All high risk patients with residual elevation of LDL should be on PCSK9 Inhibitors: PRO

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DISCLOSURES

- Advisory Boards: Amgen, astra-zeneca, Merck, Sanofi-Aventis/Regeneron, Servier
- Grants: NIH: ISCHEMIA Trial (CCTA); Merck; Amgen; Sanofi


"I never say *never*, and
I never say *always*."
—Grace Kelly

Main Reasons Why I May/Will Lose This Debate

- No RCT data (pending)
- Overactive imagination (extrapolation from early, very promising results)
- PCSK9 inhibitors are too expensive (will availability of 3 or more, and public/payor pressure change this?)
- Dr. McPherson is way smarter and more level-headed than me (always has, always will be; she has taught me everything I know!)

All high risk patients with residual elevation of LDL-C should be on PCSK9 inhibitors: PRO

- What is “high risk?”
- What are the indications for PCSK9 inhibitors?
  - North America vs Europe
- What is not an indication but “high risk?”
- When is “low or intermediate risk” actually “high enough” to warrant aggressive therapy?
- What about Goal-inhibiting Statin Intolerance (GISI)?

What is High Risk Using Traditional Concepts?

- Using CCS as the national standard, high risk is:
  - Clinical CVD, including AAA (i.e. secondary prevention and obvious vascular disease)
  - Familial Hypercholesterolemia (high, lifelong risk due to high, lifelong LDL-C)

General Wording of Regulatory Approvals for PCSK9 Inhibitors

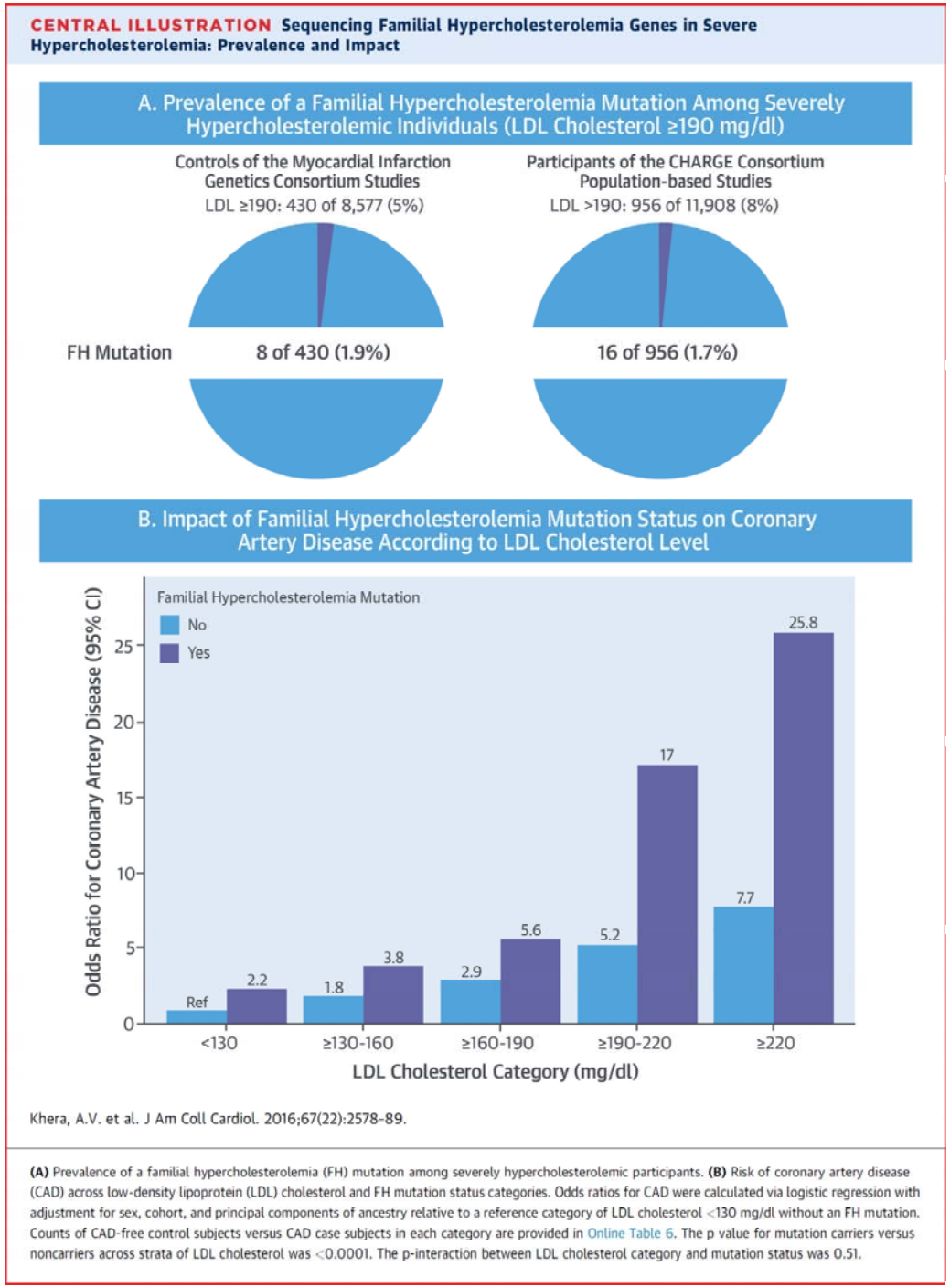
- **North America:** indicated as adjunct to diet and maximally tolerated statin therapy for the treatment of adults with ***heterozygous familial hypercholesterolemia*** or ***clinical atherosclerotic cardiovascular disease***, who require additional lowering of LDL-cholesterol (LDL-C).

- **EU:** indicated in adults with primary hypercholesterolaemia (***heterozygous familial and non-familial***) or ***mixed dyslipidaemia***, as an adjunct to diet:
  - in combination with a statin or statin with other lipid lowering therapies in patients unable to reach LDL-C goals with the maximum tolerated dose of a statin or,
  - alone or in combination with other lipid-lowering therapies in patients who are statin-intolerant, or for whom a statin is contraindicated.

What is High Risk Using Traditional Concepts?

- Using CCS as the national standard, high risk is:
  - ASCVD, including AAA (i.e. secondary prevention and obvious vascular disease)
  - Familial Hypercholesterolemia (high, lifelong risk due to high, lifelong LDL-C)
  - **High LDL-C ≥ 5.0 mmol/L, not necessarily FH**
  - **Diabetes mellitus, mainly T2DM (hyperglycemia augments effects of all CV risk factors leading to accelerated atherosclerosis)**
  - **Pre-dialysis CKD (augmentation of all CV risk factors in setting of poor eGFR and proteinuria)**
  - **"High risk hypertension": HTN with end-organ damage (LVH, proteinuria), Family history of premature CVD**
  - **FRS calculation of 20%/decade rate of CVE**

Diagnostic yield and clinical utility of sequencing FH genes in patients with severe hypercholesterolemia. Khera et al: JACC 2016;67:2578



Cholesterol, not just CV risk, is important in deciding who should receive statin treatment. Soran et al. Eur Heart J 2015; 36:2975.

IMPACT OF GETTING CONSISTENTLY < 2 MMOL/L

Table 4 The number needed to treat to prevent one cardiovascular disease event (*NNT) with atorvastatin 20–80 mg daily titrated (plus, if necessary, adjunctive therapy) to reach a therapeutic goal of 1.8 mmol/L (70 mg/dL) at a 5–30% cardiovascular disease risk in the next 10 years according to the pretreatment LDL cholesterol concentration

10-year cardiovascular disease risk, %	Pretreatment LDL cholesterol (change on treatment), mmol/L					
	2 (−0.2) NNT*	3 (−1.2)		4 (−2.2)	5 (−3.2)	6 (−4.2)	7 (−5.2)
5	412	78		48	36	31	28
7.5	274	52		32	24	20	18
10	206	38	30	24	18	15	14
20	103	19	16	12	9	8	7
30	69	13		8	6	5	5

Figures in parentheses are the changes in LDL cholesterol concentration. At pretreatment LDL cholesterol levels higher than 4 mmol/L, adjunctive cholesterol-lowering medication will generally be required to hit the target, because maximum dose atorvastatin at 80 mg daily lowers LDL cholesterol by a mean of 55%.[6]
LDL, low-density lipoprotein; NNT, number needed to treat to prevent one event.

NNT-based assessment of effectiveness across all levels of risk and all levels of LDL-C

Cholesterol, not just CV risk, is important in deciding who should receive statin treatment. Soran et al. Eur Heart J 2015; 36:2975.

IMPACT OF PERCENT REDUCTION

Table I The number needed to treat to prevent one cardiovascular disease event (*NNT) with atorvastatin 20 mg daily at a 5–30% cardiovascular disease risk in the next 10 years according to the pretreatment LDL cholesterol concentration with no LDL cholesterol therapeutic goal assuming a 43% decrease in LDL cholesterol[6]

10-year cardiovascular disease risk, %	Pretreatment LDL cholesterol (change on treatment), mmol/L					
	2 (−0.86)	3 (−1.29)	4 (−1.72)	5 (−2.15)	6 (−2.58)	7 (−3.01)
	NNT* with atorvastatin 20 mg daily					
5	103	73	57	48	42	38
7.5	69	49	38	32	28	25
10	52	36	29	24	21	19
20	26	18	14	12	11	9
30	17	12	10	8	7	6

33
16

Figures in parentheses are the changes in LDL cholesterol concentration.
LDL, low-density lipoprotein; NNT, number needed to treat to prevent one event.

NNT-based assessment of effectiveness across all levels of risk and all levels of LDL-C

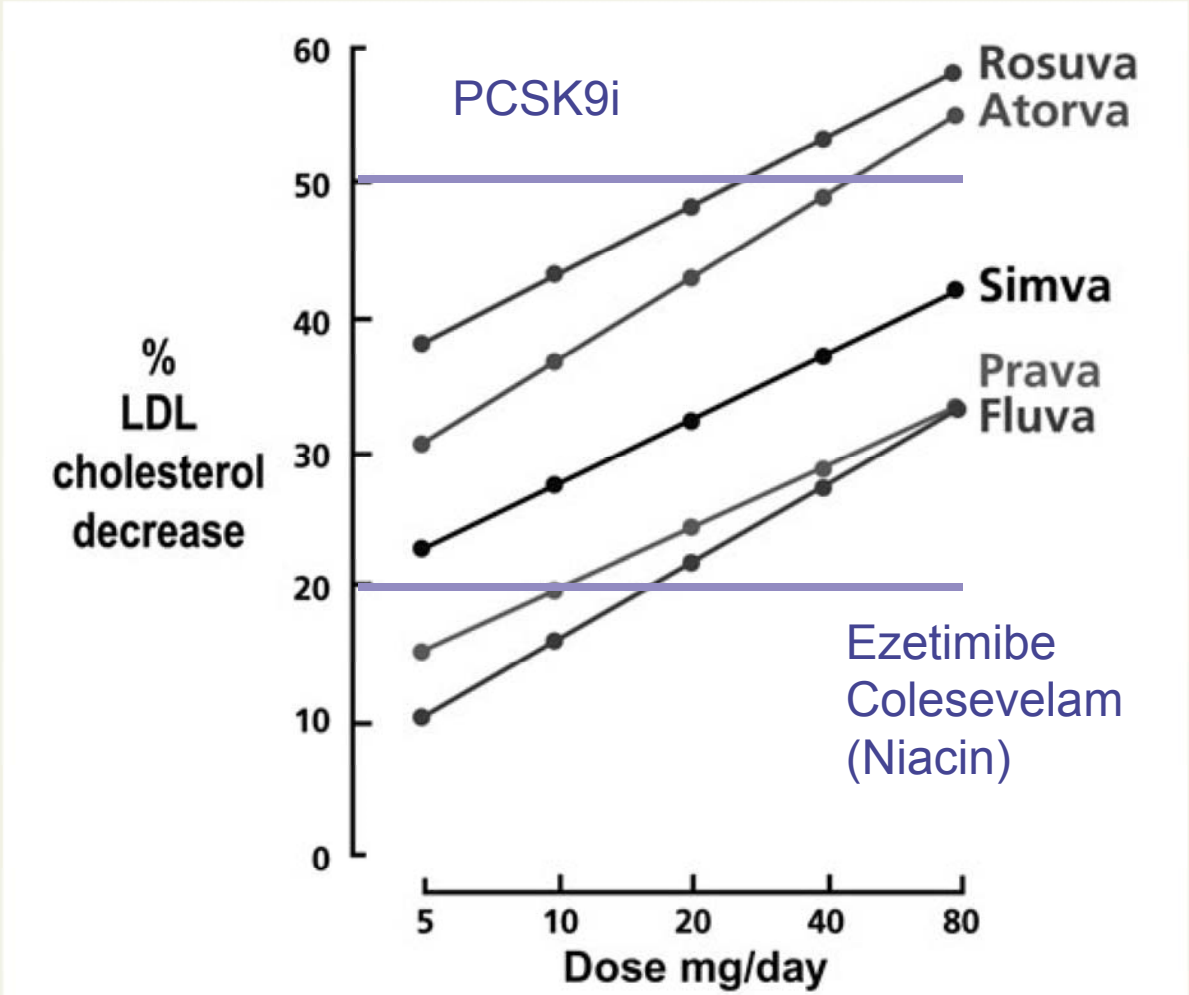
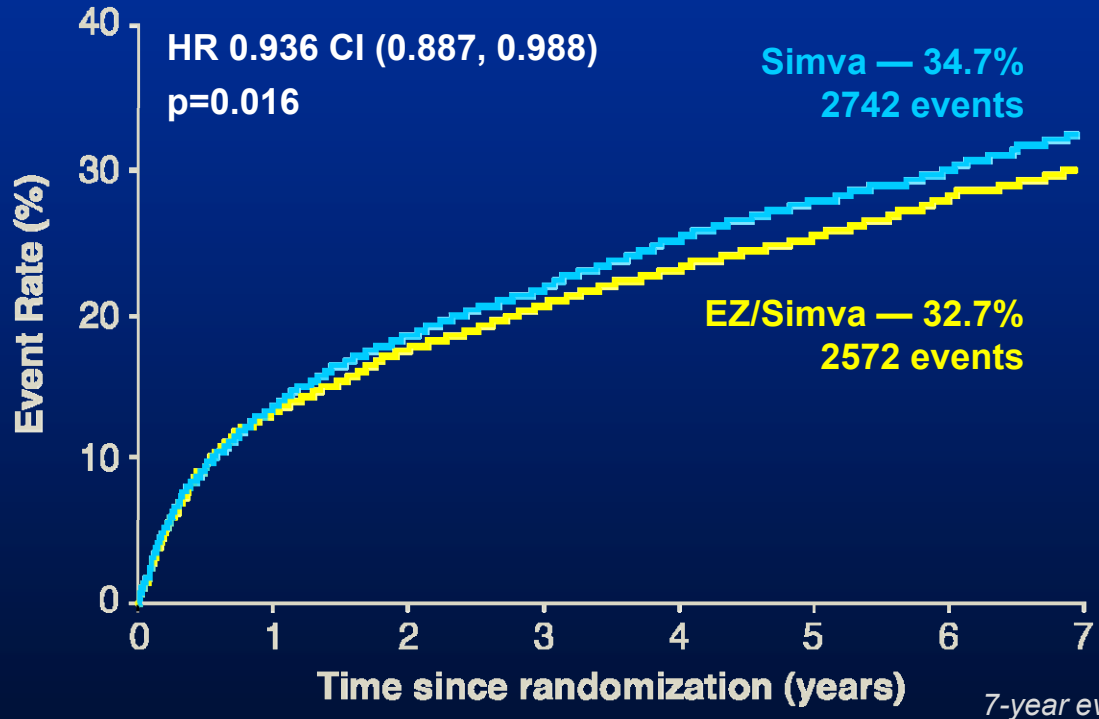


Figure 1 Statin dose as a function of percentage lowering of low-density lipoprotein (LDL) cholesterol concentration. Data from NICE clinical guideline CCG181 (table 36; p136) in Ref. 6. Atorva, atorvastatin; Fluva, fluvastatin; Prava, pravastatin; Simva, simvastatin; Rosuva, rosuvastatin.

Cholesterol, not just CV risk, is important in deciding who should receive statin treatment. Soran et al. Eur Heart J 2015; 36:2975.

Primary Endpoint — ITT

Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



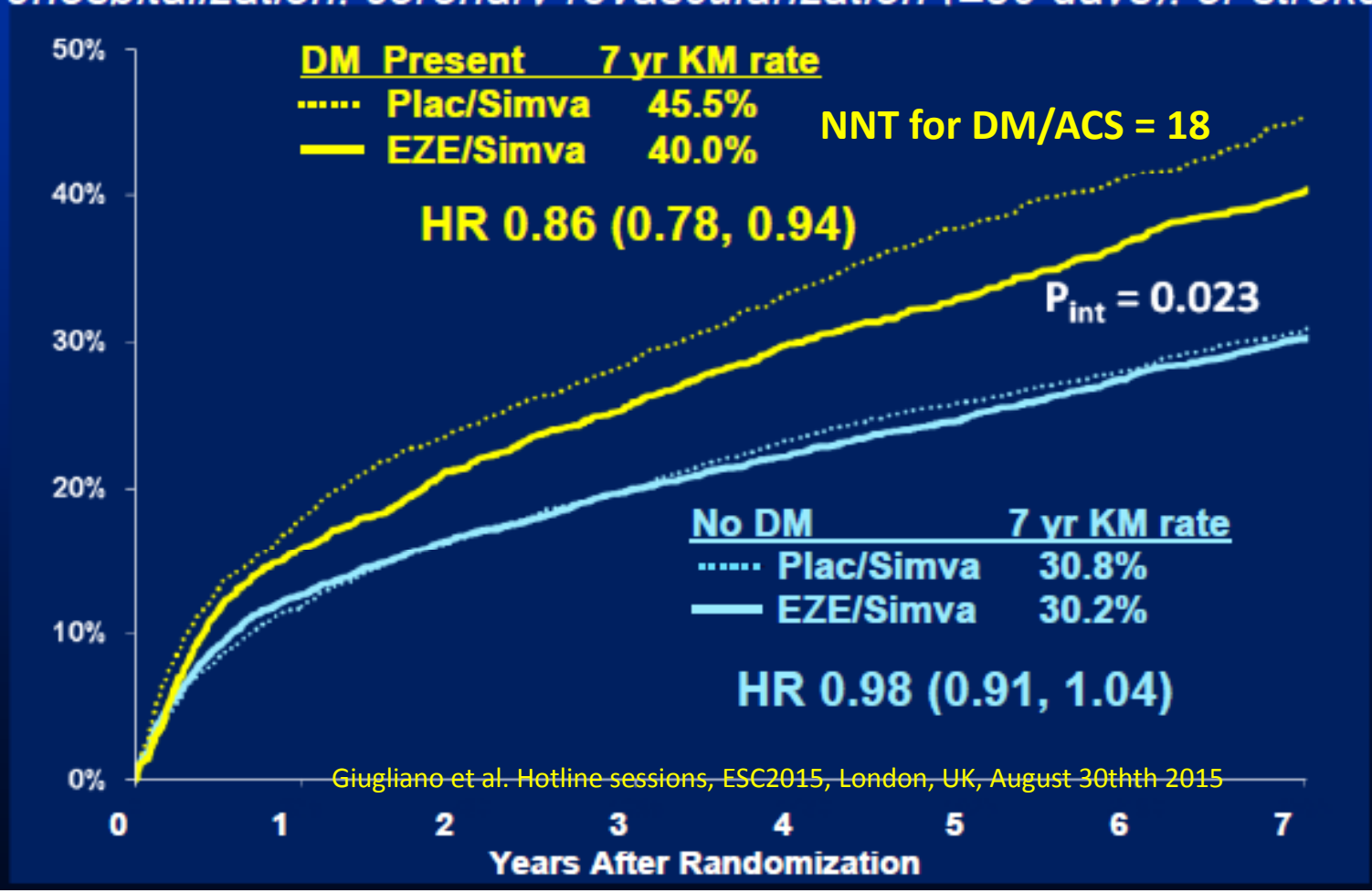
LDL-C:
1.8 vs 1.4
mmol/L

7-year event rates

Primary Endpoint — ITT

IMPROVE-IT

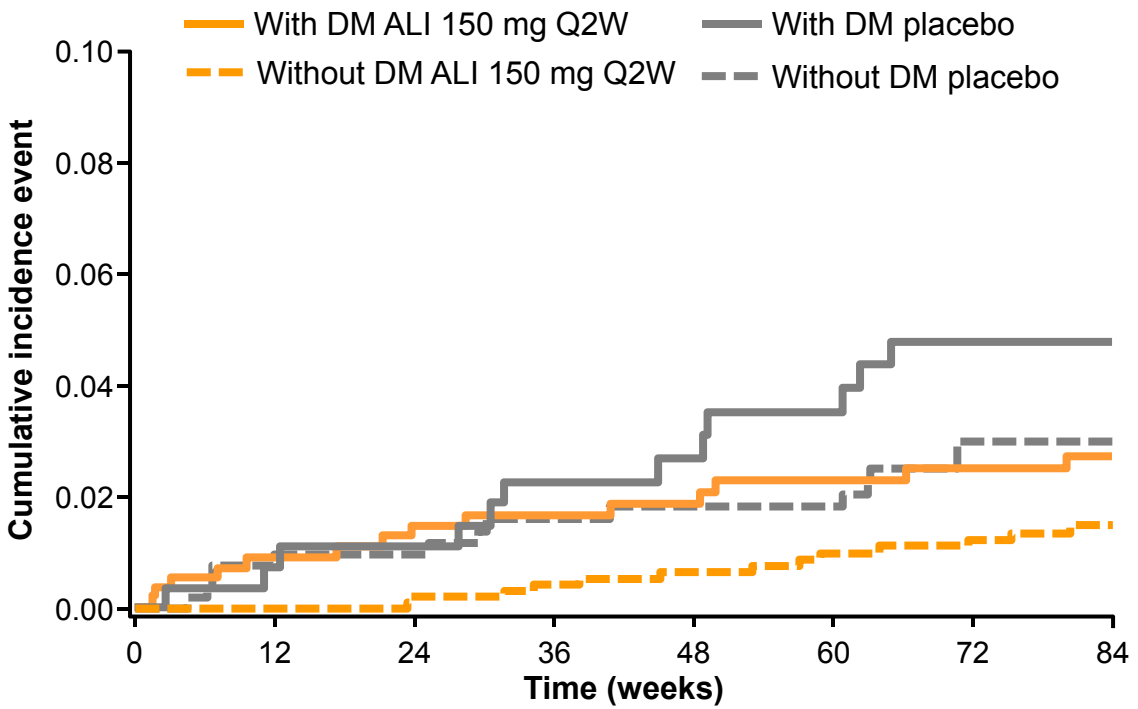
Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke



Giugliano et al. Hotline sessions, ESC2015, London, UK, August 30thth 2015

Safety analysis (LONG TERM)
Adjudicated MACE by DM Status

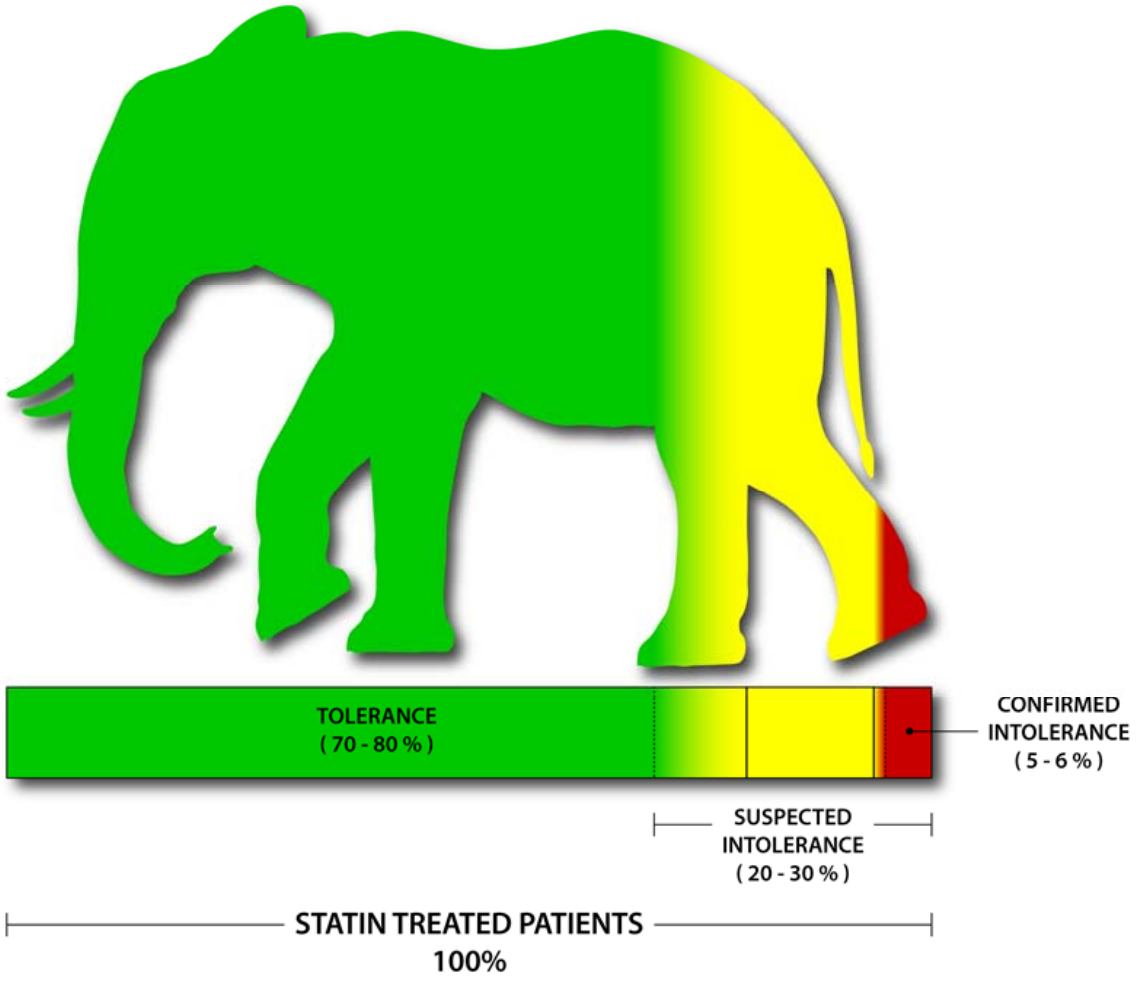
ESC 2015: Helen M. Colhoun,[1] Henry N. Ginsberg,[2] Lawrence A. Leiter,[3] Umesh Chaudhari,[4] Christelle Lorenzato,[5] Robert Pordy,[6] Jennifer G. Robinson[7]



No. at risk:

DM	Placebo	279	273	256	245	235	230	227	223
	Alirocumab	556	549	516	493	479	470	451	441
Non-DM	Placebo	509	503	475	455	440	431	418	415
	Alirocumab	994	984	929	899	871	860	835	817

Clinical Experience vs Randomized Clinical Trials:
The Elephant in the Room regarding Goal-Inhibiting Statin Intolerance (GISI)



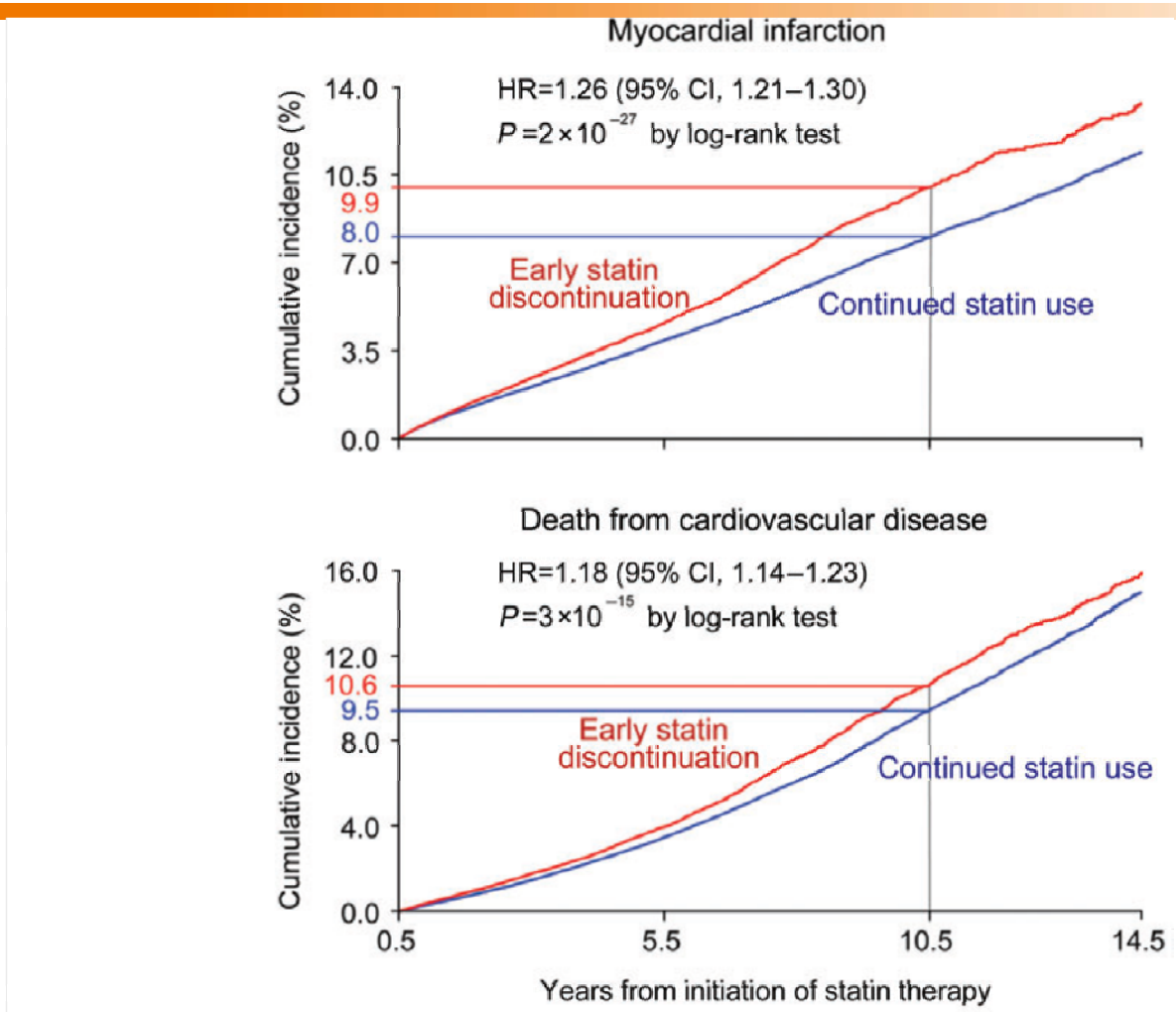
Mancini et al, DOI: http://dx.doi.org/10.1016/j.cjca.2016.01.003

GOAL-INHIBITING CONCEPT:
Intolerance vs Resistance (vs Reluctance)

- **Goal-inhibiting Statin Intolerance (GISI)**
  - A clinical syndrome
  - Characterized by significant symptoms and/or biomarker abnormalities that
  - Prevent long term, indicated use of and adherence to statins as
  - Documented by challenge/de-challenge/re-challenge, when appropriate using statins, including atorvastatin and rosuvastatin, that is
  - Not due to drug-drug interactions or untreated risk factors for intolerance (e.g. hypothyroidism), and leading to
  - Failure to maintain therapeutic goals as defined by national guidelines
- **Goal-inhibiting Statin Resistance (GISR) is present in patients who adhere to but do not achieve expected or adequate lipid lowering with tolerated and maximal doses of statins.**
- **Both groups may require combinations of lipid lowering drugs but side effects may be perceived differently.**

Mancini et al, DOI: http://dx.doi.org/10.1016/j.cjca.2016.01.003

Negative statin-related news stories decrease statin persistence and increase MI and CV Mortality: a nationwide prospective cohort study. Nielsen and Nordestgaard, Eur H J, Nov 2015



Statin Intolerance is Associated with Increased Risk for Recurrent CHD Hospitalizations: Kent et al, ACC 2016

- 79,240 Medicare beneficiaries
- Moderate to high intensity statin users (56.5% of group) vs SI-patients (statin switch to EZE, ↓statin + EZE, rhabdo, AE with d/c or ↓ statin or use of 3 different statins; 2.1% of group)

	Statin Intolerance	High Adherence	
	Incidence/1,000 pt-yrs		HR (adjusted)
Recurrent MI	41	32	1.35 (1.14-1.60)
CHD-hospitalization	53	40	1.33 (1.15-1.55)
Mortality	80	90	1.02 (0.90-1.14)

All high risk patients with residual elevation of LDL-C should be on PCSK9 inhibitors: PRO

If you follow the guidelines, you are dealing in all circumstances with NNT's in the 30's or better

Main Reasons Why I May/Will Lose This Debate

- **No RCT data (pending)**
- **Overactive imagination (extrapolation from early, very promising results)**
- **PCSK9 inhibitors are too expensive (will availability of 3 or more, and public/payor pressure change this?)**
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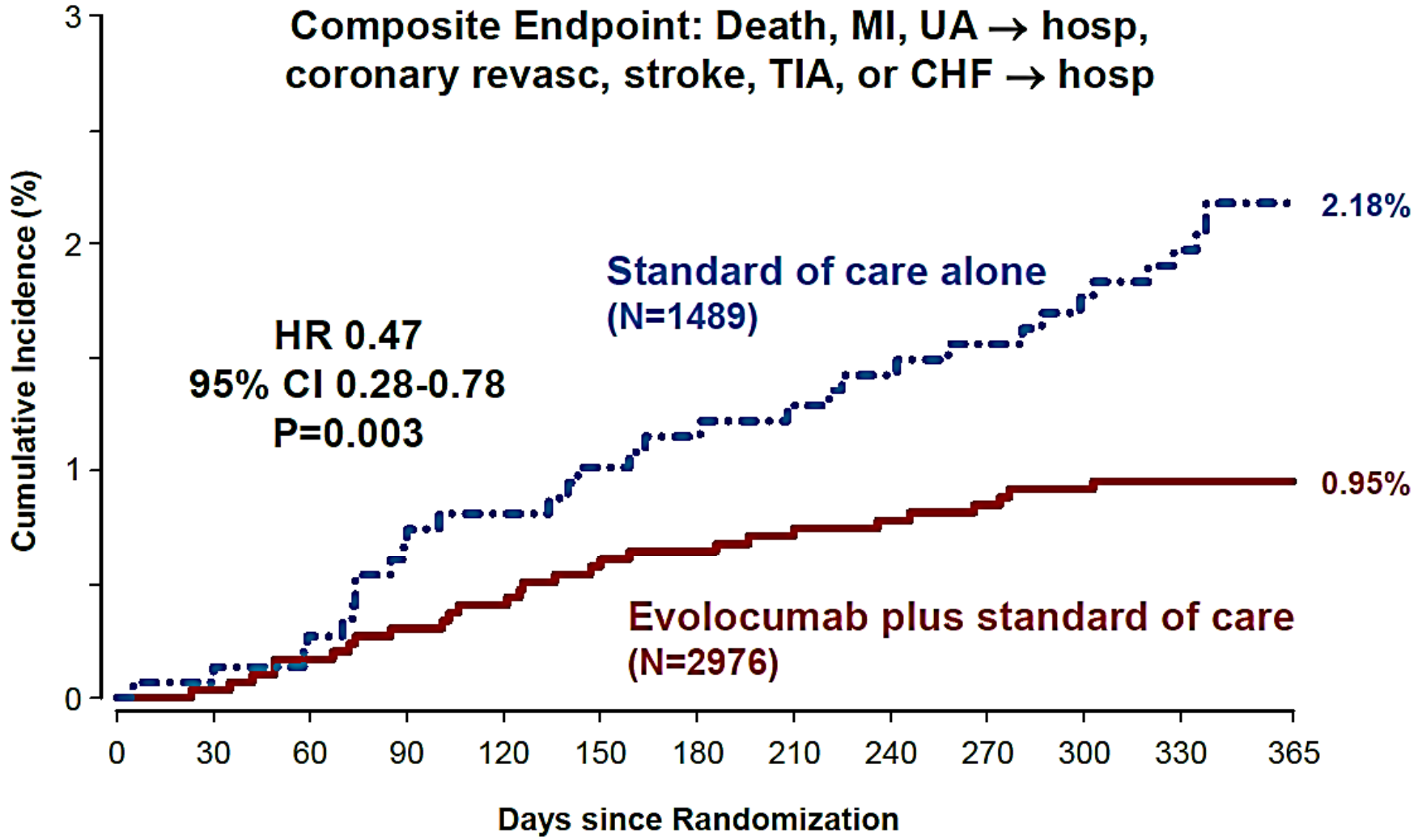
Ongoing Outcome Trials with PCSK9 Inhibitors

Study	FOURIER	ODYSSEY OUTCOMES	SPIRE-1
Treatment	Evolocumab 420 mg Q4W or 140 mg Q2W with atorvastatin Background: EZE allowed	Alirocumab 75 mg Q2W (up titrated to 150 mg Q2W if LDL > 1.3 mmol/L; down titrated if LDL < 0.65mmol/L) Background: optimized lipid lowering therapy	Bococizumab 150 mg Q2W Background: Lipid lowering therapy
Population	• Recent **MI or stroke** (≤ last 6 months) *OR* • Recent history (≤ 5 years) **MI or stroke** and either a history of T2DM or, if not diabetic, additional risks factors	Patients hospitalized for **ACS** (<12 months before randomization)	Patients at high risk of a CV event
# patients	**27,500**	**18,000**	**12,000**
LDL-C for eligibility	LDL-C ≥ 1.8 mmol/L (or non-HDL-C ≥ 2.6 mmol/L) after 4 week stabilization with atorva ± EZE	≥ 1.8 mmol/L	LDL C ≥1.8 and < 2.6 mmol/L
Est. study completion	February 2018	January 2018	August 2017

EZE = ezetimibe

Source: clinicaltrials.gov

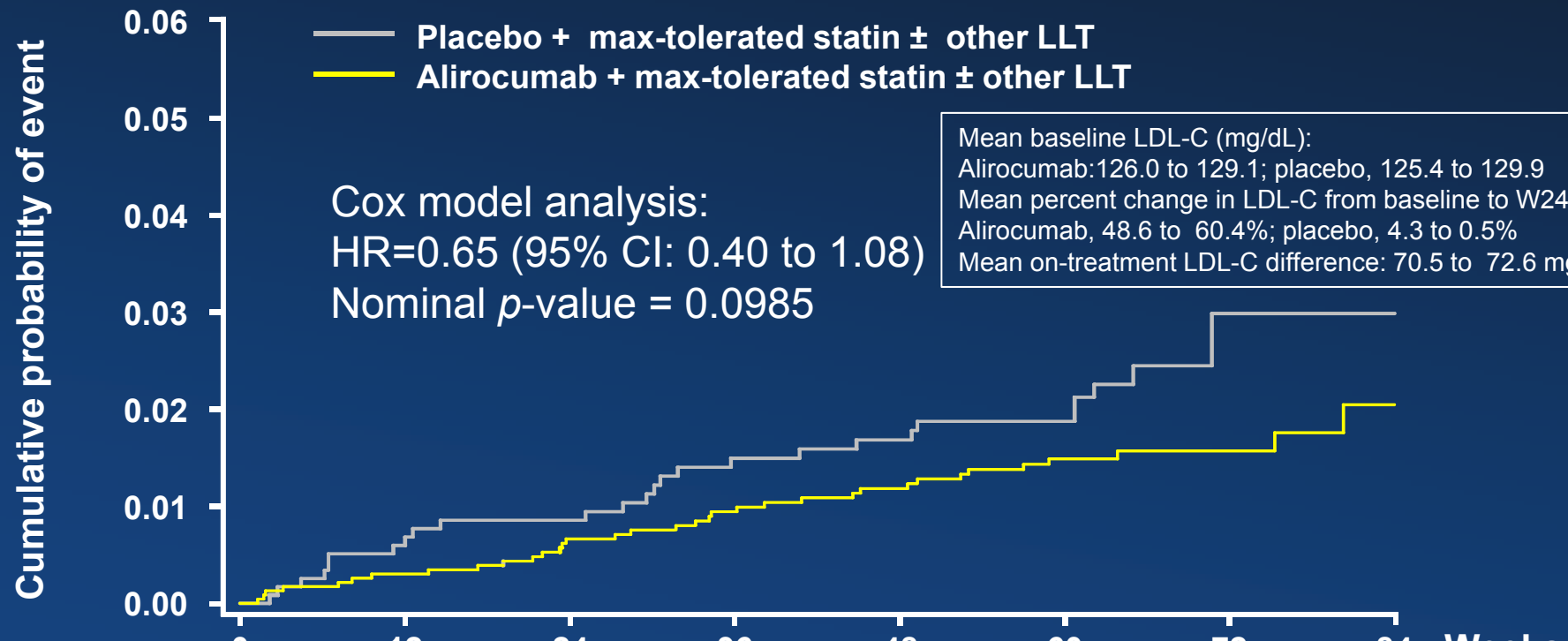
Cardiovascular Outcomes



Post-hoc Adjudicated Cardiovascular TEAEs† Pooled from Phase 3 Placebo-controlled Trials

Kaplan-Meier Estimates for Time to First Adjudicated Major CV Event

Pooled Safety Analysis from five Phase 3 placebo-controlled trials (N=3459)
(at least 52 weeks for all patients continuing treatment)



No. at Risk								
Placebo	1174	1160	1098	1057	1026	862	349	127
Alirocumab	2318	2294	2171	2087	2030	1713	698	252

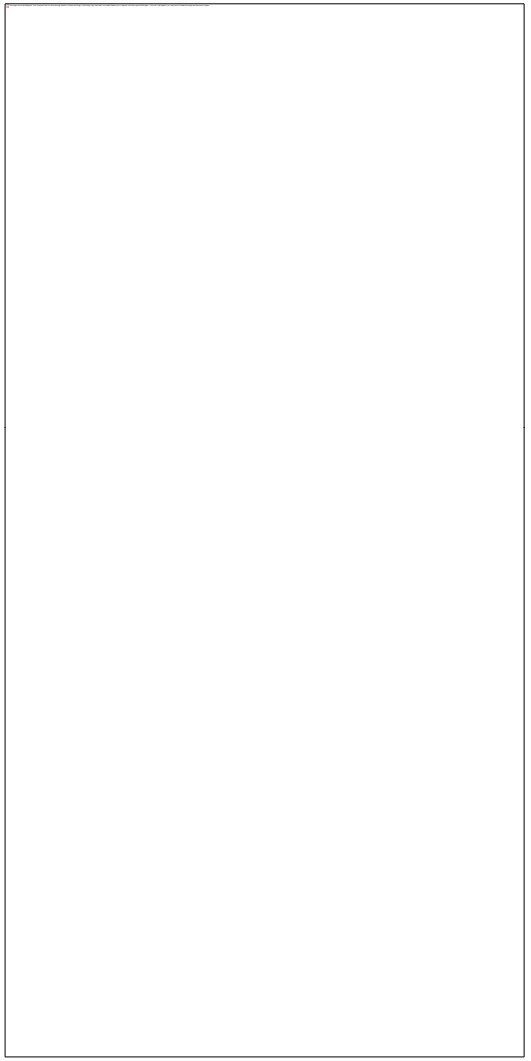
†Primary endpoint for the ODYSSEY OUTCOMES trial: CHD death, Non-fatal MI, Fatal and non-fatal ischemic stroke, Unstable angina requiring hospitalization. LLT, lipid-lowering therapy

ODYSSEY

Lipinski MJ et al: The impact of PCSK9 inhibitors on lipid levels and outcomes in patients with primary hypercholesterolemia: a network meta-analysis. Eur H J Nov 17, 2015

OR's for Placebo-controlled trials of ≥ 6 months duration			
Outcome	OR	Lower CI	Upper CI
Total Mortality	0.43	0.22	0.82
CV Mortality	0.50	0.20	1.13
MACE	0.67	0.43	1.04

17 RCT's, 13,083 patients, 2012 – 2015, 12 to 78 weeks of observation, most patients on statins



Difference between Alirocumab and Ezetimibe in % Change in LDL-C from Baseline to Week 24

Subgroup Analysis According to Patient History

Subgroup	Alirocumab (n)	Ezetimibe (n)	LS mean difference vs. placebo (95% CI)	Interaction *p*-value
History of MI				**0.68**
Yes	303	157	–30.6 (–36.2 to –24.9)	
No	164	83	–28.5 (–36.2 to –20.8)	
Total PCSK9 level				**0.33**
Below median	221	115	–32.3 (–38.8 to –25.8)	
At or above median	226	109	–27.6 (–34.2 to –20.9)	
Free PCSK9 level				**0.62**
Below median	234	101	–30.8 (–37.5 to –24.1)	
At or above median	212	123	–28.5 (–34.9 to –22.0)	
Moderate CKD				**0.79**
Yes	61	23	–27.9 (–42.2 to –13.5)	
No	406	217	–29.9 (–34.8 to –25.1)	
Diabetes				**0.85**
Yes	142	76	–30.5 (–38.8 to –22.3)	
No	325	164	–29.6 (–35.0 to –24.1)	
High-intensity statin				**0.35**
Yes	302	152	–28.2 (–33.9 to –22.5)	
No	165	88	–32.8 (–40.4 to –25.1)	

Cannon CP et al. *Eur Heart J* 2015 [epub ahead of print].

Safety summary

Including all data collected to last patient visit at Week 52

n (%) of patients All patients on background max tolerated statin	**Alirocumab** (n=479)	**Ezetimibe** (n=241)
Any TEAE	341 (71.2)	162 (67.2)
Treatment-emergent SAE	90 (18.8)	43 (17.8)
TEAE leading to death†	2 (0.4)	4 (1.7)
TEAEs leading to discontinuation	36 (7.5)	13 (5.4)
TEAEs occurring in ≥5% of patients in either group or TEAEs of interest		
Accidental overdose	30 (6.3)	16 (6.6)
Upper respiratory tract infection	31 (6.5)	14 (5.8)
Dizziness	23 (4.8)	13 (5.4)
Myalgia	21 (4.4)	12 (5.0)
Injection-site reaction	12 (2.5)	2 (0.8)
Neurocognitive disorder	4 (0.8)	3 (1.2)

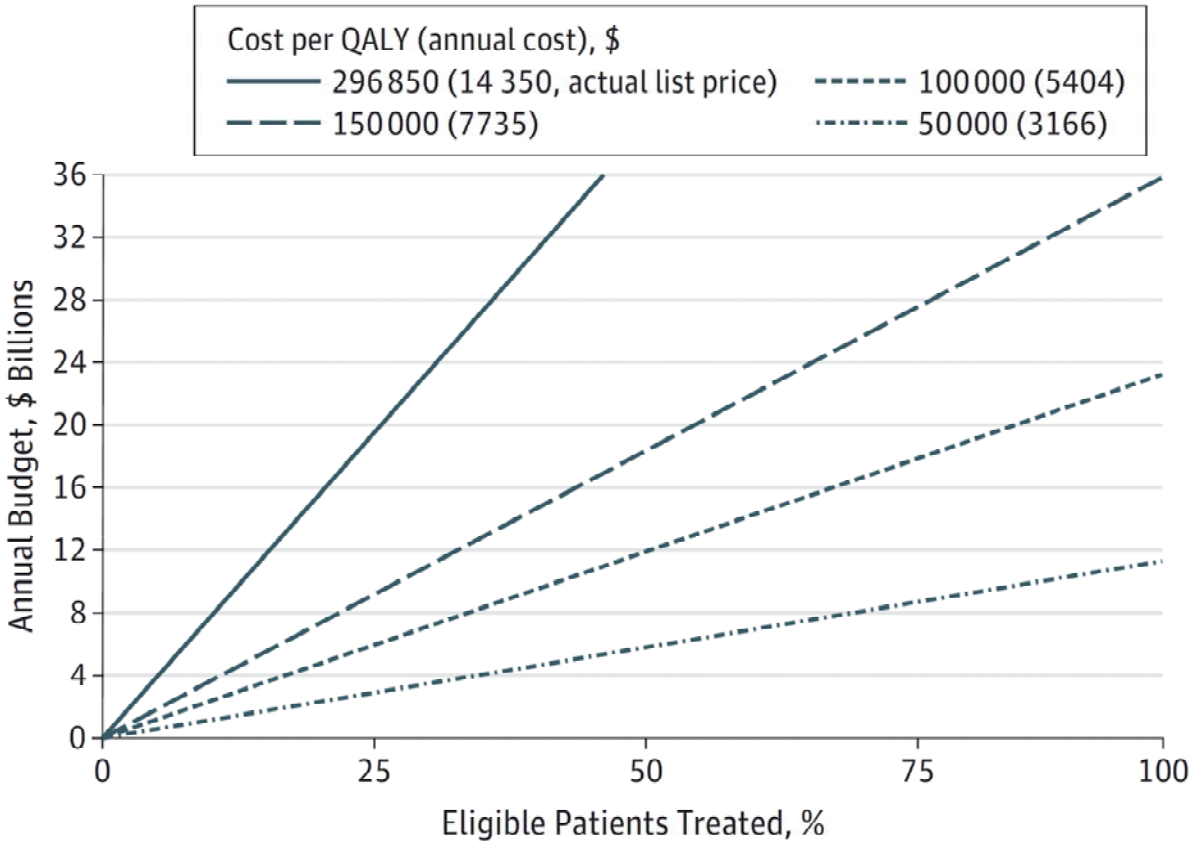
SAE, serious adverse event; TEAE, treatment-emergent adverse event

†Both deaths in the alirocumab arm were due to CV events (cardiac arrest and sudden cardiac death). Of the four deaths in the ezetimibe arm (malignant lung neoplasm, suicide, defect conduction intraventricular plus sudden cardiac death, and sudden death—one patient was counted in two categories), two were due to CV events.

Cannon CP et al. *Eur Heart J* 2015 [epub ahead of print].

PCSK9 inhibitors for treatment of high cholesterol levels. Tice et al. JAMA Int Med 2015

Figure. Cost-effectiveness Analysis of PCSK9 Inhibitor Treatment in 4 Cost Scenarios



PCSK9-directed Therapies in Development

Company	Drug	Agent	Indication	Phase
Inhibition of PCSK9 binding to LDLR				
Amgen	Evolocumab	Fully Human mAb	Hypercholesterolemia	3
Sanofi/Regeneron	Alirocumab	Fully Human mAb	Hypercholesterolemia	3
Pfizer/Rinat Neuroscience	Bococizumab	mAb	Hypercholesterolemia	3
Novartis	LGT209	mAb	Hypercholesterolemia	2
Roche/ Genentech	RG7652	mAb	Hypercholesterolemia	2
Eli-Lilly	LY3015014	mAb	Hypercholesterolemia	2
PCSK9 protein binding fragment				
BMS/ Adnexus	BMS-962476	Adnexins	Hypercholesterolemia	1
Inhibition of PCSK9 synthesis (gene silencing)				
Alnylam	ALN-PCS02	siRNA oligonucleotides	Hypercholesterolemia	2
Inhibition of PCSK9 autocatalytic processing				
Seometrix	SX-PCK9	Small peptide mimetic	Hypercholesterolemia	Preclinical
Shifa Biomedical	TBD	Small molecule	Metabolic Disorders	Preclinical
Cadila Healthcare	TBD	Small molecule		Preclinical

mAb = monoclonal antibody; CVD = cardiovascular disease

Adapted from Rhainds D, et al. Clin Lipidol. 2012;7:621-640; Lambert G, et al. J Lipid Res. 2012;53:2515-24; clinicaltrials.gov; Stein EA, Swergold GR. Curr Atheroscler Rep. 2013;15:310.

All high risk,
and all "high enough risk"
patients as identified by national guidelines,
with residual elevation of LDL should
have access to and
be on PCSK9 Inhibitors
to achieve nationally supported goals of therapy!

This is compatible with NNT's in the 30's or less!

ACC/AHA 2016 Update: Treat to Goals

(Optional soluble fibre/stanols/ sterols)	Optional Add-on	Optional Second line Add-on Medication	Optional Additional Add-on	Medications not Recomended
FH + ASCVD or other major CV risk factor	Eze	Cole Niacin	PCSK9i	
FH	Eze	Cole	PCSK9i	Niacin
ASCVD, Ischemic CHF Class II-III, Recent ACS or Stroke, recurrent ACS, ± DM	Eze	Cole	PCSK9i	Niacin
DM, Primary Prevention	Eze	Cole		Niacin, PCSK9i

In women contemplating pregnancy or who are pregnant (or breast feeding) only colesevelam is an option, no other medications are recommended.

High Enough Risk and LDL-C > 20% from goal, despite maximally tolerated statin monotherapy.

- Because of expense, ezetimibe and colesevelam may be required before access to PCSK9i is allowed
- Under these circumstances, PCSK9i may be the THIRD OR FOURTH DRUG on board
- Patients (and many physicians) will logically ask which agent can be discontinued, particularly if resultant LDL-C is perceived to be “too low.”
- Will foster pressure to stop stop statins i.e. **primacy of statin therapy is vulnerable under this step-wise approach that ignores likelihood of achieving goal with one additional agent when gap is large**.

LDL-related Residual Risk (treated but still vulnerable).

- Rhetorical question: Patient X is seen in ER for an ACS. On or off of prior statins, at what level of LDL-C (other than 0.00 mmol/L) would you NOT lower LDL-C further? At what level of LDL-C would you feel that the ACS was not influenced by LDL-C?
- Rhetorical question: Patient Y has an LDL-C of 3.5 mmol/L, is low risk, has a negative carotid US and zero CACS. At what level of LDL-C would you impart the best opportunity to remain without subclinical atherosclerosis over the long term?

Canada: Cost of Atherosclerotic CVD (ASCVD)

CV health states mean event costs

Event/Health state	Acute + Short-term Cost (Year1)	Cost for Subsequent Years	Reference
ACS	$11,104[a]	$3,629[b]	Assume that one third of ACS cost is due to UA and two thirds are due to MI [a,b]
Ischemic Stroke	$63,625	$8,942	Mittmann et al. 2012 for 1st year and Blackhouse et al. 2013 for subsequent years
HF	$18,536	$7,232	Goeree et al. 2009
Fatal CHD	$22,354 [c]	-	Assume that one third of cost of fatal CHD is due to fatal UA and two thirds are due to fatal MI [c]
Fatal HF	$24,793[d]	-	Smolderen et al. 2010
Fatal IS	$35,081[e]	-	Smolderen et al. 2010

Abbreviations: ACS, acute coronary syndrome; CV, cardiovascular; CVD, cardiovascular disease; HF, heart failure; MI,; myocardial infarction; UA, unstable angina.

a: Assume that one third of ACS cost for Year 1 is due to UA ($6,385; Goeree et al. 2009) and two thirds are due to MI ($13,463; Goeree et al. 2009).

b: Assume that one third of ACS cost for subsequent years is due to UA ($3,763; Goeree et al. 2009) and two thirds are due to MI ($3,562; Goeree et al. 2009).

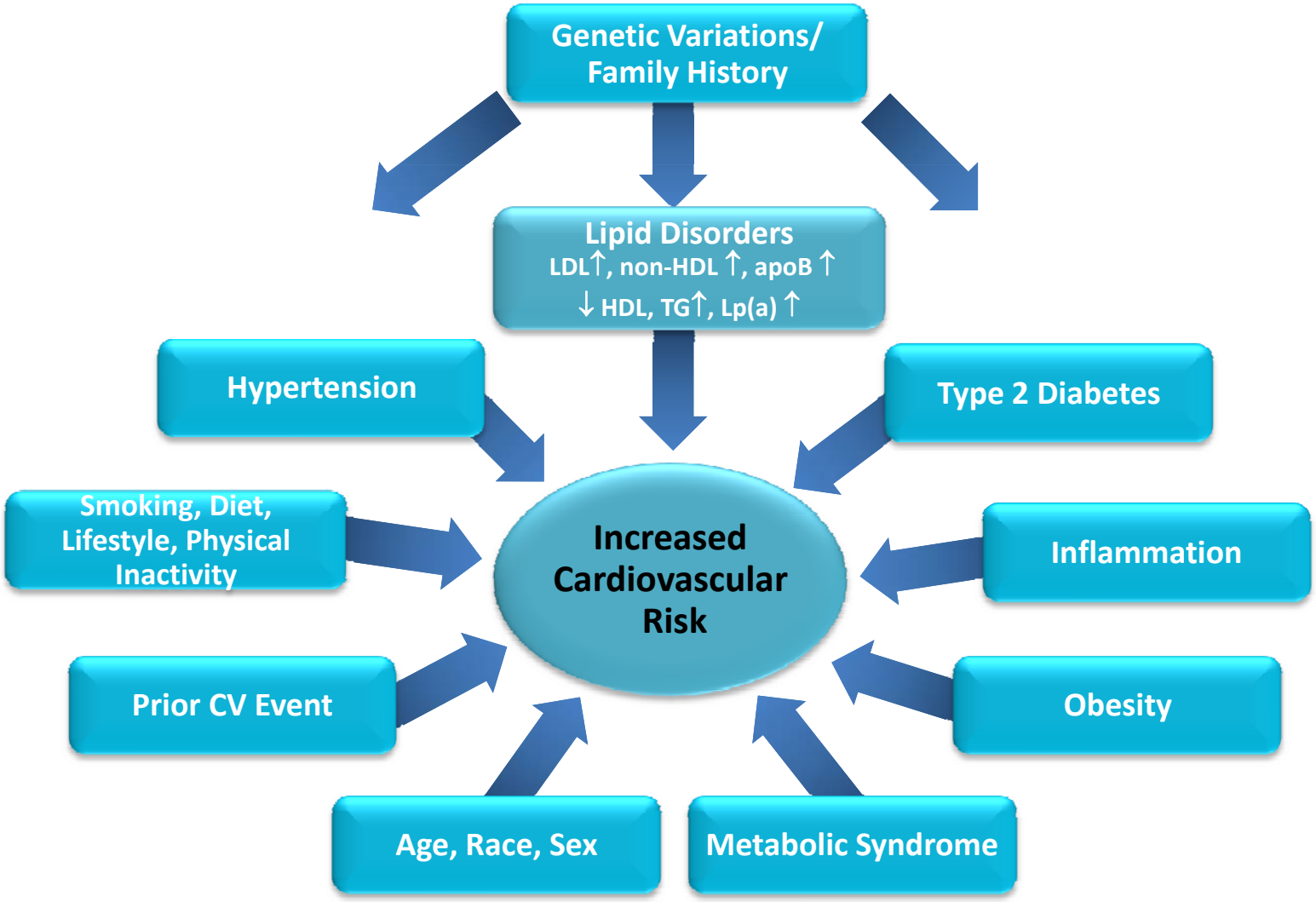
c: Assume that one third of cost of fatal CHD is due to fatal UA ($24,793 which was approximated by the cost of "other cardiovascular death"; Smolderen et al. 2010) and two thirds are due to fatal MI ($21,134; Smolderen et al. 2010).

d: Other cardiovascular death (Smolderen et al. 2010).

e: Fatal stroke (Smolderen et al. 2010).

Temporal Issues (e.g. age, duration of exposure, duration of therapy)

Multiple Factors Contribute to Increased Cardiovascular Risk



HDL = high-density lipoprotein; TG = triglycerides; LDL = low-density lipoprotein

Adapted from: National Cholesterol Education Program (NCEP). Circulation. 2002;106:3143-3421. Abifadel M, et al. In: Toth PP. The Year in Lipid Disorders. Vol. 2. Oxford, UK: Atlas Medical Publishing Ltd. 2010:3-23.