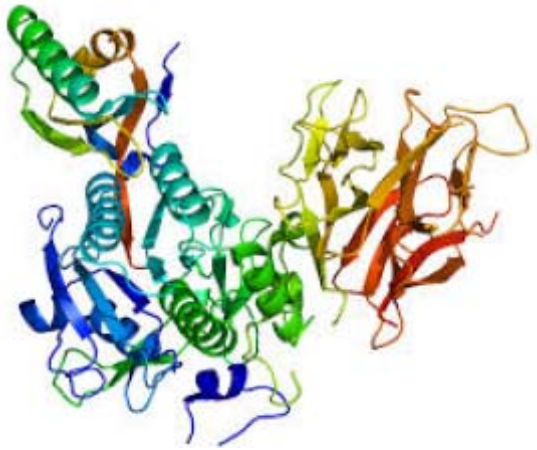
UNIVERSITY OF OTTAWA
HEART INSTITUTE
INSTITUT DE CARDIOLOGIE
DE L'UNIVERSITÉ D'OTTAWA



PCSK9 inhibitors

not for every patient with LDL-C above target

Ruth McPherson, MD, PhD, FRCPC, FACP

Faculty / Presenter Disclosure

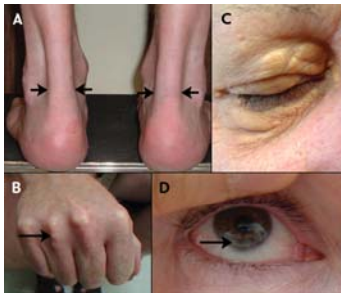
- **Faculty: Ruth McPherson**

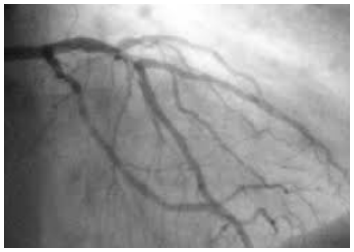
- **Relationships with commercial interests:**
  - **Grants / Research Support:** Pfizer
  - **Speakers Bureau / Honoraria:** Amgen, Merck, AstraZeneca, Valeant, Johnson & Johnson
  - **Consulting Fees:** Amgen, Sanofi, Aegerion

Beyond Statins
Need for New Therapies

Statin intolerance

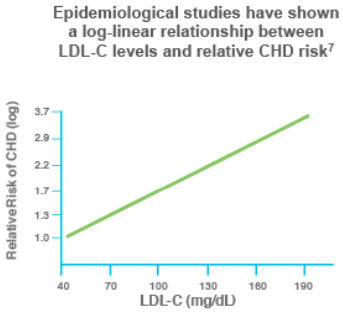
Severe familial dyslipidemia

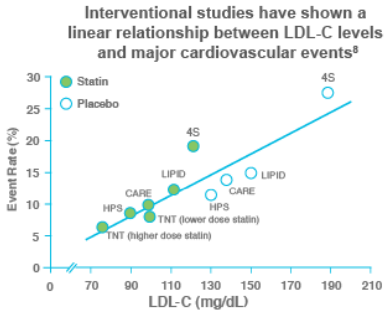




Aggressive CAD

Lower targets





Why Not?

1. Statin intolerance – real or imagined
2. Familial hypercholesterolemia – treated or not
3. ASCVD – how great is the benefit of further LDL lowering when LDL-c is 1.8?
4. PCSK9 – why do we have it?
5. Economics – cost/benefit ratios

Statin Intolerance
How Great is the Problem?

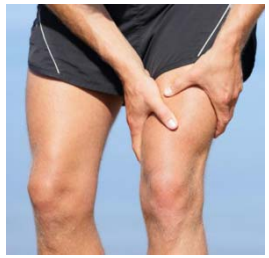
Adverse events may be related to specific statin, not entire drug class; most patients can tolerate a subsequent trial of statin

In a large, retrospective cohort study 92% of those rechallenged were still taking a statin 12 months after statin-related event

ODYSSEY ALTERNATIVE (statin-intolerance) STUDY

a significant proportion of subjects withdrew due to muscle related side-effects during *placebo run-in*.

	Discontinuation on blinded Rx
alirocumab (PCSK9 mAb)	18.3%
ezetimibe	25.0%
atorvastatin 20mg	25.4%



ORIGINAL RESEARCH | Annals of Internal Medicine

Discontinuation of Statins in Routine Care Settings

A Cohort Study

Huabing Zhang, MD; Jorge Plutzky, MD; Stephen Skentzos, BA, BS; Fritha Morrison, MPH; Perry Mar, PhD; Maria Shubina, ScD; and Alexander Turchin, MD, MS

Ann Intern Med. 2013;158:526-534.

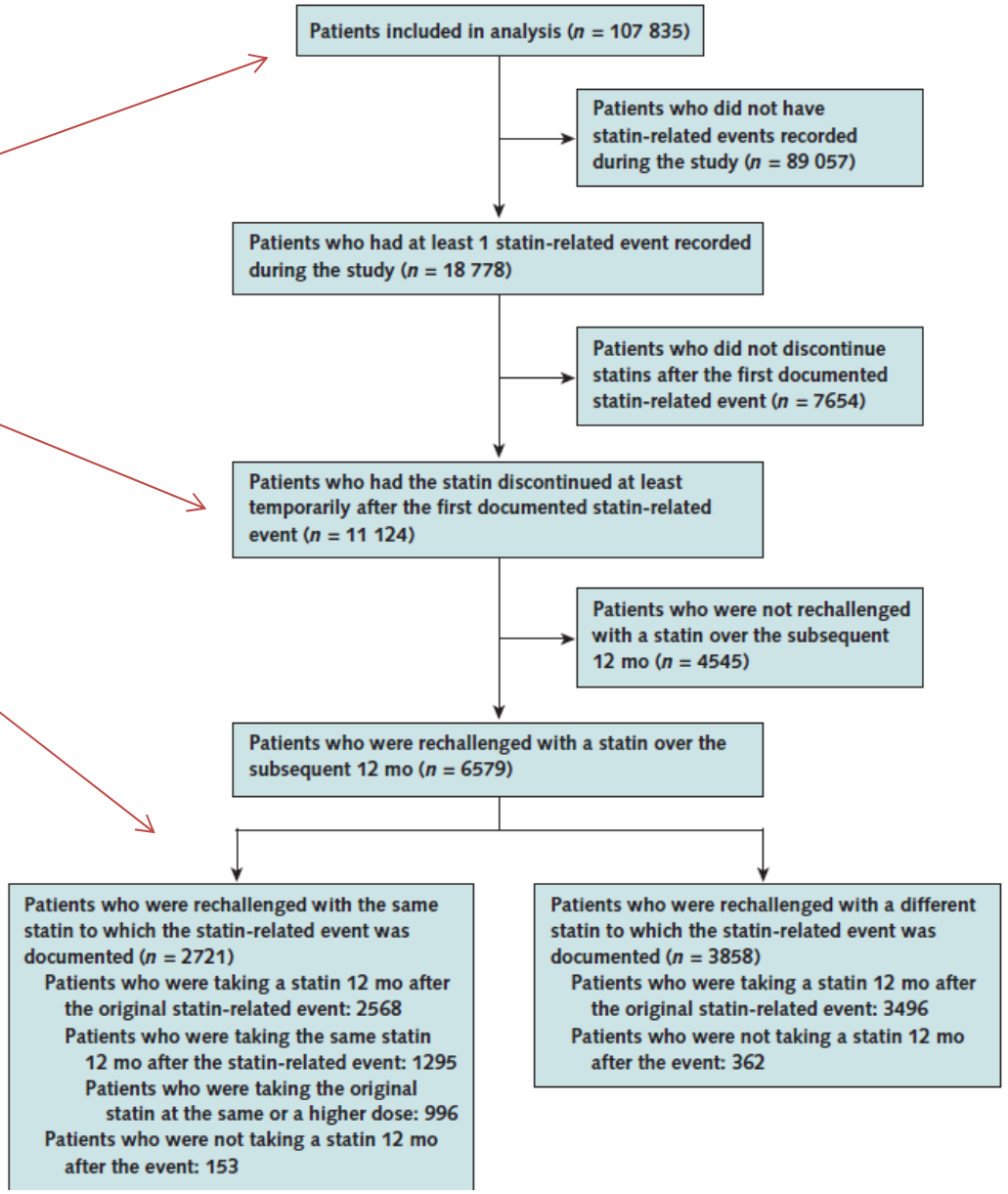
Conclusion: Statin-related events are commonly reported and often lead to statin discontinuation. However, most patients who are rechallenged can tolerate statins long-term. This suggests that many of the statin-related events may have other causes, are tolerable, or may be specific to individual statins rather than the entire drug class.

107,835 patients prescribed statins

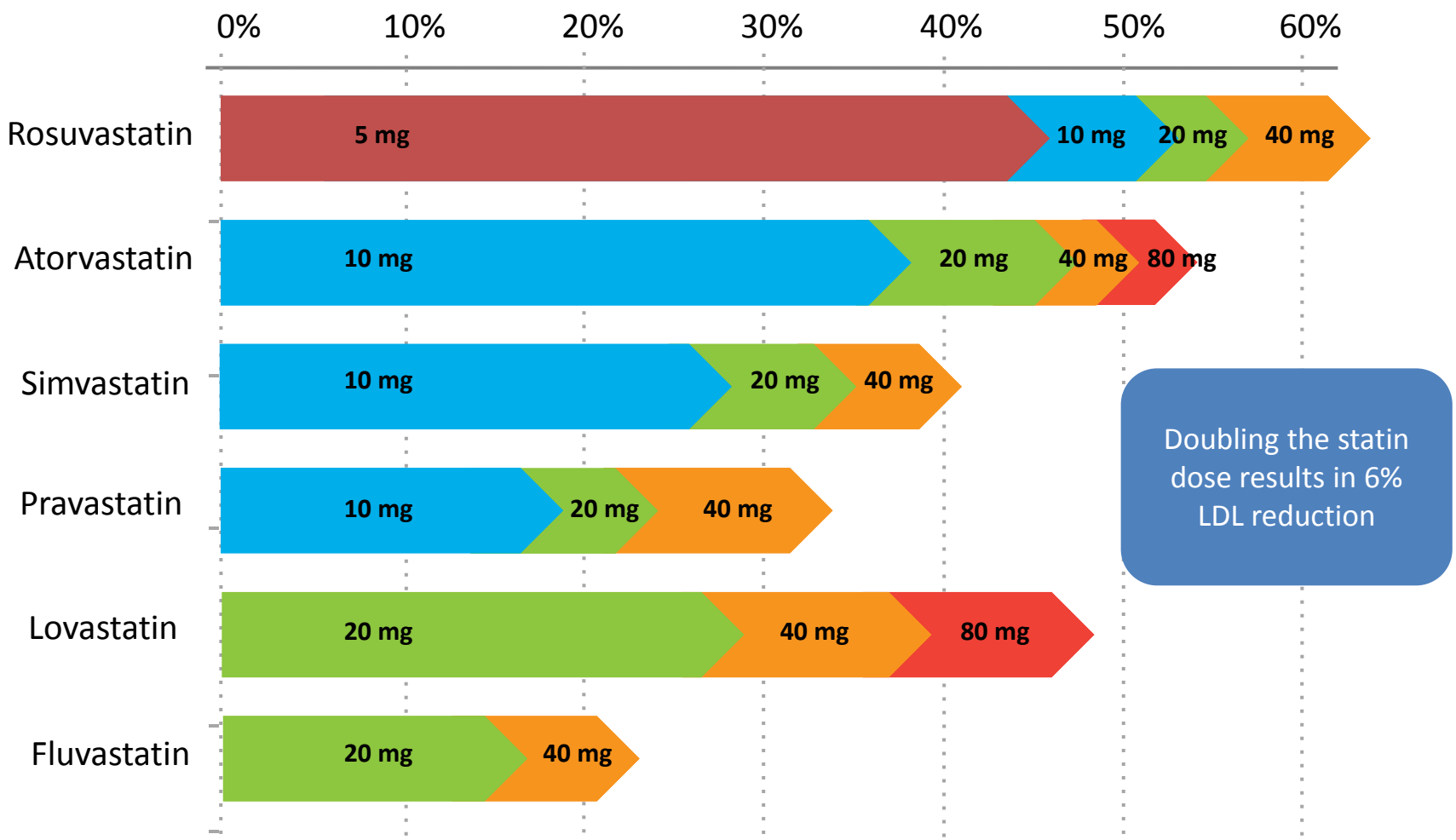
10% of patients discontinued statin therapy because of perceived side-effects.

When rechallenged with the same or different statin, >90% of these initially "statin intolerant" patients were able to resume and continue statin Rx

Figure 2. Statin discontinuation by patients with statin-related events.

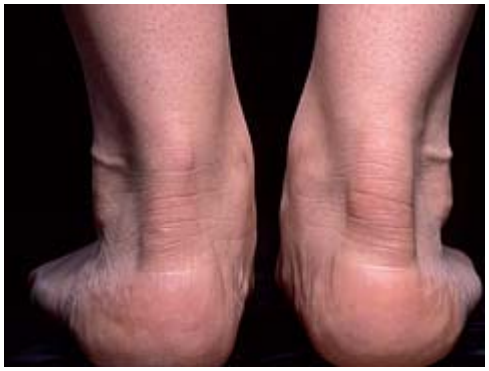


Statin Monotherapy: LDL-C ↓ 20-60%



Familial Hypercholesterolemia

No longer looks like this

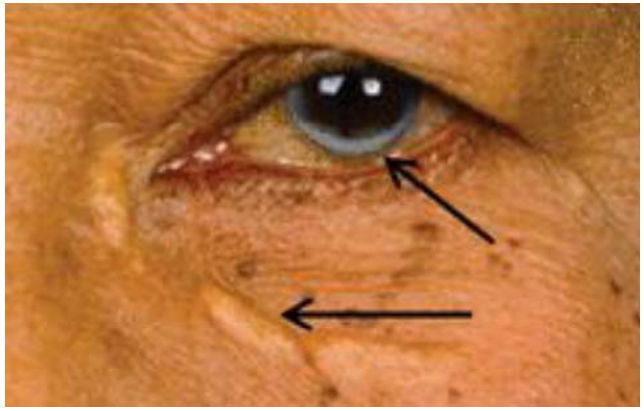


Early treatment with statin + ezetimibe

@ age 8 to 10 years of age

Sustained LDLc reduction

Marked decrease in ASCVD risk



BMJ

RESEARCH

Efficacy of statins in familial hypercholesterolaemia: a long term cohort study

Jorie Versmissen, researcher,[1] Daniëlla M Oosterveer, researcher,[1] Mojgan Yazdanpanah, epidemiologist,[1] Joep C Defesche, senior researcher,[2] Dick C G Basart, clinician,[3] Anho H Liem, clinician,[4] Jan Heeringa, statistician,[5] Jacqueline C Witteman, professor of epidemiology,[5] Peter J Lansberg, clinician,[2] John J P Kastelein, professor of vascular medicine,[2] Eric J G Sijbrands, associate professor[1]

BMJ 2008;337:a2423

Design Cohort study with a mean follow-up of 8.5 years.
Setting 27 outpatient lipid clinics.
Subjects 2146 patients with familial hypercholesterolaemia without prevalent coronary heart disease before 1 January 1990.

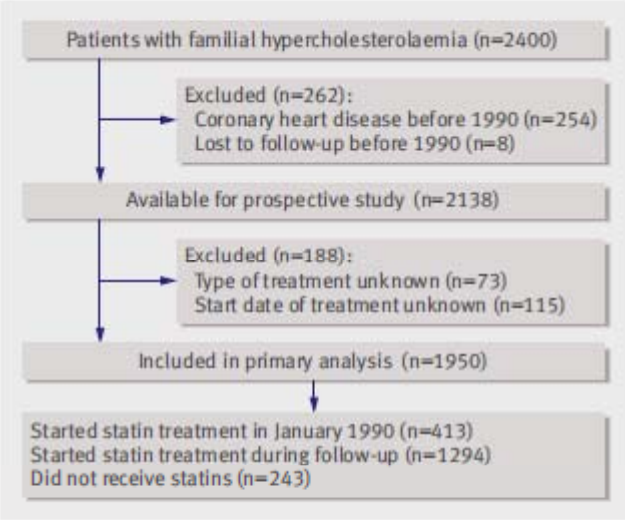


Fig 1| Flow of patients through study

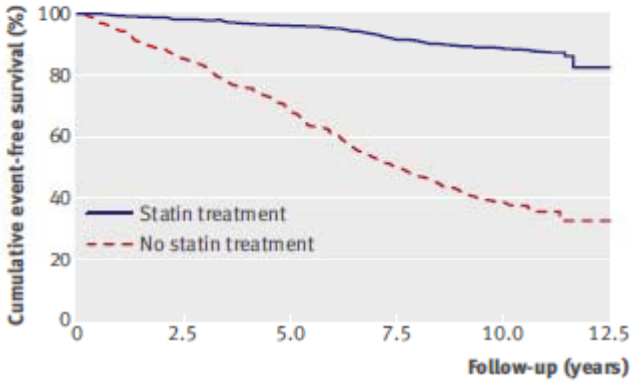


Fig 2| Kaplan-Meier curve estimates of cumulative coronary heart disease-free survival among patients with familial hypercholesterolaemia according to statin treatment (P<0.001 for difference)

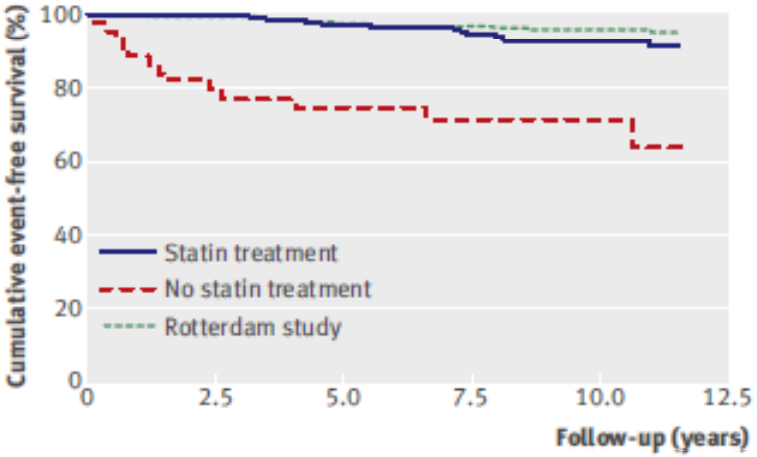


Fig 4 | Kaplan-Meier curve estimates of cumulative myocardial infarct-free survival among patients with familial hypercholesterolaemia older than 55 years according to statin treatment compared with a sample from the general population (Rotterdam study). (P<0.001 for difference between untreated patients and general population; P=0.07 for difference between treated patients and general population)

Statin treated FH patients older than 55 years had a similar risk of MI as did a sample of the same age from the general population (Rotterdam Study)

European Heart Journal (2008) **29**, 2625–2633
doi:10.1093/eurheartj/ehn422

Reductions in all-cause, cancer, and coronary mortality in statin-treated patients with heterozygous familial hypercholesterolaemia: a prospective registry study

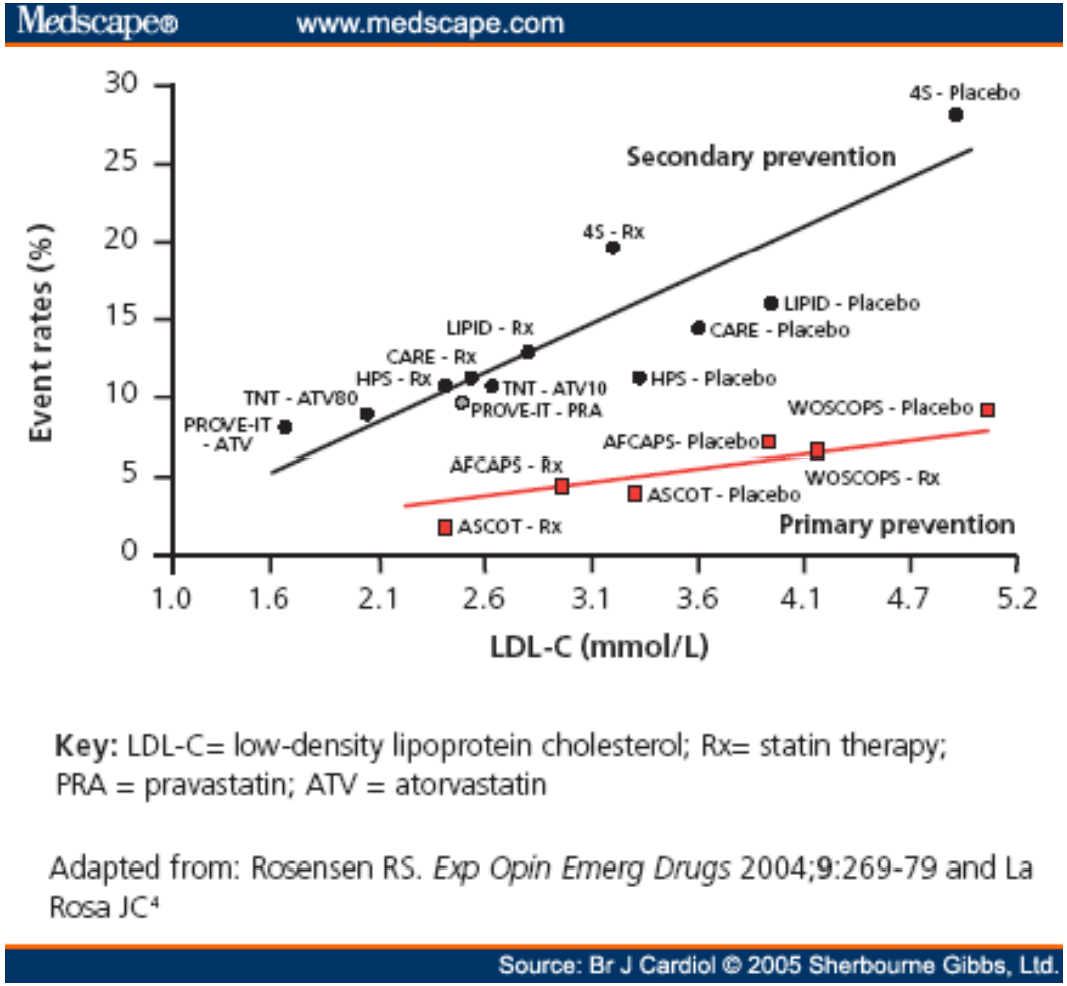
Andrew Neil[1]*, Jackie Cooper[2], John Betteridge[3], Nigel Capps[4], Ian McDowell[5], Paul Durrington[6], Mary Seed[7], and Steve E. Humphries[2] on behalf of the Simon Broome Familial Hyperlipidaemia Register Group

Table 3 Observed and expected deaths from coronary heart disease by age group and time period for patients with and without known coronary disease at registration

Attained age (years)	Person-years observation	1 January 1980 to 31 December 1991						Person-years observation	1 January 1992 to 31 December 2006					
		Observed	Expected	SMR	95% CI	*P*-value	Rate/ 100 000		Observed	Expected	SMR	95% CI	*P*-value	Rate/ 100 000
Primary prevention														
20–39	2031	3	0.08	3750	773–10 959	<0.001	148	8227	3	0.26	1153	238–3372	<0.01	37
40–59	2181	8	2.34	342	148–674	<0.01	367	13123	13	9.19	141	75–242	0.28	99
60–79	686	1	3.63	27	1–153	0.25	146	8219	29	34.33	84	57–121	0.41	353
20–79	4898	12	6.05	198	102–346	0.04	212	29 569	45	43.78	103	75–138	0.89	145
Secondary prevention														
20–39	178	5	0.01	50000	16 235–116 683	<0.0001	2816	229	1	0			0	436
40–59	1016	9	1.58	570	260–1081	<0.0001	886	3419	34	3.83	888	615–1241	<0.0001	995
60–79	539	11	3.24	340	169–607	<0.001	2038	4509	73	24.01	304	238–382	<0.0001	1619
20–79	1733	25	4.83	515	335– 764	<0.0001	1442	8157	108	27.84	388	318–468	<0.0001	1324

A total of 3382 patients (1650 men) aged <80 years were recruited from 21 lipid clinics in the United Kingdom and followed prospectively between 1980 and 2006 for 46 580 person-years. There were 370 deaths, including 190 from coronary heart disease (CHD) and 90 from cancer. The standardized mortality ratio (compared with the population in England and Wales) was calculated before and from 1 January 1992. In patients aged 20–79 years, CHD mortality fell significantly by 37% (95% CI = 7–56) from 3.4- to 2.1-fold excess. Primary prevention resulted in a 48% reduction in CHD mortality from 2.0-fold excess to none, with a smaller reduction of nearly 25% in patients with established disease. Coronary mortality was reduced more in women than in men. In patients without known CHD at registration, all-cause mortality from 1992 was 33% (21–43), lower than in the general population, mainly due to a 37% (21–50) lower risk of fatal cancer.

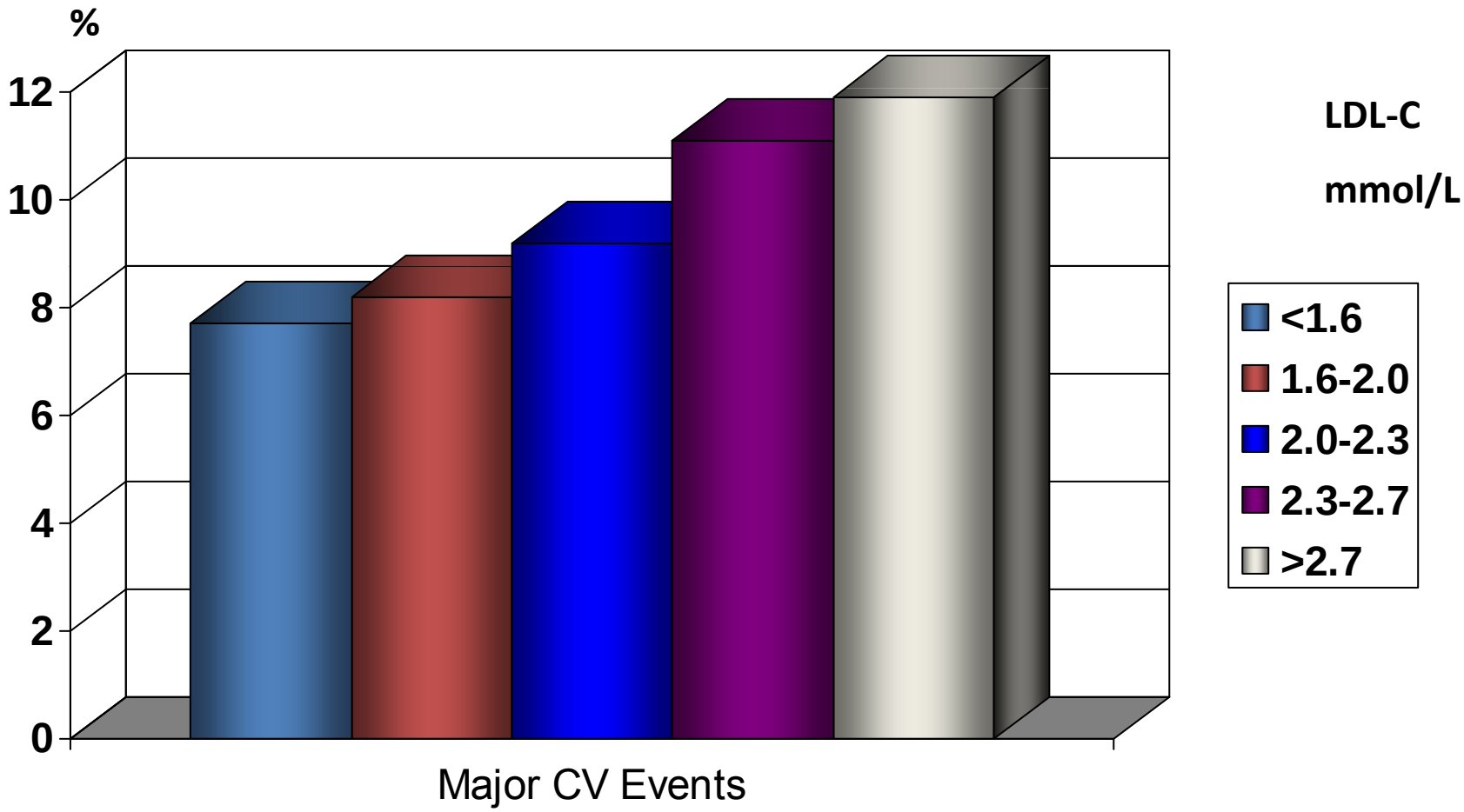
ASCVD- Lower is (how much?)Better



Key: LDL-C= low-density lipoprotein cholesterol; Rx= statin therapy; PRA = pravastatin; ATV = atorvastatin

Adapted from: Rosensen RS. *Exp Opin Emerg Drugs* 2004;**9**:269-79 and La Rosa JC[4]

TNT: CV Events by On-treatment LDL-C



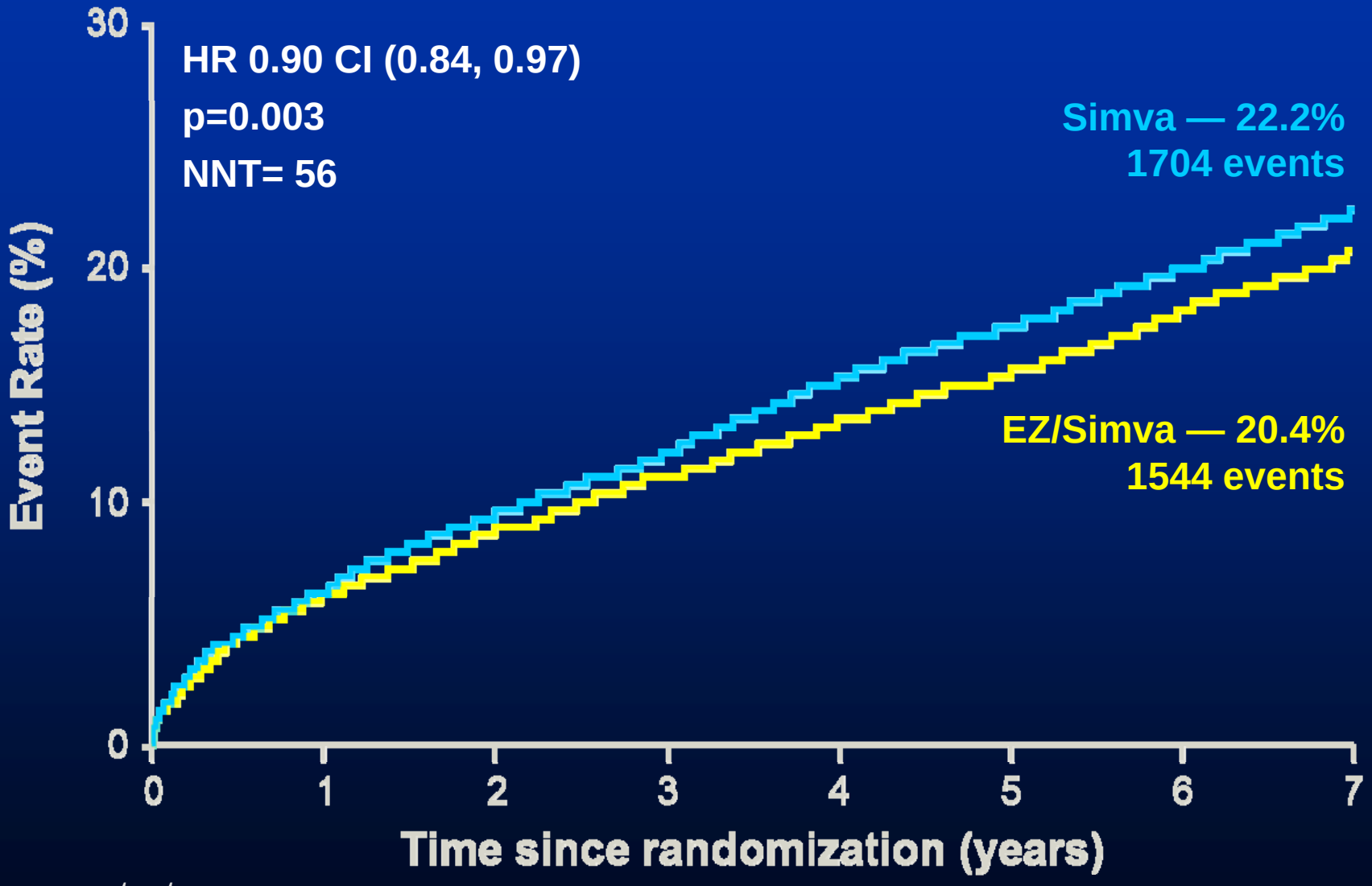
LDL-C and Lipid Changes

1 Yr Mean	LDL-C	TC	TG	HDL	hsCRP
Simva	1.81	3.75	1.55	1.24	3.8 mg/dl
EZ/Simva	1.38	3.25	1.36	1.26	3.3 mg/dl
Δ in mmol/L	-0.43	-0.50	-0.19	+0.2	-0.5mg/dl

Number at risk:

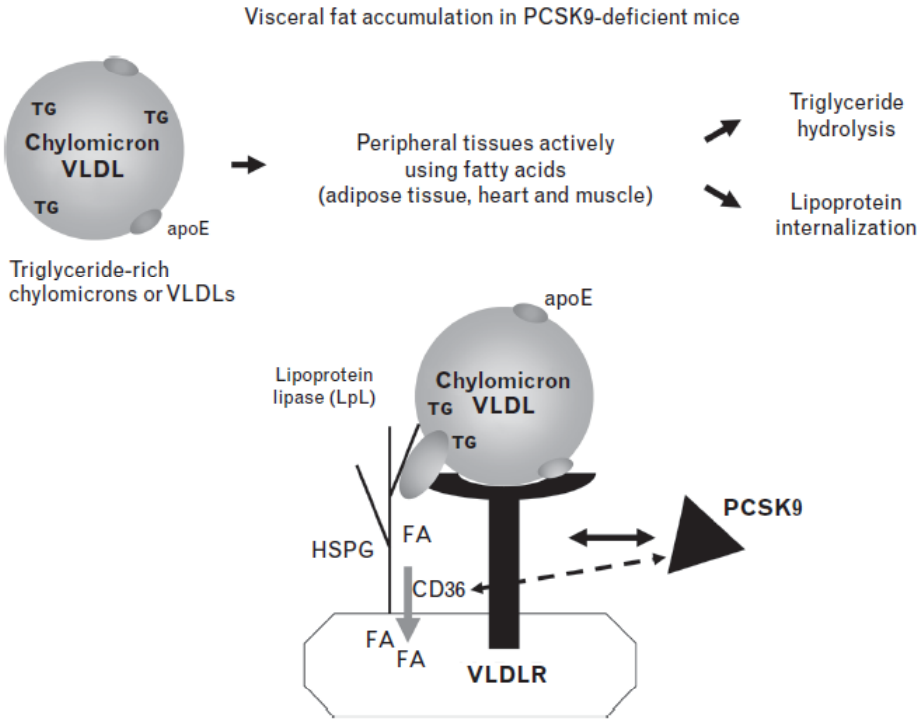
EZ/Simva	8990	8889	8230	7701	7264	6864	6583	6256	5734	5354	4508	3484	2608	1078
Simva	9009	8921	8306	7843	7289	6939	6607	6192	5684	5267	4395	3387	2569	1068

CV Death, Non-fatal MI, or Non-fatal Stroke



7-year event rates

PCSK9 – A function beyond increasing LDLc?



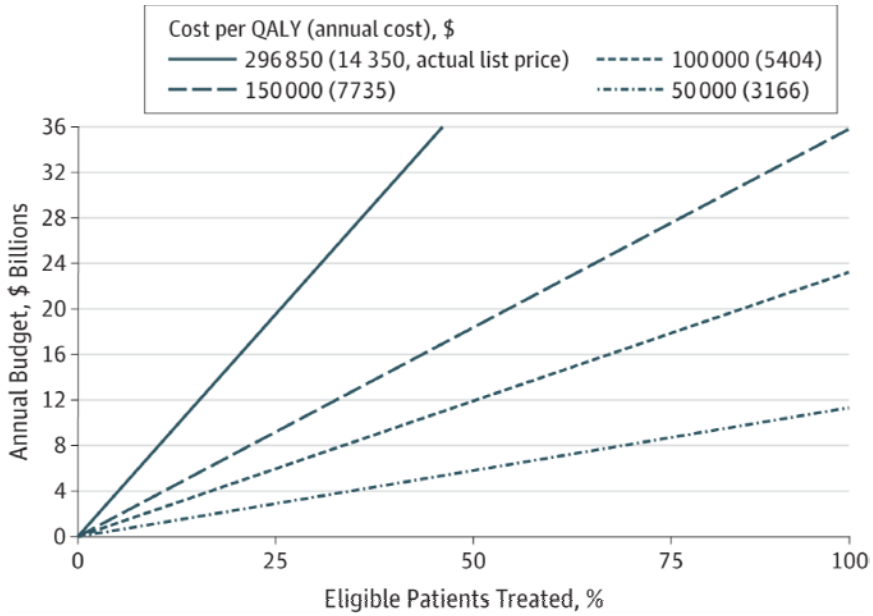
CURRENT OPINION
New developments in proprotein convertase subtilisin–kexin 9's biology and clinical implications
Nabil G. Seidah
Volume 27 • Number 3 • June 2016

PCSK9 also targets other receptors for degradation, including the VLDLR, ApoER2, low density lipoprotein receptor-related protein 1, CD36, and CD81. The role of PCSK9 in the induced degradation of VLDLR and CD36 rationalizes some of its functions in the regulation of triglyceride metabolism, whereas its ability to enhance the degradation of LDLR, VLDLR, and CD81 likely explains its proposed protective role in HCV infection, especially for HCV genotype 3.

Economics of evolocumab/alirocumab Rx

From: **Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors for Treatment of High Cholesterol Levels: Effectiveness and Value**

JAMA Intern Med. 2016;176(1):107-108. doi:10.1001/jamainternmed.2015.7248



CVDPolicyModel

- familial hypercholesterolemia
- CVD statin intolerant
- CVD not at target

Figure Legend:

Cost-effectiveness Analysis of PCSK9 Inhibitor Treatment in 4 Cost ScenariosThe lines represent results from 4 scenarios, varying possible annual drug prices, percentage of eligible patients treated, and their effect on cost-effectiveness ratios and the potential effect on budget. PCSK9 indicates proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life-year.

CDN Costs @ Current Price

Patient Group	Estimated # pts	NNT_5	Cost per QALY
Familial Hypercholesterolemia	60,000	28	$145,000
CVD/Statin intolerant	146,000	21	$137,000
CVD/LDL-C>1.8 on max statin	727,000	21	$151,000
	933,000		

Role for PCSK9 Directed Therapies

- **Statins are the cornerstone of therapy for lipid lowering and CVD prevention**
- **Ezetimibe is a useful 2nd agent now with supportive RCT data**
- **Accumulating evidence that lower (*than guideline recommendations*) is better**
- **Many high risk individuals do not achieve ideal LDLc levels**

Potentially Important Role for PCSK9 inhibitors in Optimizing Rx in a select group of patients

A major issue is cost

PCSK9 Pyramid

on background of maximally tolerated dose of statin + ezetimibe