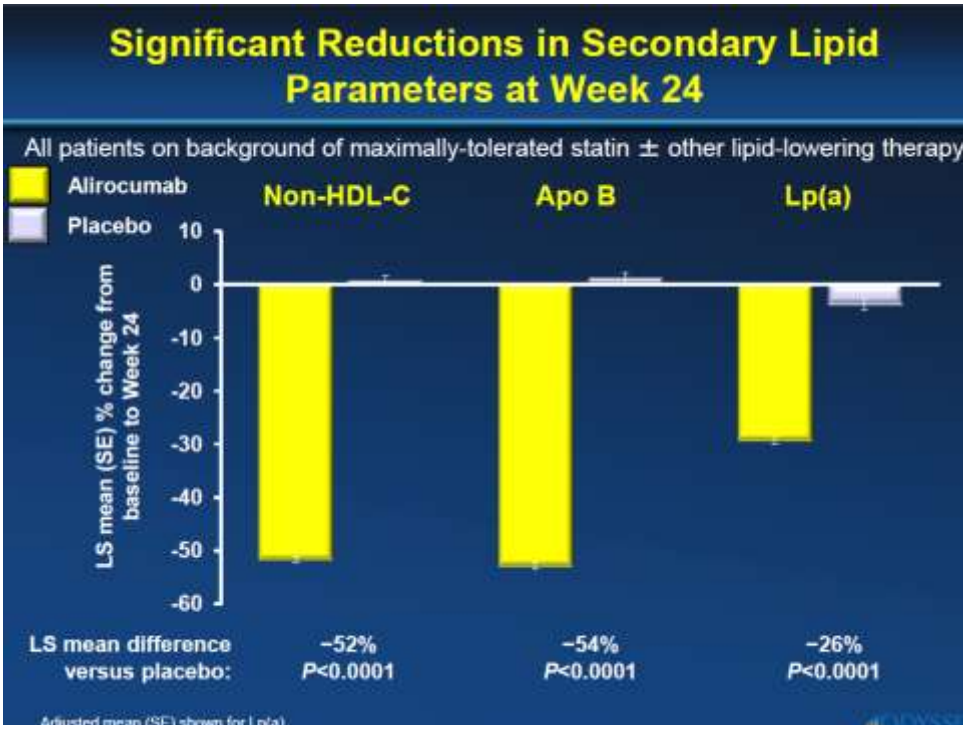


Figure 2. Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).

Calculated LDL cholesterol levels are shown in milligrams per deciliter (left axis) and millimoles per liter (right axis). Values above the data points indicate least-squares mean absolute LDL cholesterol levels, and values below the data points indicate least-squares mean percentage changes from baseline. Values below the chart indicate the number of patients with LDL cholesterol values available for the intention-to-treat analysis at each time point; these include levels measured while the study drug was being taken and, in the case of patients who discontinued the study drug but returned to the clinic for assessments, after the study drug was discontinued. Missing data were accounted for with the use of a mixed-effects model with repeated measures. For statin therapy, the maximum tolerated dose was the highest dose associated with an acceptable side-effect profile. LLT denotes lipid-lowering therapy.



Baseline Demographics

	Individuals with DM (N=838)		Individuals without DM (N=1503)	
	Alirocumab 150 mg Q2W (n=559)	Placebo (n=279)	Alirocumab 150 mg Q2W (n=994)	Placebo (n=509)
Age, years	61.7 (9.6)	61.0 (10.1)	59.8 (10.7)	60.3 (10.6)
Male, n (%)	327 (58.5)	144 (51.6)	656 (66.0)	330 (64.8)
Race, white, n (%)	477 (85.3)	237 (84.9)	964 (97.0)	493 (96.9)
BMI, kg/m^2	32.0 (6.2)	32.7 (5.7)	29.2 (5.2)	29.4 (5.0)
HeFH, n (%)	38 (6.8)	20 (7.2)	238 (23.9)	119 (23.4)
Diabetes and ≥2 other risk factors, n (%)	315 (56.4)	168 (60.2)	–	–
Prior CHD†, n (%)	302 (54.0)	147 (52.7)	752 (75.7)	405 (79.6)

- Values are mean (SD), unless otherwise stated; †Diagnosis by invasive or non-invasive testing
- BMI, body mass index; CHD, coronary heart disease; DM, diabetes mellitus; HeFH, heterozygous familial hypercholesterolemia; SD, standard deviation

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Baseline Lipid Profile

	Individuals with DM (N=838)		Individuals without DM (N=1503)	
Baseline lipids, mg/dL	Alirocumab 150 Q2W n=559	Placebo n=279	Alirocumab 150 mg Q2W n=994	Placebo n=509
Calculated LDL-C	116.7 (36.3)	117.2 (36.4)	126.1 (45.4)	124.5 (43.8)
HDL-C	48.3 (11.3)	48.8 (12.5)	50.7 (12.6)	50.7 (12.3)
Triglycerides, median (IQR)	153.1 (111.5–214.0)	149.6 (105.0–208.0)	122.6 (87.6–166.4)	127.4 (90.3–177.0)
Non-HDL-C	151.0 (41.9)	149.5 (43.1)	153.5 (49.0)	153.3 (47.2)
Total cholesterol	199.3 (43.2)	198.1 (43.7)	204.1 (49.6)	203.9 (48.7)
Lp(a), median (IQR)	18.6 (5.7–49.0)	17.1 (5.4–58.0)	26.1 (9.8–73.6)	23.3 (7.1–71.8)
Apo B	101.7 (25.9)	99.9 (26.3)	102.0 (28.6)	102.2 (27.8)
Apo A1	146.2 (24.4)	146.3 (26.6)	146.7 (25.5)	147.9 (27.6)

- Values are mean (SD), unless otherwise stated;
- Apo A1; apolipoprotein A1; Apo B; apolipoprotein B; IQR, interquartile range; SD, standard deviation

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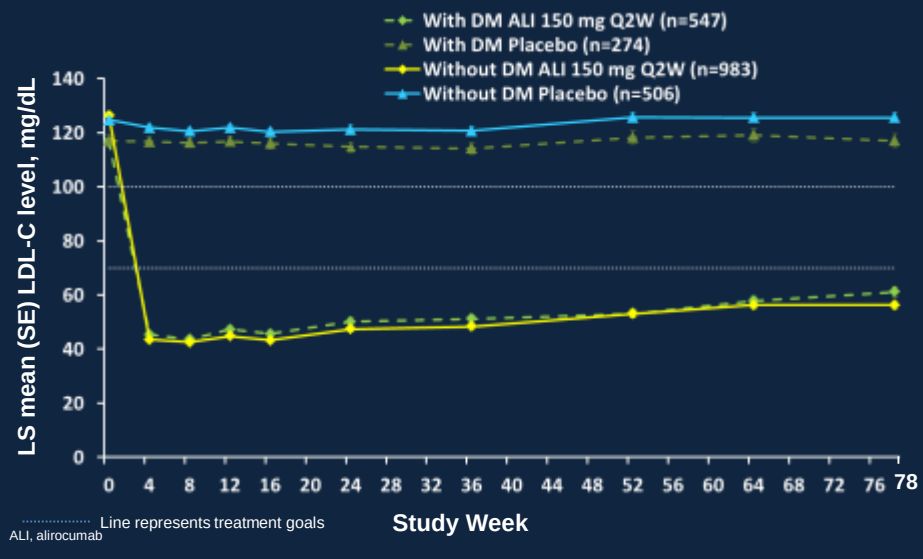
LDL-C Levels by Diabetes Mellitus Status



ALI, alirocumab

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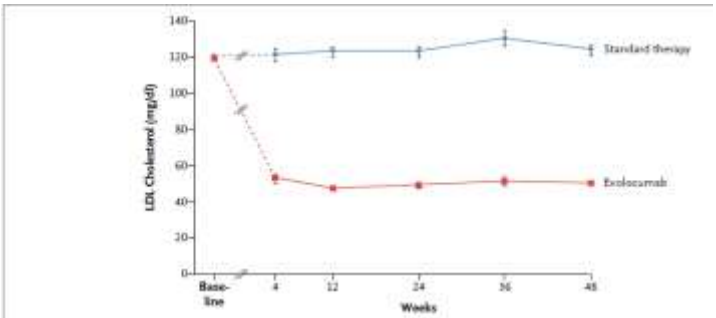
Osler Trial Results



No. at Risk						
Standard therapy	1489	394	1388	1376	402	1219
Evolocumab	2976	864	2871	2828	841	2508
Absolute reduction (mg/dl)		60.4	73.4	70.4	72.7	70.5
Percentage reduction		45.3	60.9	58.8	54.0	58.4
P value		<0.001	<0.001	<0.001	<0.001	<0.001

Figure 1. Low-Density Lipoprotein (LDL) Cholesterol Levels.

LDL cholesterol was measured in both the OSLER-1 and OSLER-2 trials at 12, 24, and 48 weeks and in the OSLER-1 trial at 4 and 36 weeks. Shown are median values with 95% confidence intervals in the two studies. Values for the baseline measurement were obtained before randomization into a parent study. The dashed lines indicate that patients were receiving either evolocumab or placebo during the period from baseline to enrollment into OSLER. In the chart below the graph, the absolute and percentage reductions in the LDL level in the evolocumab group are compared with those in the standard-therapy group and are presented as means. To convert the values for cholesterol to millimoles per liter, multiply by 0.0259.

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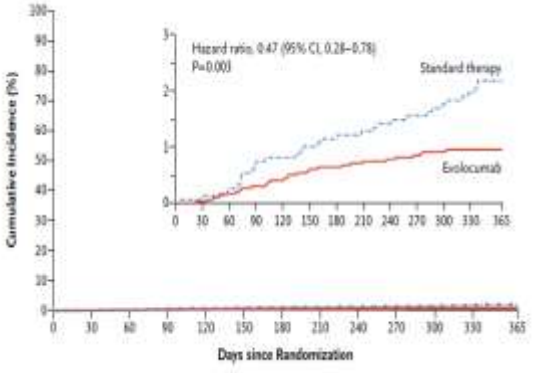
Osler Trial Results



No. at Risk													
Standard therapy	1489	1486	1481	1473	1467	1463	1458	1454	1447	1438	1428	1361	407
Evolocumab	2976	2970	2962	2949	2938	2930	2920	2910	2901	2885	2871	2778	843

Figure 2. Cumulative Incidence of Cardiovascular Events.

Included among the cardiovascular events were death, myocardial infarction, unstable angina requiring hospitalization, coronary revascularization, stroke, transient ischemic attack, and hospitalization for heart failure. Cardiovascular events were reported in 29 of 2976 patients in the evolocumab group (Kaplan–Meier 1-year event rate, 0.95%) and in 31 of 1489 patients in the standard-therapy group (Kaplan–Meier 1-year event rate, 2.18%). The inset shows the same data on an expanded y axis. The P value was calculated with the use of a log-rank test.

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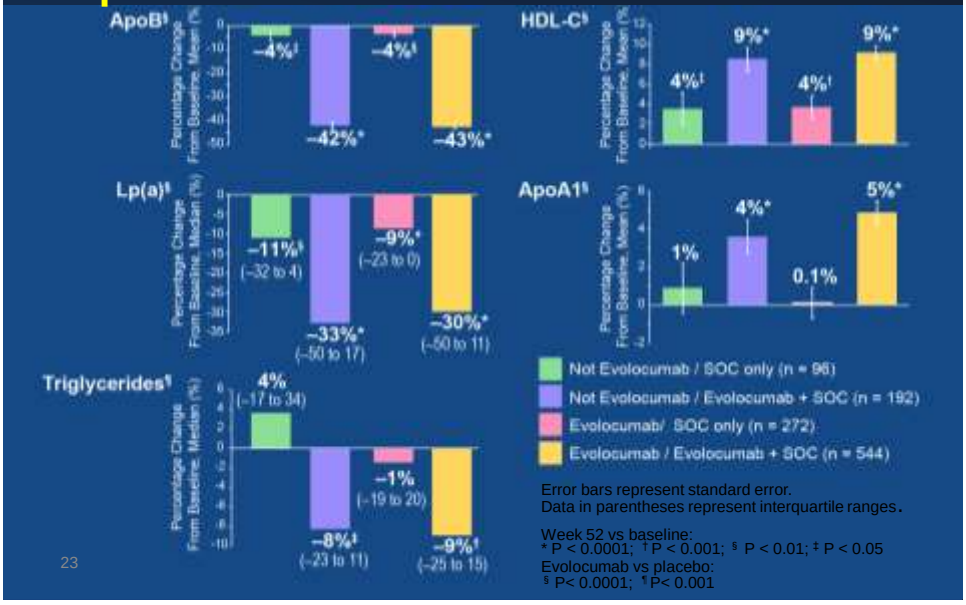
OSLER: Effect of Evolocumab on Other Lipid Parameters at 1 Year



Error bars represent standard error.
Data in parentheses represent interquartile ranges.

Week 52 vs baseline:
* P < 0.0001; † P < 0.001; § P < 0.01; ‡ P < 0.05
Evolocumab vs placebo:
§ P< 0.0001; † P< 0.001

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Lipid-lowering efficacy of the PCSK9 inhibitor evolocumab (AMG 145) in patients with type 2 diabetes: a meta-analysis of individual patient data

Naveed Sattar*, David Preiss*, Jennifer G Robinson, C Stephen Djedjos, Mary Elliott, Ransi Somaratne, Scott M Wasserman, Frederick J Raal

Interpretation Evolocumab markedly reduces atherogenic lipoproteins in patients with type 2 diabetes, an effect that is consistent across subgroups and similar to that seen in patients without type 2 diabetes. Results from ongoing cardiovascular outcome trials of PCSK9 inhibitors will provide additional data to inform the use of these drugs in patients with type 2 diabetes.

***Lancet Diabetes Endocrinol* 2016**

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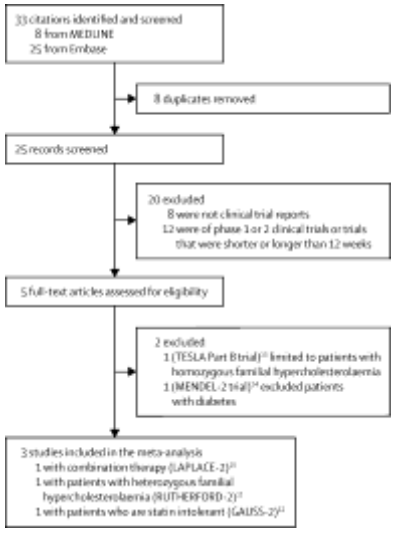
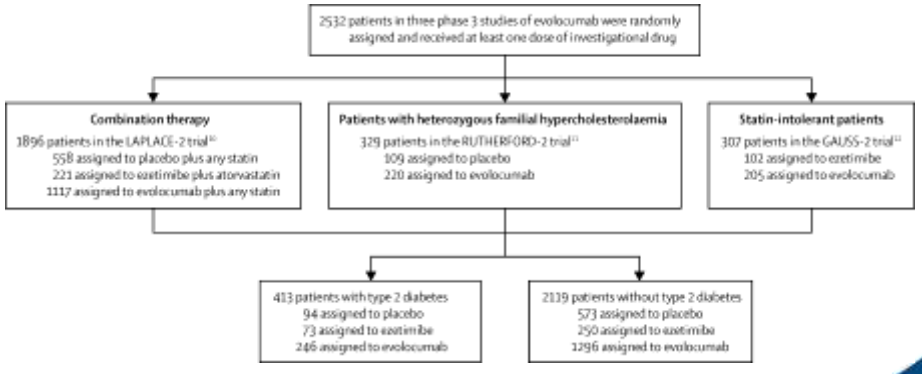


The Lancet Diabetes & Endocrinology 2016 4, 403-410DOI: (10.1016/S2213-8587(16)00003-6)



The Lancet Diabetes & Endocrinology 2016 4, 403-410DOI: (10.1016/S2213-8587(16)00003-6)
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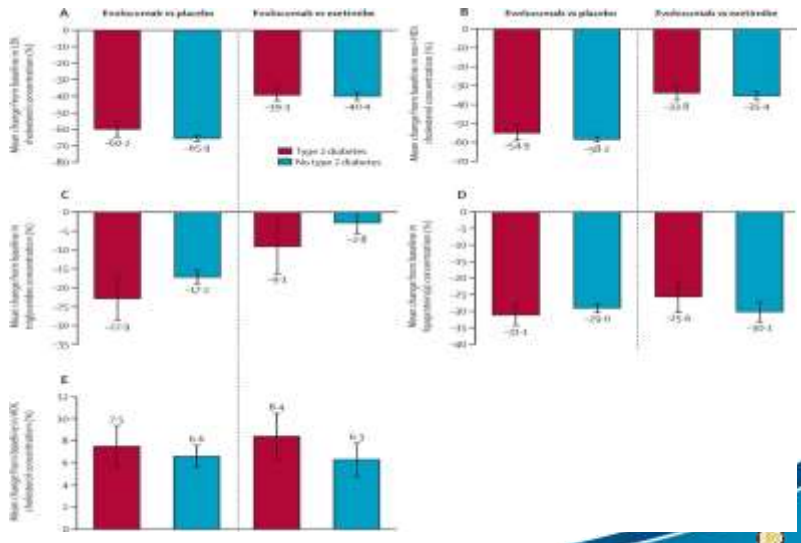

The Lancet Diabetes & Endocrinology 2016 4, 403-410DOI: (10.1016/S2213-8587(16)00003-6)

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	Number of patients		Mean percentage change from baseline (95% CI)
	Evolocumab	Placebo	
Baseline insulin use			
Yes	23	16	-57·4% (-72·0 to -42·8)
No	174	73	-60·5% (-68·8 to -52·2)
History of cardiovascular disease			
Yes	88	36	-58·6% (-72·2 to -45·0)
No	109	53	-60·5% (-68·4 to -52·5)
Baseline HbA_{1c}			
<median	94	44	-62·1% (-72·4 to -51·7)
≥median	102	45	-56·8% (-67·4 to -46·1)
Baseline eGFR			
≥60 mL/min per 1·73 m^2	160	77	-58·9% (-67·3 to -50·4)
<60 mL/min per 1·73 m^2	37	12	-60·1% (-72·9 to -47·3)
Overall	**197**	**89**	**-59·4% (-66·7 to -52·0)**

-80 -60 -40 -20 0
Mean change from baseline (%)

The Lancet Diabetes & Endocrinology 2016 4, 403-410DOI: (10.1016/S2213-8587(16)00003-6)
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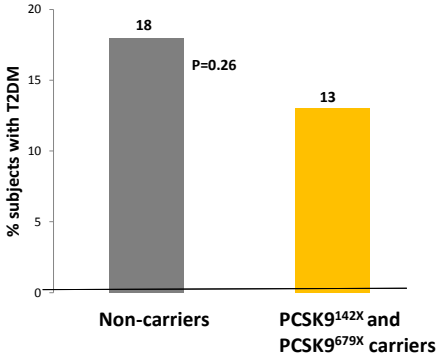
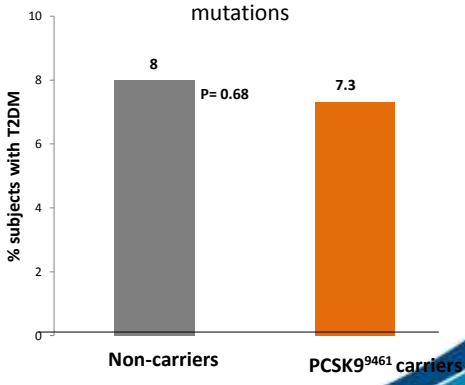
T2DM and Loss of Function PCSK9 Mutations

T2DM prevalence amongst 3363 black subjects with and without PCSK9 mutations



T2DM prevalence amongst 9524 white subjects with and without PCSK9 mutations



Cohen JC et al N Engl J Med 2008

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T2DM and PCSK9 Mutations

Association between PCSK9-pR46L variant and type 2 diabetes risk and incidence*

	n	T-allele frequency	OR or HR (95%CI)	p value
Type 2 Diabetes Case-Control Analysis				
Normal Glucose controls	**2207**	**2.15%**	**0.81**	**0.261**
Type 2 diabetes cases	**1469**	**1.97%**	**(0.56-1.17)[a]**	
Type 2 Diabetes Incidence Analysis				
Non-diabetic participants	**4280**	**2.09%**	**0.34**	**0.065**
Incident type 2 diabetes cases	**184**	**0.83%**	**(0.11-1.07)[b]**	

***Data are n unless otherwise indicated**

[a]OR from a logistic regression model adjusted for age, sex, and BMI

[b]HR from a Cox regression model adjusted for age, sex, and BMI at baseline

Diabetologica 2015; 58:2051-5

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Evolocumab: Incidence of glycemic changes

	Initial Phase 2/3 Studies		Open-label Year 1 Control	
	Any Control (%)	Any Evo (%)	SoC (%)	Evo + SoC (%)
Median study exposure (mo)	3.2	3.1	10.2	10.3
Baseline normoglycemia and impaired fasting glucose (FBG<1.2%mg/Dl)	N=1796 1.7	N=3320 1.9	N=1234 2.7	N=2478 2.9
Incidence of new onset diabetes				
Baseline normoglycemia (FBG <100mg/dL)	N=1234 0.6	N=2161 0.5	N=831 1.4	N=1633 1.1
Baseline impaired fasting glucose (100%FBG<126mg/dL)	N=564 4.1	N=1159 4.6	N=403 5.2	N=645 6.3

From FDA EMDAC Briefing Document

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Alirocumab: Change in fasting plasma glucose

	Placebo-Controlled pool		Ezetimibe-controlled pool	
	Placebo	Alirocumab	Placebo	Alirocumab
Baseline fasting plasma glucose (mg/dL)	N=117 110.8 (34.2)	N=2316 109.5 (31.2)	N=618 108.5 (27.0)	N=864 112.3 (28.2)
Mean Change (SD) from baseline to				
Last on-treatment	N=1136 4.3 (31.3)	N=2238 3.8 (30.3)	N=589 3.2 (28.8)	N=820 2.8 (24.6)
Worst (highest) on-treatment	N=1136 16.8 (35.4)	N=2238 17.0 (35.7)	N=589 10.0 (28.8)	N=820 11.9 (26.6)
Week 52 (placebo)/ Week 24 (ezetimibe)	N=969 2.4 (29.6)	N=1930 2.8 (27.3)	N=496 2.9 (24.4)	N=727 1.5 (23.0)

From FDA EMDAC Briefing Document

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PCSK9 Inhibtiors

- Currently 2 PCSK9 inhibitors on the market
  - Repatha/ Evolocumab (Amgen)
  - Praluent/Alirocumab (Sanofi/Regeneron)
- FDA indication for these agents are:

" approved for use in addition to diet and maximally-tolerated statin therapy in adult patients with:

1. Heterozygous familial hypercholesterolemia
2. Homozygous familial hypercholesterolemia
3. or clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol."

- Outcome Trials Pending

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Avoiding Misuse

- PCSK9 inhibitors do not yet have cardiovascular outcome data to support their use in diabetics for primary prevention
- All trials of PCKS9 inhibitors have been conducted on top of baseline statin therapy.
- Long term data on the impact of PCSK9 inhibitors on glucose levels in diabetics and pre-diabetics not known

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Conclusions

1. In patients with diabetes need to look beyond LDL C for better cardiovascular risk factor stratification as they often have elevated triglycerides, non-HDL cholesterol/LDL P
2. PCSK9 inhibitors reduce LDL cholesterol and have favorable safety profile
   - LDL-C reductions in those with diabetes were similar to those without diabetes
3. PCSK9 inhibitors lower non HDL cholesterol , Lp(a) and maybe an important tool in reducing residual risk
4. PCKS9 inhibitors appear to have no impact on blood glucose levels (but duration of follow up is limited)
5. Outcome data pending on PCSK9 inhibitors