Does IMPROVE-IT & FOURIER Confirm or Refute the LDL Hypothesis?

Controversies and Advances in the
Treatment of Cardiovascular Disease
The Seventeenth in the Series
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Role of Non-statin Therapies in ASCVD

Expert Consensus Decision Pathway: 2016 to 2017 Focused Updates

Scenario	2016 ECDP	2017 ECDP
Adults ≥21 Years of Age With Clinical ASCVD, on Statin for Secondary Prevention, Baseline LDL-C 70–189 mg/d	ASCVD without comorbidities: LDL reduction ≥50%, and LDL-C <100 mg/dL (optional) ASCVD with comorbidities: LDL reduction >50%, and	All pts with ASCVD: LDL reduction ≥50%, and LDL-C <70mg/dL or non-HDL <100 (optional)
Neither Ezetimibe nor PCSK9 inhibitors are approved by FDA for ASCVD risk reduction!		
Addition of non-statin therapy in adults ≥21 Years of Age With Clinical ASCVD, on Statin for Secondary Prevention, Baseline LDL-C 70–189 mg/d	Reasonable to consider the addition of **ezetimibe** as the **initial** agent and a **PCSK9 inhibitor** as the **second** agent.	**Ezetimibe** preferred as the initial agent if <25% additional LDL ↓ required, or high-risk pts with recent ACS <3m **PCSK9 inhibitor** preferred as the initial agent if >25% additional LDL ↓ required

Lloyd-Jones, D et al. JACC 2017 DOI: 10.1016/j.jacc.2017.07.745

Role of Non-statin Therapies in ASCVD
IMPROVE-IT and FOURIER

- IMPROVE-IT (AHA 2014, NEJM 2015)
  - Ezetimibe + Simvastatin vs. Simvastatin + Placebo post-Acute Coronary Syndrome
  - PEP: Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke
  - Median f/u: 7y
- FOURIER (ACC 2017, NEJM 2017)
  - Secondary prevention with evolocumab in patients with established ASCVD
  - PEP: Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization, or stroke
  - Median f/u: 2.2y

Consumer Reports Guide
Interpreting 'Positive' ($P<\alpha$) Trials

Rank	Quality	Quantity	Benefit-Risk
★★★★★	High	• Large effect size • Statistically persuasive	B>>>R
★★★★	High	• Modest effect size • Statistically persuasive	B>>R
★★★	Modest	• Large effect size • Statistically persuasive	B>R
★★	Modest	• Small to modest effect size • Statistically not persuasive	B>R
★	Low	• Small effect size • Statistically not persuasive	B=/<R

IMPROVE-IT and FOURIER
Key Quality Attributes

Trial	Type	Blind	Power	MDD (δ)	Missing data	Prematurely d/cd
IMPROVE-IT (N=18,144)	Superiority	DB	90%	RR 0.91	11%	No
FOURIER (N=27,564)	Superiority	DB	90%	RR 0.85 (3p-MACE)	0.5%	No

DB=double blind; MDD=minimal detectable difference; β=type II error

IMPROVE-IT & FOURIER
Quantity of Evidence

Trial	Endpoint	Outcome			Substantial evidence
		RR (95% CI)	P value	Min. BF	
IMPROVE-IT (N=18,144)	-CVD, MI, Stroke, HUA, CR	0.94 (0.89, 0.99)	0.016	0.06	No
	-CVD	1.00 (0.89, 1.13)	1.000	1.000	No
FOURIER (N=27,564)	-CVD, MI, Stroke, HUA, CR	0.85 (0.79, 0.92)	<0.0001	0.00009	Yes
	-CVD, MI, Stroke	0.80 (0.73, 0.88)	<0.00001	0.00001	Yes
	-CVD	1.05 (0.88, 1.25)	0.62	0.88	No

FDA-approved label for ezetimibe does not include ASCVD risk reduction!

Consumer Reports Guide
Interpreting 'Positive' (P<α) Trials

Rank	Quality	Quantity	Benefit-Risk	Trial
★★★★★	High	• Large effect size • Statistically persuasive	B>>>R	
★★★★	High	• Modest effect size • Statistically persuasive	B>>R	- FOURIER*
★★★	Modest	• Large effect size • Statistically persuasive	B>R	
★★	Modest	• Small to modest effect size • Statistically not persuasive	B>R	- IMPROVE-IT
★	Low	• Small effect size • Statistically not persuasive	B=/<R	

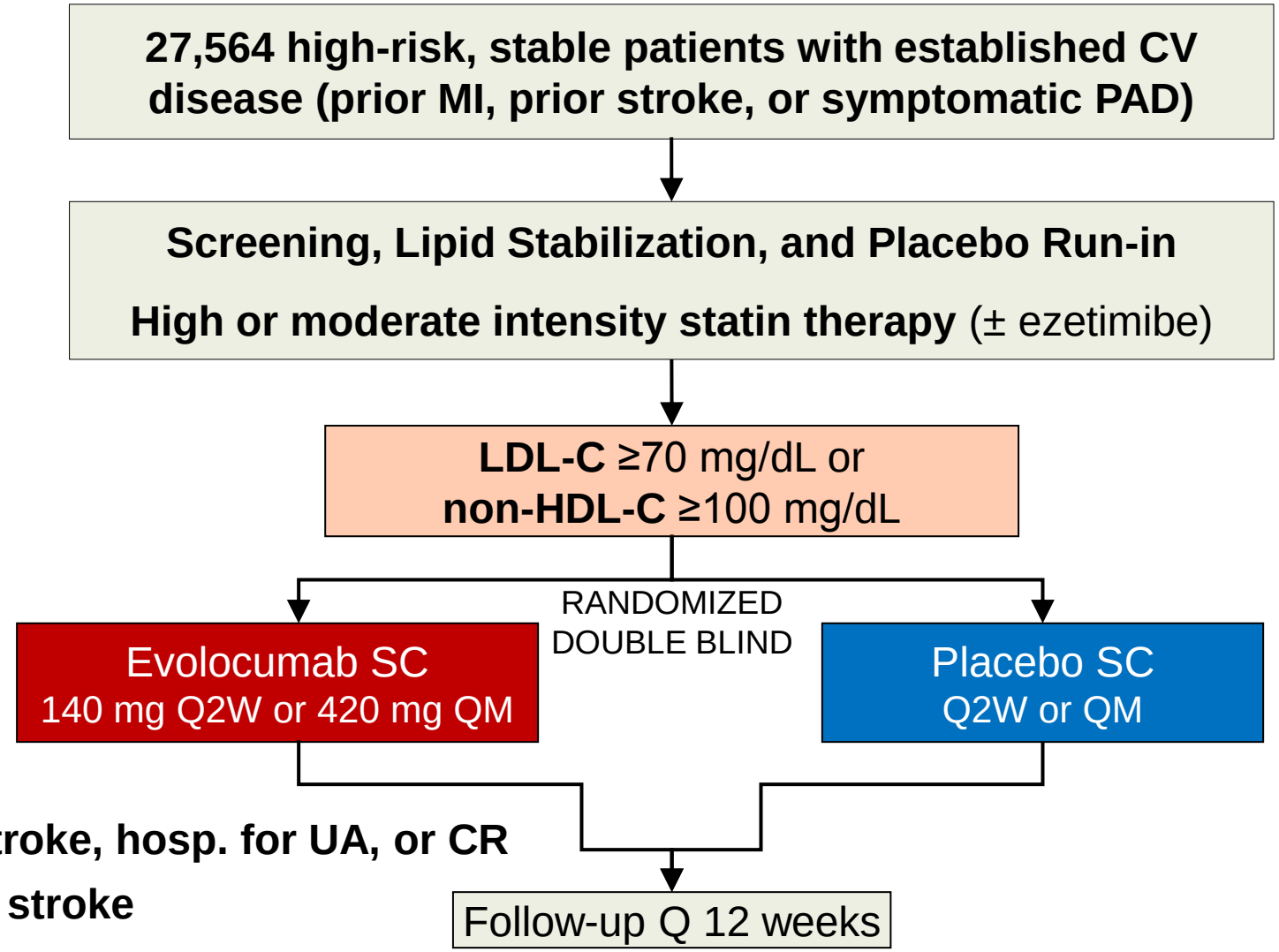
*Limited f/u to reliably assess safety

*Cost per MACE avoided over 2.2 years = $14,000 x 2.2 x 67 (NNT) = $2,063,600

CVOT With PCSK9 Inhibitors

Trial	Type	Blind	Power	MDD (δ)	Number of Events	Baseline LDL (mg/dL)	Follow-up (median)
FOURIER (N=27,564)	Evolocumab vs placebo (Superiority)	DB	90%	RR 0.85	1630	≥70	Planned: 43m Actual: 26m
SPIRE-1 (N=16,817)	Bococizumab vs placebo (Superiority)	DB	90%	HR 0.80	844	≥70	Planned: 4.8y Actual: 7m N=346 events
SPIRE-2 (N=10,621)	Bococizumab vs placebo (Superiority)	DB	90%	HR 0.75	508	≥100	Planned: 3.9y Actual: 12m N=403 events
ODYSSEY (N=18,000)	Alirocumab vs placebo (Superiority)	DB	90%	HR 0.85	1613	≥70	Planned: 2y (min) Actual:
ORION-4 (N=15,000)	Inclisiran vs placebo	DB	90%	HR 0.85	~900	≥100	Planned: 4y (min) Actual:

FOURIER
Trial Design

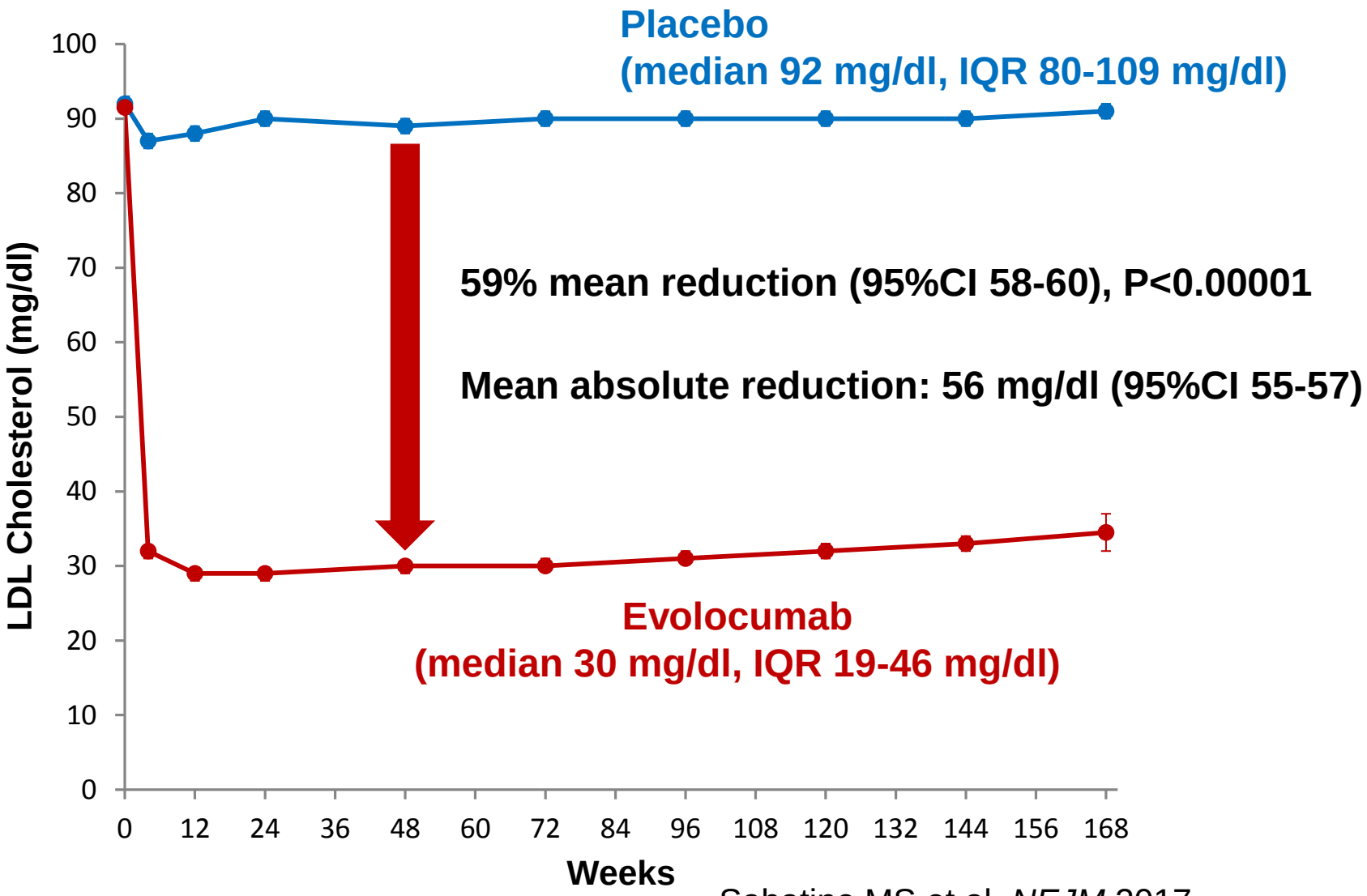


PEP: CV death, MI, stroke, hosp. for UA, or CR

SEP: CV death, MI or stroke

Sabatine MS et al. *Am Heart J* 2016;173:94-101

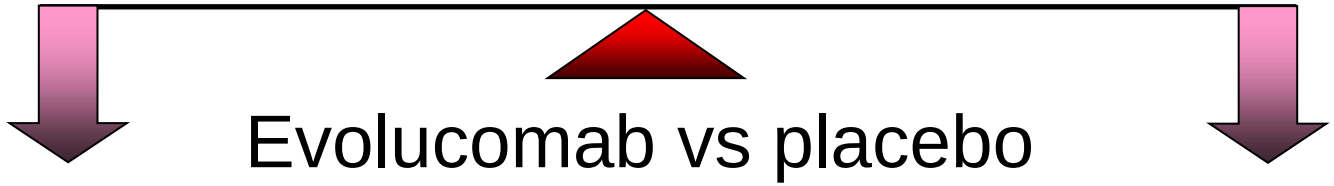
FOURIER
Impact on LDL Cholesterol



Sabatine MS et al. *NEJM* 2017

Benefit-Risk Balance of Evolocumab (FOURIER)

1000 patients treated with Evolocumab for 2.2 years



Evolucomab vs placebo

Benefit

- Prevent 15 MACE events
  - 12 fewer MIs
  - 4 fewer strokes
  - 15 fewer revascularization

? Types of MIs or strokes
55/1107 (4.97%) of MIs were fatal
64/469 (13.65%) of strokes were fatal

Harm

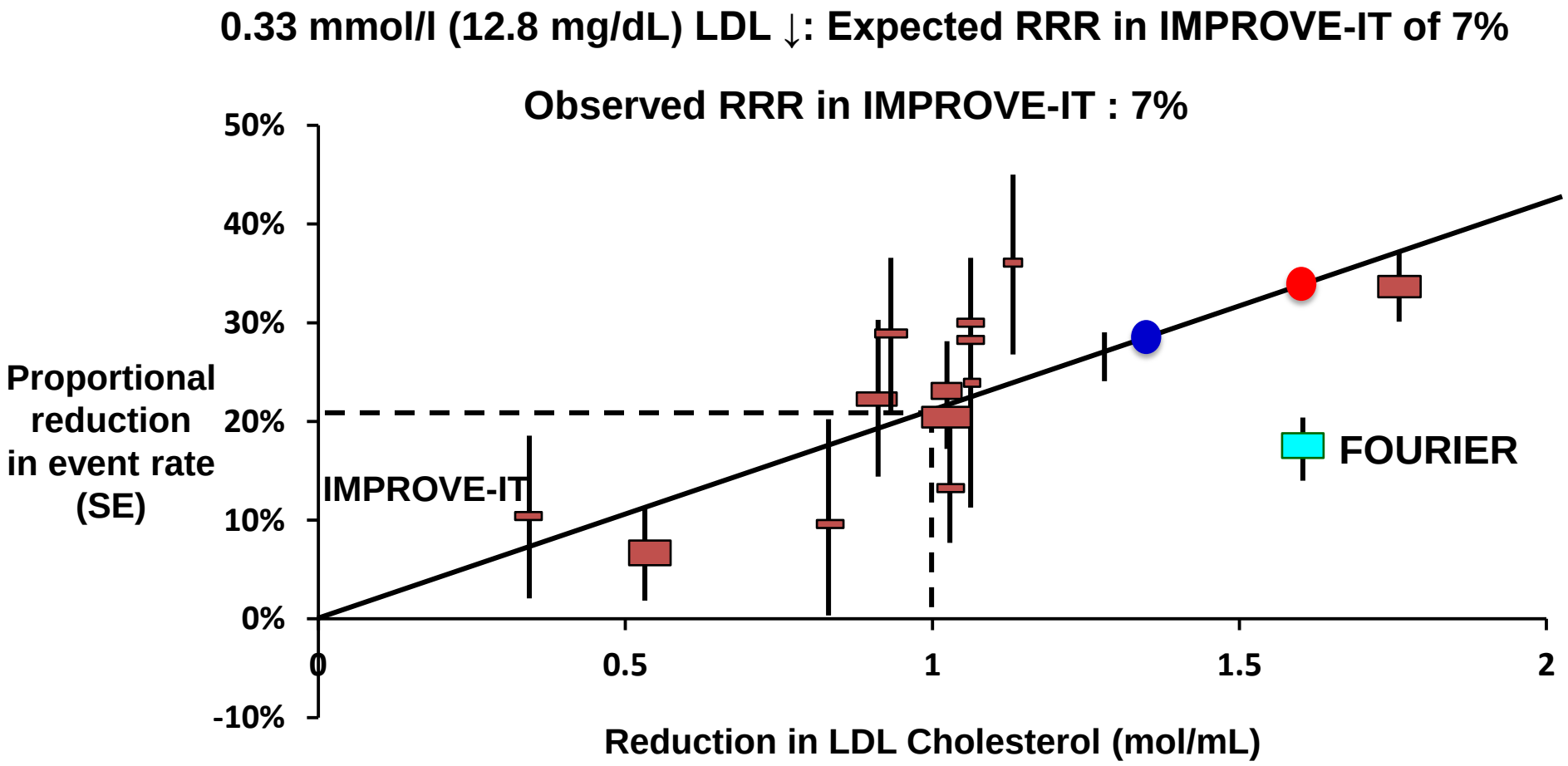
- 5 excess injection-site reaction
- No excess serious AEs
  - No excess myopathy
  - No excess neurocognitive AE
  - No excess diabetes
  - No excess abnormal LFTs
  - No excess cataract

CVOT With PCSK9 Inhibitors

Trial	Endpoint	Outcome		Median LDL-C (mg/dL)		% mean LDL, Δ
		RR (95% CI)	P value	Pre-Rx	Post-Rx	
FOURIER (N=27,564)	-CVD, MI, Stroke, HUA, CR -CVD, MI, Stroke -CVD	0.85 (0.79, 0.92) 0.80 (0.73, 0.88) 1.05 (0.88, 1.25)	<0.0001 <0.00001 0.62	92 (2.4mmol)	30 (48 wk) (0.78mmol)	-59 (48 wk) (1.62mmol)
SPIRE-1 (N=16,817)	-CVD, MI, Stroke, HUA (UR) -CVD, MI, Stroke -CVD	0.99 (0.80, 1.22) 1.03 (0.82, 1.30) 1.20 (0.74, 1.95)	0.94 0.78 0.46	94	39 (14 wk) 46 (52 wk)	-61 (14 wk) -52 (52 wk)
SPIRE-2 (N=10,621)	-CVD, MI, Stroke, HUA (UR) -CVD, MI, Stroke -CVD	0.79 (0.65, 0.97) 0.74 (0.60, 0.92) 0.82 (0.50, 1.36)	0.02 0.007 0.45	133	60 (14 wk) 77 (52 wk)	-57 (14 wk) -43 (52 wk)
ODYSSEY (N=18,000)	-CVD, MI, Stroke, HUA -CHD, HUA, ID-CR -ACM	NR	NR	NR	NR	NR

- Null effects in SPIRE-1, thereby refuting LDL hypothesis suggested by CTTC meta-analysis
- Bococizumab program terminated due to neutralizing antibodies attenuating LDL lowering

Meta-Analysis of Statin Trials: 1 mmol/L Reduction in LDL-C Associated with 22% RRR in Major Vascular Events (CTTC)



Proportion risk reduction in IMPROVE-IT aligned with CTTC meta-analysis!

CVOT With Ezetimibe (IMPROVE-IT)
Relation of Outcome Benefit and LDL Reduction

LDL-C reduction in IMPROVE-IT: **16.8 mg/dL** (1yr), or **12.8 mg/dL** (1 yr with imputed values for missing data)

Outcome	CTTC MA Effects (RR/mmol/L LDL ↓)	Observed effect In IMPROVE-IT	Observed effect in IMPROVE-IT* (RR/mmol/L LDL ↓)	Observed effect in IMPROVE-IT** (RR/mmol/L LDL ↓)
CTTC-EP	0.78 (0.76-0.80)	0.93 (0.88, 0.98)	0.86	0.82
All-cause death	0.90 (0.87-0.93)	0.99 (0.91, 1.07)	0.98	0.97
CV death	0.86 (0.82-0.90)	1.00 (0.89, 1.13)	1.00	0.97
Nonfatal MI	0.73 (0.70-0.77)	0.87 (0.80, 0.95)	0.70	0.61
Total Stroke	0.84 (0.79-0.89)	0.86 (0.73, 1.00)	0.68	0.58
CABG/PCI	0.75 (0.72-0.79)	0.95 (0.89, 1.01)	0.88	0.85

Based on LDL-C reduction of * 16.8 mg/dL or **12.8 mg/dL (imputed values at 1yr) and the relative risks for clinical events per 1 mmol/L reduction estimated by the Cholesterol Treatment Trialists' Collaboration (CTTC, Lancet 2010)
CTTC composite endpoint: coronary heart death, nonfatal MI, stroke, or coronary revascularization

Observed effects in IMPROVE-IT not consistently predicted by CTTC MA!

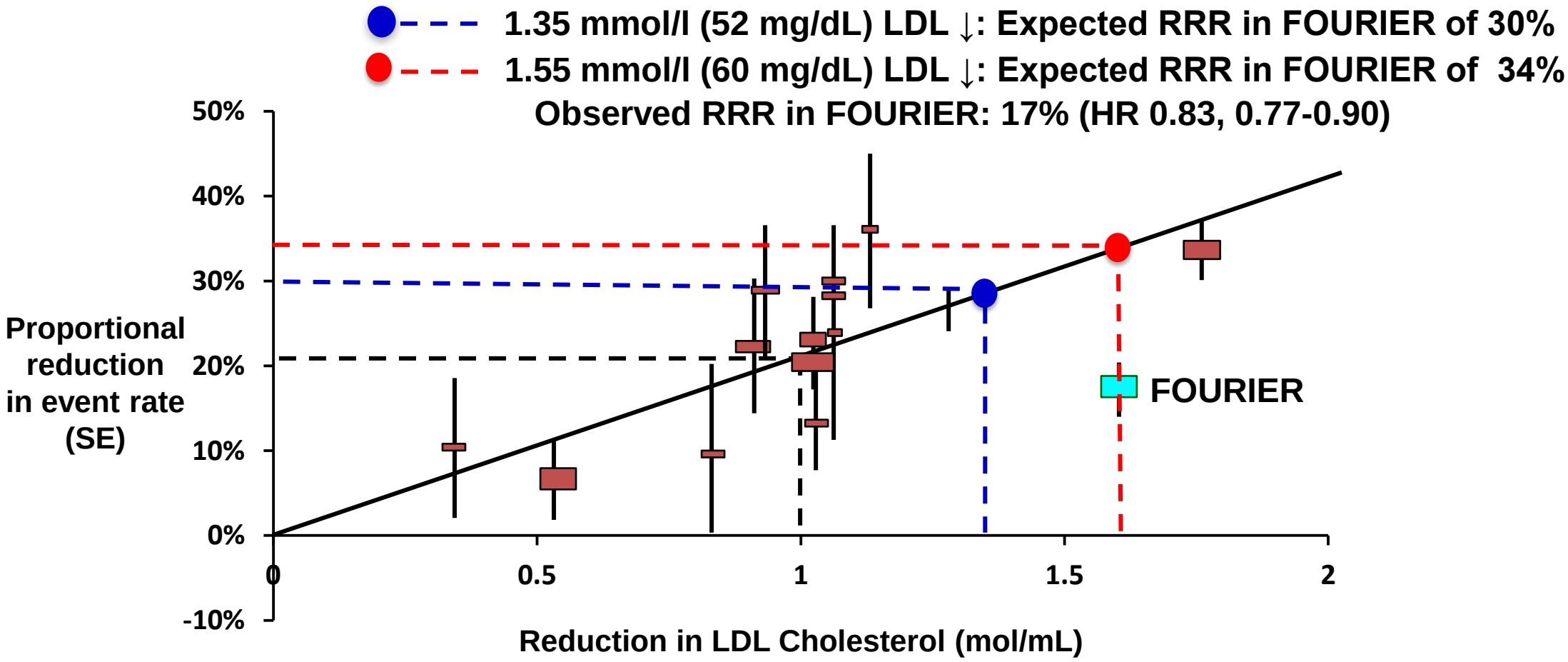
Validation of the LDL Hypothesis by IMPROVE-IT
Treatment Effects in Subgroups

Cohort	Δ LDL-c, mg/dL (% D)	Placebo N (KM %, 7y)	Ezetimibe N (KM %, 7y)	HR (95% CI)	P value	P interaction
Diabetes, Yes (N=4,933)	-15.8 (-19%)	949 (45.51%)	824 (40.04%)	0.86 (0.78, 0.94)	0.001	0.021
Diabetes, No (N=13,202)	-13.6 (-14.9%)	1792 (30.84%)	1748 (30.16%)	0.98 (0.91, 1.04)	0.48	
Age ≥75 years (N=2,798)	-13.6 (-16%)	563 (47.60%)	454 (38.95%)	0.80 (0.70, 0.90)	0.0003	0.005
Age <75 years (N=15,346)	-14.3 (-15.9%)	2179 (32.46%)	2118 (31.67%)	0.97 (0.91, 1.03)	0.35	

Changes in LDL-c are baseline minus time-weighted average LDL-C levels.
% change in LDL-c are shown in parentheses.
Interaction P values are not adjusted for multiple comparisons.

A Clear Verdict or Probable Grounds for Appeal?

Meta-Analysis of Statin Trials: 1 mmol/L Reduction in LDL-C Associated with 22% RRR in Major Vascular Events (CTTC)



Proportion risk reduction in FOURIER about half that predicted by CTTC meta-analysis!

CVOT With PCSK9 Inhibitor (FOURIER)
Relation of Outcome Benefit and LDL Reduction

LDL-C reduction in FOURIER: 1.62 mmol/L or 62mg/dL (median), 1.45 mmol/L or 58 mg/dL (mean); 1.35 mmol/L or 52 mg/dL (mean with imputed values for missing data)

Outcome	CTTC MA Effects (RR/1mmol/L LDL ↓)	Expected effect based on CTTC MA* (1.35mmol/L LDL ↓)	Observed effect in FOURIER (HR)
CTTC composite EP	0.78 (0.76-0.80)	0.70 (0.68-0.73)	0.83 (0.77-0.90)
All-cause death	0.90 (0.87-0.93)	0.86 (0.84-0.91)	1.04 (0.91-1.19)
CV death	0.86 (0.82-0.90)	0.81 (0.76-0.86)	1.05 (0.88-1.25)
MI	0.73 (0.70-0.77)	0.64 (0.60-0.69)	0.73 (0.65-0.82)
Stroke	0.84 (0.79-0.89)	0.78 (0.72-0.85)	0.79 (0.66-0.95)
Unstable angina	NR	NR	0.99 (0.82-1.18)
Revascularization	0.75 (0.72-0.79)	0.66 (0.62-0.72)	0.78 (0.71-0.86)

*Based on LDL-C reduction of 52 mg/dL (1.35 mmol/L with imputed values for missing data) and the relative risks for clinical events per 1 mmol/L reduction estimated by the Cholesterol Treatment Trialists' Collaboration (CTTC, Lancet 2010)
CTTC composite endpoint: coronary heart death, nonfatal MI, stroke, or coronary revascularization

Observed effects in FOURIER (except for stroke) lower than predicted by CTTC meta-analysis!

CVOT With PCSK9 Inhibitor (FOURIER)
Relation of Outcome Benefit and LDL Reduction

LDL-C reduction: 1.62 mmol/L or 62mg/dL (median), 1.45 mmol/L or 58 mg/dL (mean); 1.35 mmol/L or 52 mg/dL (mean with imputed values for missing data)
CTT Meta-analysis: Mean LDL ↓ of 1mmol = 22% RRR in MVE (RR 0.78, 0.76-0.80)

Outcome	Expected effect based on CTTC MA (RR)* (1.35mmol/L LDL ↓)	Expected effect based on CTTC MA (RR)** (1.55mmol/L LDL ↓)	Observed effect in FOURIER (HR)
CTTC composite EP	0.70 (0.68-0.73)	0.66 (0.63-0.69)	0.83 (0.77-0.90)
All-cause death	0.86 (0.84-0.91)	0.86 (0.81-0.89)	1.04 (0.91-1.19)
CV death	0.81 (0.76-0.86)	0.81 (0.75-0.86)	1.05 (0.88-1.25)
MI	0.64 (0.60-0.69)	0.58 (0.52-0.66)	0.73 (0.65-0.82)
Stroke	0.78 (0.72-0.85)	0.75 (0.67-0.93)	0.79 (0.66-0.95)
Unstable angina	NR	NR	0.99 (0.82-1.18)
Revascularization	0.66 (0.62-0.72)	0.61 (0.57-0.66)	0.78 (0.71-0.86)

Based on LDL-C reduction of 52 mg/dL (1.35 mmol/L with imputed values for missing data)* or 60 mg/dL (1.55 mmol/L)** and the relative risks for clinical events per 1 mmol/L reduction estimated by the Cholesterol Treatment Trialists' Collaboration (CTTC, Lancet 2010); CTTC composite endpoint: coronary heart death, nonfatal MI, stroke, or coronary revascularization

Observed effects in FOURIER (except for stroke) lower than predicted by CTTC meta-analysis!

CVOT With PCSK9 Inhibitor (FOURIER)
Relation of Outcome Benefit and LDL Reduction

LDL-C reduction in FOURIER: 1.62 mmol/L or 62mg/dL (median), 1.45 mmol/L or 58 mg/dL (mean); 1.35 mmol/L or 52 mg/dL (mean with imputed values for missing data)

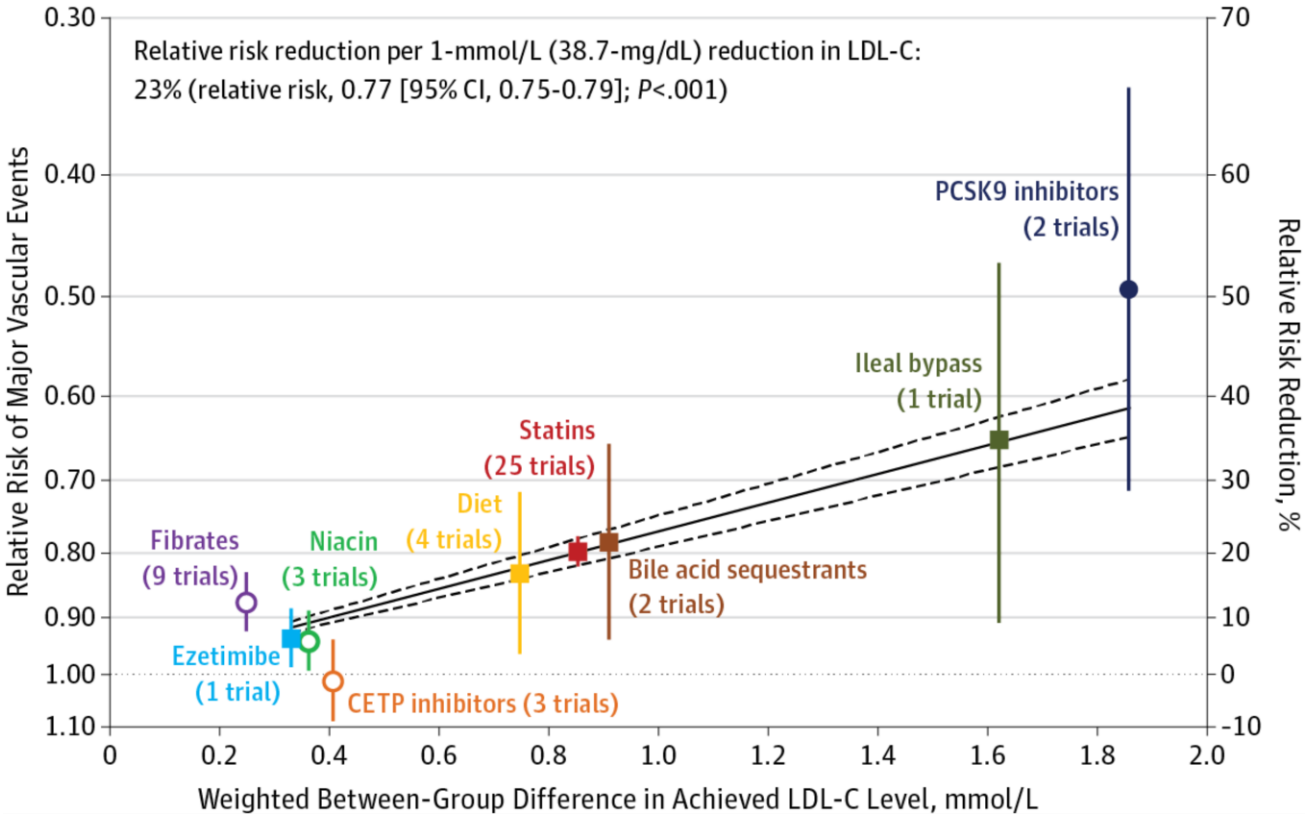
Outcome	*Earlier MA Effects (RR/1mmol/L LDL ↓)	Expected effect based on Earlier MA*	Observed effect in FOURIER (HR)
All-cause death	0.45 (0.23-0.86)	0.48 (0.27-0.85)	1.04 (0.91-1.19)
CV death	0.50 (0.23-1.10)	0.49 (0.23-1.07)	1.05 (0.88-1.25)
MI	0.49 (0.26-0.93)	0.49 (0.26-0.93)	0.73 (0.65-0.82)
Stroke	NR	NR	0.79 (0.66-0.95)
Unstable angina	0.61 (0.06-6.14)	0.51 (0.05-4.86)	0.99 (0.82-1.18)
Revascularization	NR	NR	0.78 (0.71-0.86)

*Navarese EP, et al. *Ann Intern Med.* 2015. 24 trials (17: <6m, 2: 6-12m, 4: >1y), n=10159 LDL-C ↓ with PCSK9i: -47%

Observed effects in FOURIER substantially lower than predicted by earlier meta-analysis of 24 trials!

Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions

A Systematic Review and Meta-analysis



MVE: cardiovascular death, acute myocardial infarction or other acute coronary syndrome, coronary revascularization, or stroke, when available

PCSK9 Trials

No. of Trials = 2 (ODYSSEY, OSLER)

Number of pts: 6806

Mean F/U = 1.2 yrs

Δ, LDL-C: 1.86 mmol/L

MVE, n=111

Pooled RR: 0.49 (0.34, 0.71)

Pooled RR/mmol LDL: 0.74 (0.62, 0.82)

FOURIER RR/mmol LDL @1y: 0.90 (0.84-0.98)

(LDL ↓ = 1.35 mmol/L)

FOURIER RR/mmol LDL @1y: 0.92 (0.86-0.98)

(LDL ↓ = 1.62 mmol/L)

Observed effects in FOURIER lower than predicted by pooled analysis of ODYSSEY and OSLER

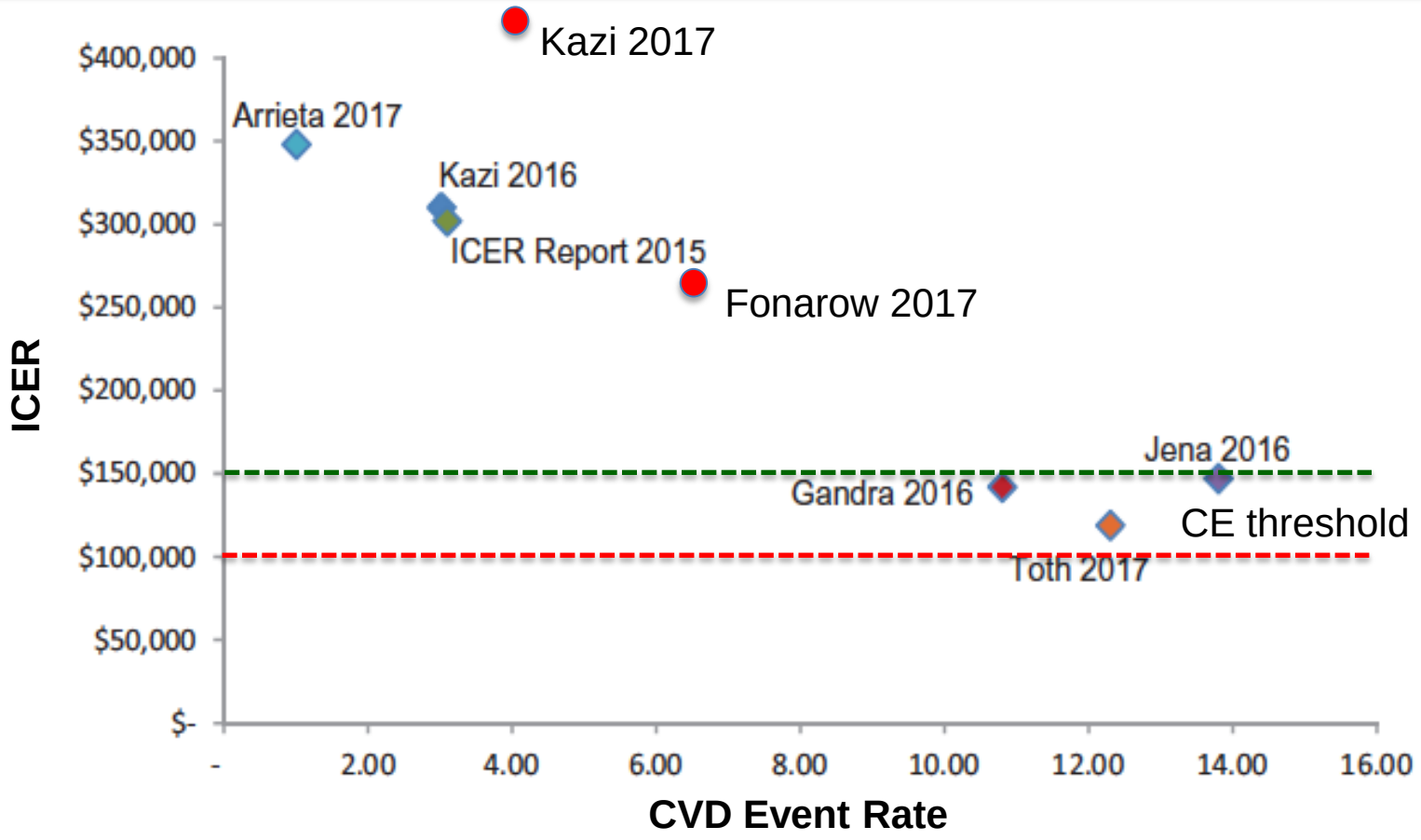
JAMA. 2016;316:1289-1297. doi:10.1001/jama.2016.13985

Do PCSK-9 Inhibitors Provide Value?
Modeling Exercises or Realistic Expectations!

Variable	ICER	Kazi 2016	Kazi 2017	Fonarow 2017
CVD risk reduction	Assumed benefit based on CTT Meta-analysis, etc	Assumed benefit based on CTT Meta-analysis, etc	Based on FOURIER	Based on FOURIER
ICER ($/QALY)	- $290,000 (FH) - $274,000 (ASCVD, SI) - $302,000 (ASCVD, LDL>70)	- $503,000 (FH) - $414,000 (ASCVD)	- $450,000 - $1,795,000 (no mortality benefit)	- $268,637 (CV event=6.4/100PY) - $413,579 (CV event = 4.2/100PY)
Discount to meet CE threshold (WTP)	- 60-63%; $5300-5700 ($100K) - 42-47%; $7600-8300 ($150K) - $2177; 85% (VBP)	68%; $4536 ($100K)	71%; <$4125 ($100K)	- 48%; $7623 ($100K) - 43%; $9669 ($150K)

Cost per MACE avoided over 2.2 years = $14,542 (annual cost) x 2.2 (yrs) x 67 (NNT) = $2,143,491

Why Published Studies of Cost-effectiveness of PCSK-9 inhibitors Yield such Markedly Different Results?



Inverse relation between ICER and baseline CVD event rate

Key determinants:

1. CVD event rate

- RWD (observational, administrative database) vs RCT or FR model
- First vs recurrent events
- Hard (MACE) vs soft (MACE + UA + CR) events

2. CVD risk reduction and utility

- CTT meta-analysis 22% RRR in fatal/ nonfatal CVE per 1mmol/L LDL ↓ vs RCT data (15-20% RRR in nonfatal CVE)

3. Price discount

- CE threshold met at >70% discount

4. Sponsor (usually favorable) vs independent (not favorable)

Adapted from Toth et al. J of Medical Economics 2017;20:749-751

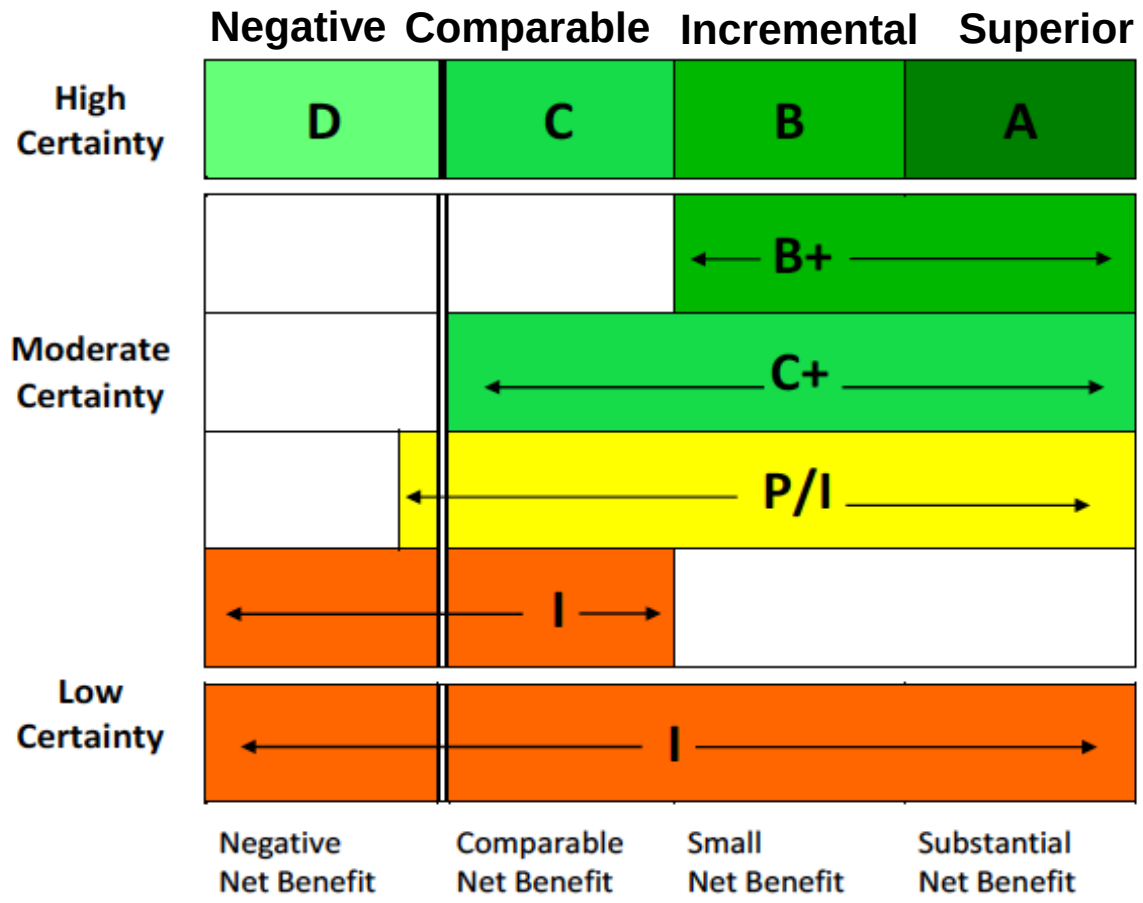
Outcomes-Based Pricing
The Illusion of Money-Back Guarantee

Events = PEP of FOURIER (CVD, MI, Stroke, hospitalization for USAP, coronary revascularization)
Placebo annual event rate: 5.2% (11.3%/2.2)
Treatment effect with PCSK9i = 15% RRR
Cost of PCSK9i= $14.5K per year
For every 1000 patients, 52 will develop CV events without PCSK9i at 1 year
Events prevented by PCSK9i = 52 x 0.15 = 8 per 1000
Events occurring on PCSK9i= 44 per 1000
Cost of treating 1000 patients on PCSK91=$14.5K x 1000 = $14.5M
Refund for 44 events occurring on PCSK9i = $14.5K x 44 = $638,000
% refund = $638,000/$14,500,500 = 4.4%
Number of adults with ASCVD in the US = 23.5M
Patients eligible for PCSK9i = 0.14 x 23.5M = 3.29M
Cost after rebate = $9300 per year
Cost of treating 3.29M = $9300 x 3.29M = $30.6B
Refund from Amgen = $30.6B x 0.044 = $1.35B
Total cost after rebate and refund = $29.25B

3.29 million people (out of a total of 23.5 million people with heart disease) would need a PCSK9 inhibitor @ a cost of $29 billion per year (after rebates and refunds for those with events). Is this good value for money?

Hernandez I. *JAMA Intern Med*. 2017;177(9):1388-1390

ICER Evidence Rating Matrix
Comparative Clinical Effectiveness for PCSK9 Inhibitor (Evolocumab)



Incremental or better

Comparable or better (2017)

Promising but inconclusive (2015)

Inconclusive

https://icer-review.org/wp-content/uploads/2016/01/Final-Report-for-Posting-11-24-15-1.pdf
ICER_PCSK9_NEU-CLINICAL_061317.pdf

Evolocumab and CV Outcomes in FOURIER
Issues for Discussion

- Study powered for 15% RRR in MACE, not 34% RRR predicted by CTTC regression!
- Observed events higher than expected leading to shorter follow up which might have attenuated treatment benefit (event-driven trial without fixed time of f/u)
- 3-year KM estimates of 2% ARR not reliable: based on 5% of subjects (1,375/27,564)
- Landmark analyses based on censoring of fatal events, not MACE events
- CV risk reduction lower than predicted by CTTC meta-analysis or Ph2/3 PCSK9i trials
- Cost-effectiveness models based on the assumption that mortality benefit will emerge at longer follow (not supported by landmark analysis of FOURIER >1 y or IMPROVE-IT where no mortality benefit seen at 7 years)
- 50-70% price discount to meet CE threshold ($100-150K/QALY); 85% discount for value-based pricing

PCSK9 Inhibitors for Mitigating CV Risk
Final Observations

- Conceptual advance (Yes)

  Gene discovery (2003) leading to targeted therapy approval in 12 years (2015)!

- Therapeutic advance (?)

  - NNT of 67 for MACE over 2.2y without mortality benefit at a cost of $2.14M per MACE

  - Cost & affordability as important as science for true therapeutic advance

- Validation of LDL hypothesis (1mmol/L LDL ↓= 22% RRR in MVE) (No)

  - For 1.55 mmol/L (60mg/dL) LDL ↓, expected RRR of 34% vs observed RRR of 17%

  - Does this confirm or refute the LDL hypothesis?

  - Study powered for 15% RRR in MACE, not 34% RRR predicted by CTTC regression!

“The aim of science is not only to

open the door to endless wisdom

but also to put a limit to endless error”

Galileo