Supplementary Online Content

Fonarow GC, Keech AC, Pederse TR. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. *JAMA Cardiol*. Published online August 23, 2017. doi:10.1001/jamacardio.2017.2762

This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1. Population Event Rates per 100 Patients from US Clinical Practice Population (Standard Background Therapy vs. Evolocumab plus Standard Background Therapy)

	Evolocumab + SBT	SBT
10-year Horizon		
Rate of Non-fatal MI	18	29
Rate of Non-fatal IS	18	26
Rate of CV death	23	25
Rate of revascularization	27	38
Rate of MI, IS or CV death	58	79
Risk of MI, IS or CV death (%)	44	55
Lifetime Horizon		
Rate of Non-fatal MI	41	65
Rate of Non-fatal IS	43	58
Rate of CV death	51	56
Rate of revascularization	58	79
Rate of MI, IS or CV death	135	179
Risk of MI, IS or CV death (%)	74	83

Abbreviations: CV, cardiovascular; IS, ischemic stroke; MI, myocardial infarction; SBT, standard background therapy. Rate represents event rates per 100 patients and can exceed 100 as patients may experience multiple events over a lifetime. The risk represents the % of patients experiencing one or more events over 10-years or lifetime.

eTable 2. Population Event Rates per 100 Patients from FOURIER Trial Population (Standard Background Therapy vs. Evolocumab plus Standard Background Therapy)

	Evolocumab + SBT	SBT
10-year Horizon		
Rate of Non-fatal MI	10	16
Rate of Non-fatal IS	10	14
Rate of CV death	13	14
Rate of revascularization	28	40
Rate of MI, IS or CV death	33	45
Risk of MI, IS or CV death (%)	28	36
Lifetime Horizon		
Rate of Non-fatal MI	30	47
Rate of Non-fatal IS	31	42
Rate of CV death	36	40
Rate of revascularization	78	105
Rate of MI, IS or CV death	97	129
Risk of MI, IS or CV death (%)	62	72

Abbreviations: CV, cardiovascular; IS, ischemic stroke; MI, myocardial infarction; SBT, standard background therapy. Rate represents event rates per 100 patients and can exceed 100 as patients may experience multiple events over a lifetime. The risk represents the % of patients experiencing one or more events over 10-years or lifetime.

eTable 3. Derivation of Model Inputs for Cardiovascular Death

Given that the median follow-up of FOURIER was only 26 months and cost-effectiveness modeling requires a lifetime horizon, the assumptions regarding timing and magnitude of cardiovascular mortality effects are critical.

Current evidence supports that treatment with statins, ezetimibe, and PCSK9 inhibitors yield risk reductions that are proportional to the LDL-cholesterol reductions achieved and sustained over time, as these therapies each increase upregulation of the LDL-receptor. A recent analysis of 49 lipid-lowering clinical trials demonstrated that the clinical benefits of the aforementioned classes were proportional to the absolute reduction in LDL-cholesterol.[1]Further support comes from multiple Mendelian randomization studies showing that per unit lower of LDL-cholesterol mediated by variants in HMGCR, NPC1L1, and PCSK9, there were virtually identical lower odds of cardiovascular events.[2] Importantly, this relationship also held true for coronary heart deaths.[2] Thus, for estimating the effects on cardiovascular mortality beyond the period of follow-up in FOURIER, the CTTC meta-analysis[3] was leveraged for estimating the magnitude of cardiovascular mortality reduction in the base case and sensitivity analyses described below, with a 5-year delay before the emergence of cardiovascular mortality reduction was assumed in the base case.

Risk reduction in CV mortality per 1mmol/L LDL-C reduction	Description	Calculation
Base case: 9.5%	Data derived from the ratio of CVD/CHD in the CTTC meta-analysis, CHD in the more vs less statin trials, and reduction in CHD, MI and stroke from	(RRR_CTTC_CVD/RR_CTTC_CHD)*RRR_MorevsLess_CHD*(RRR_FOURIER_CHD,MI,S/RR_CTTC_Major vascular event)= (14%/20%)*15%*(20%/22%)=9.5%

	FOURIER relative to that in the overall CTTC to derive the anticipated treatment effect on CV mortality	
Sensitivity analysis: 6.4%	Data derived similar to the base case, but apply the reduction in major vascular event from FOURIER relative to that in more vs less statin trials to derive the anticipated treatment effect on CV mortality	(RRR_CTTC_CVD/RR_CTTC_CHD)*RRR_MorevsLess_CHD*(RRR_FOURIER_Major vascular event/RRR_CTTC_Major vascular event)=(14%/20%)*15%*(17%/28%)=6.4%
Sensitivity analysis: 14.0%	Data derived directly from the CV mortality reduction in overall CTTC. FOURIE	RRR_CTTC_CVD=14.0%

	R results are largely consistent with CTTC. The treatment benefit in CV mortality is expected to follow what was observed in CTTC	
Scenario analysis: key composite secondary endpoint from FOURIER	Data derived from the FOURIER key composite secondary endpoint (time to MI/stroke/CV death) for the treatment effect on MI, stroke, and CV death, with this composite risk reduction applied to each individual endpoint from the start of treatment	RRR_FOURIER_Key secondary endpoint (year 1 / beyond 1 year)=12%/19%
Scenar	Data	RRR_FOURIER_Key secondary endpoint (year 1 / beyond 1

io analysis: key composite secondary endpoint in the US subgroup from FOURIER	derived from the FOURIER key composite secondary endpoint (time to MI/stroke/CV death) for the treatment effect on MI, stroke, and CV death obtained only from the US subgroup enrolled in the FOURIER trial (n=4013) applied to each individual endpoint from the start of treatment	year)=26%/27%

Abbreviations: CHD, coronary heart disease; CTTC, Cholesterol Treatment Trialists' Collaboration; CV, cardiovascular; CVD, cardiovascular disease; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction, RRR relative rate ratios.

References

1. Silverman MG, Ference BA, Im K, et al. Association between lowering LDL-C and cardiovascular risk reduction among different therapeutic interventions: a systematic review and meta-analysis. *JAMA.* 2016;316(12):1289-1297.
2. Ference BA, Robinson JG, Brook RD, et al. Variation in PCSK9 and HMGCR and risk of cardiovascular disease and diabetes. *N Engl J Med.* 2016;375(22):2144-2153.
3. Cholesterol Treatment Trialists Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet.* 2010;376(9753):1670-1681.

eTable 4. Impact Inventory for Cost-effectiveness Analysis

Sector	Type of Impact (list category within each sector with unit of measure if relevant)[a]	Included in This Reference Case Analysis From Societal Perspective?		Notes on Sources of Evidence
		Health Care sector	Societal	
Formal Health Care Sector				
Health	Health outcomes (effects)			
	Longevity effects	□	X	FOURIER,[1] CTTC[2]
	Health-related quality-of-life effects	□	X	Time trade-off study[3]
	Other health effects (eg, adverse events and secondary transmissions of infections)	□	X	FOURIER[1]
	Medical costs			
	Paid for by third-party payers	□	X	WAC and Credit Suisse[4]
	Paid for by patients out-of-pocket	□	□	
	Future related medical costs (payers and patients)	□	X	
	Future unrelated medical costs (payers and patients)	□	□	
Informal Health Care Sector				
Health	Patient-time costs	NA	X	AHA/ASA CVD burden report[5]
	Unpaid caregiver-time costs	NA	X	AHA/ASA CVD burden report[5]
	Transportation costs	NA	□	
Non−Health Care Sectors (with examples of possible items)				
Productivity	Labor market earnings lost	NA	X	AHA/ASA CVD burden report[5]
	Cost of unpaid lost productivity due to illness	NA	X	AHA/ASA CVD burden report[5]
	Cost of uncompensated household production[b]	NA	X	AHA/ASA CVD burden report[5]
Consumption	Future consumption unrelated to health	NA	□	
Social Services	Cost of social services as part of intervention	NA	□	
Legal or Criminal Justice	Number of crimes related to intervention	NA	□	
	Cost of crimes related to intervention	NA	□	
Education	Impact of intervention on educational achievement of population	NA	□	
Housing	Cost of intervention on home improvements (eg, removing lead paint)	NA	□	
Environment	Production of toxic waste	NA	□	

	pollution by intervention			
Other (specify)	Other impacts	NA	□	

[a]Categories listed are intended as examples for analysts. [b]Examples include activities such as food preparation, cooking, and clean up in the household; household management; shopping; obtaining services; and travel related to household activity.[6]
Abbreviations: NA, not applicable; WAC, wholesale acquisition cost

References

1. Sabatine MS, Giugliano RP, Keech AC, et al. Evolocumab and clinical outcomes in patients with cardiovascular disease. *N Engl J Med.* 2017;376(18):1713-1722. DOI: 1710.1056/NEJMoa1615664.
2. Cholesterol Treatment Trialists Collaboration, Baigent C, Blackwell L, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet.* 2010;376(9753):1670-1681.
3. Matza LS, Stewart KD, Gandra SR, et al. Acute and chronic impact of cardiovascular events on health state utilities. *BMC Health Serv Res.* 2015;15:173.
4. Credit Suisse. Global equity research major pharmaceuticals - Global pharma. 2015.
5. American Heart Association. Cardiovascular disease: a costly burden for America. Projections through 2035. http://www.heart.org/idc/groups/heart-public/@wcm/@adv/documents/downloadable/ucm_491543.pdf. Accessed May 5, 2017.
6. Grosse SD, Krueger KV, Mvundura M. Economic productivity by age and sex: 2007 estimates for the United States. *Med Care.* 2009;47:S94-103.

eTable 5. Reporting Checklist for Cost-effectiveness Analysis

Element	Journal Article	Technical Appendix
Introduction		
Background of the problem	Yes	
Study Design and Scope		
Objectives	Yes	
Audience	Yes	
Type of analysis	Yes	
Target populations	Yes	Yes
Description of interventions and comparators (including no intervention, if applicable)	Yes	Yes
Other intervention descriptors (eg, care setting, model of delivery, intensity and timing of intervention)	Yes	
Boundaries of the analysis; defining the scope or comprehensiveness of the study (eg, for a screening program, whether only a subset of many possible strategies are included; for a transmissible condition, the extent to which disease transmission is captured; for interventions with many possible delivery settings, whether only one or more settings are modeled)	Yes	
Time horizon	Yes	
Analytic perspectives (eg, reference case perspectives [health care sector, societal]; other perspectives such as employer or payer)	Yes	
Whether this analysis meets the requirements of the reference case	Yes	
Analysis plan		Available upon request
Methods and Data		
Trial-based analysis or model-based analysis. If model-based:		
Description of event pathway or model (describe condition or disease and the health states included)	Yes	
Diagram of event pathway or model (depicting the sequencing and possible transitions among the health states included)	Yes	
Description of model used (eg, decision tree, state transition, microsimulation)	Yes	
Modeling assumptions	Yes	
Software used	Yes	
Identification of key outcomes	Yes	
Complete information on sources of effectiveness data, cost data, and preference weights	Yes	
Methods for obtaining estimates of effectiveness (including approaches used for evidence synthesis)	Yes	Yes
Methods for obtaining estimates of costs and preference weights	No (referenced prior publications)	
Critique of data quality	Yes	
Statement of costing year (ie, the year to which all costs have been adjusted for the analysis; eg, 2016)	2017	
Statement of method used to adjust costs for inflation	Yes	

Statement of type of currency	Yes	
Source and methods for obtaining expert judgment if applicable		Yes
Statement of discount rates	Yes	
Impact Inventory		
Full accounting of consequences within and outside the health care sector	Yes	
Results		
Results of model validation	Yes	Yes
Reference case results (discounted and undiscounted): total costs and effectiveness, incremental costs and effectiveness, incremental cost-effectiveness ratios, measures of uncertainty	Yes	
Disaggregated results for important categories of costs, outcomes, or both		Yes
Results of sensitivity analysis	Yes	
Other estimates of uncertainty	Yes	Yes
Graphical representation of cost-effectiveness results	Yes	
Graphical representation of uncertainty analyses	Yes	Yes
Aggregate cost and effectiveness information	Yes	
Secondary analyses	Yes	
Disclosures		
Statement of any potential conflicts of interest due to funding source, collaborations, or outside interests	Yes	
Discussion		
Summary of reference case results	Yes	
Summary of sensitivity of results to assumptions and uncertainties in the analysis	Yes	
Discussion of the study results in the context of results of related cost-effective analyses	Yes	
Discussion of ethical implications (eg, distributive implications relating to age, disability, or other characteristics of the population)	Yes	
Limitations of the study	Yes	
Relevance of study results to specific policy questions or decisions	Yes	

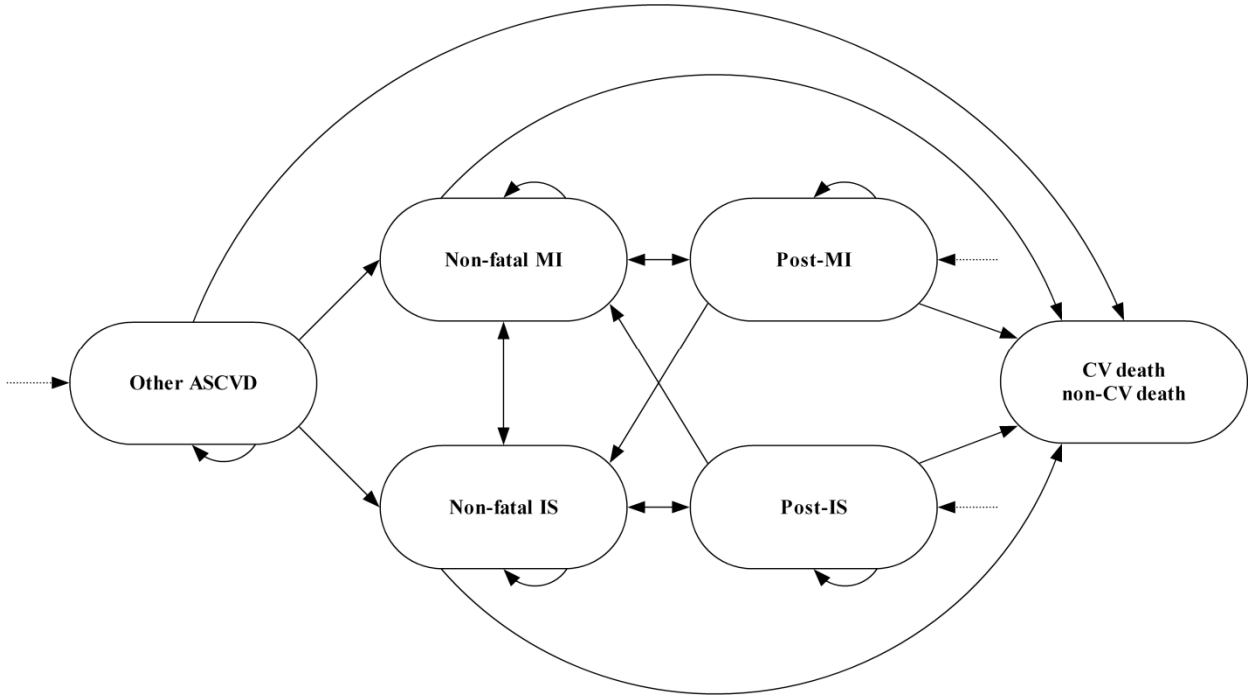
eTable 6. Derivation of Incremental Costs, Life-Years, and QALY Gained using the Base-Model Assumptions[a]

	Cost, $			Life-Years			QALY		
Components	**Evolocumab + Standard Background Therapy**	**Standard Background Therapy Alone**	**Incremental**	**Evolocumab + Standard Background Therapy**	**Standard Background Therapy Alone**	**Difference**	**Evolocumab + Standard Background Therapy**	**Standard Background Therapy Alone**	**Difference**
Medication	142,195	2,820	**139,375**						
Non-fatal MI	30,766	49,663	**-18,897**	0.28	0.45	**-0.17**	0.19	0.30	**-0.12**
Non-fatal IS	24,491	33,597	**-9,106**	0.29	0.40	**-0.11**	0.10	0.13	**-0.04**
Fatal CV events	26,947	29,751	**-2,804**						
RV	24,438	33,468	**-9,030**						
Post-CV event	91,438	85,578	**5,860**	10.59	9.90	**0.69**	7.34	6.80	**0.54**
Total	340,275	234,877	**105,398**	11.16	10.75	**0.41**	7.62	7.23	**0.39**

Abbreviations: QALY, quality-adjusted life-year; MI, myocardial infarction; IS, ischemic stroke; CV, cardiovascular; RV, coronary revascularization.

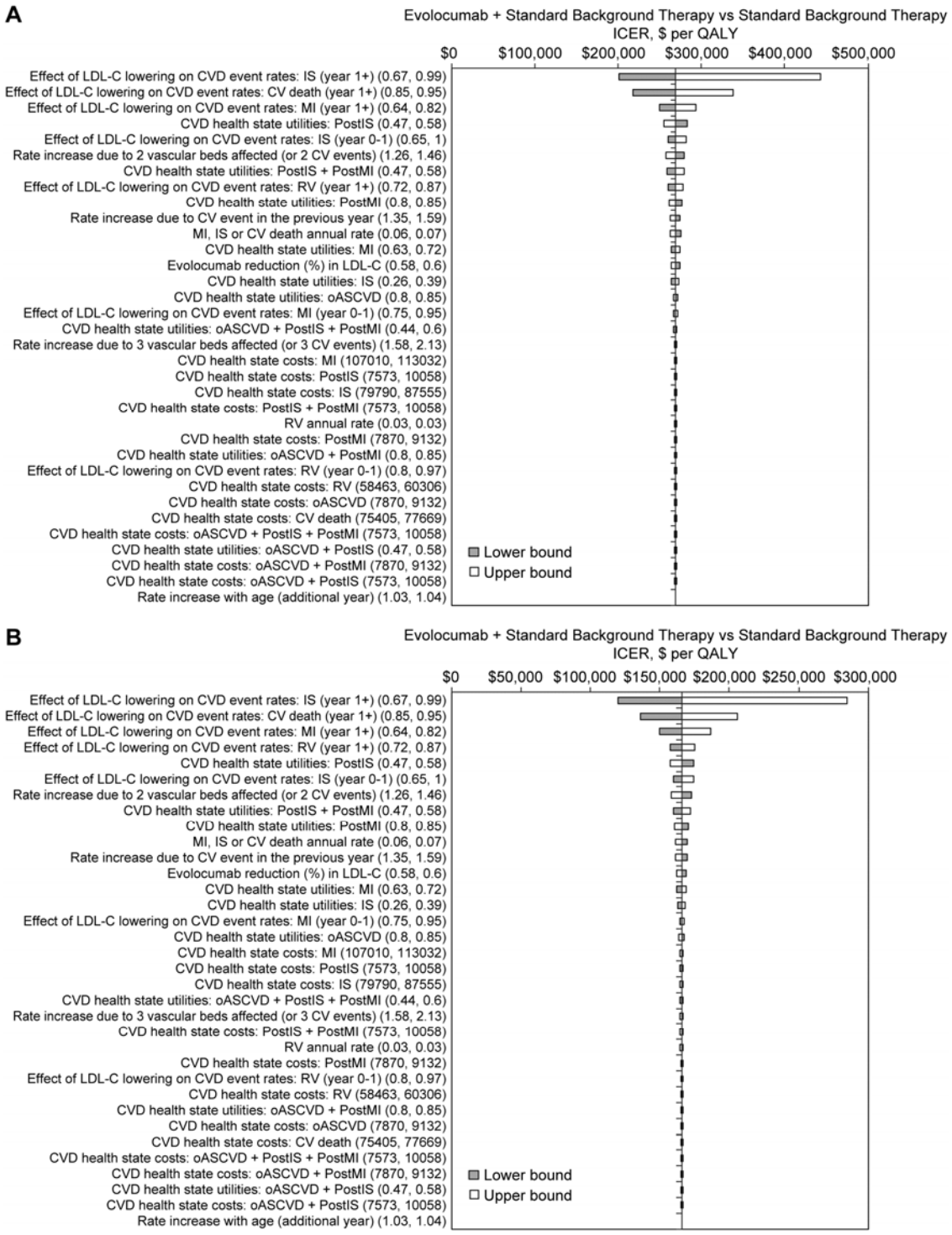
[a] Analysis uses the base-case inputs in the model, including list price for evolocumab, cost data from US Claims Data, and Utilities as shown in Table 1.

eFigure 1. Markov Cohort-State Transition Model Diagram



Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CV, cardiovascular; IS, ischemic stroke; MI, myocardial infarction.

eFigure 2. Markov Cohort-State Transition Model Diagram Tornado Diagram Based on Deterministic Sensitivity Analyses.



Tornado diagram based on deterministic sensitivity analyses. Panel A shows ICERs at full list price for evolocumab. Panel B show ICERs at net discounted price for evolocumab. Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; MI, myocardial infarction; IS, ischemic stroke; RV, revascularization; LDL-C, low-density lipoprotein–cholesterol.

eFigure 3. Value-Based Price Probabilistic Sensitivity Analysis (Mean and 95% Credible Intervals)