PCSK9 Inhibitors for Treatment of High Cholesterol: Effectiveness, Value, and Value-Based Price Benchmarks

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List of Abbreviations Used in this Report

AACE	American Association of Clinical Endocrinologists
ACC	American College of Cardiology
AHA	American Heart Association
AHRQ	Agency for Healthcare Research and Quality
ASCVD	Atherosclerotic cardiovascular disease
AE	Adverse event
CHD	Coronary heart disease
CHF	Congestive heart failure
CK	Creatinine kinase
CVD	Cardiovascular disease
EAS	European Atherosclerosis Society
ESC	European Society of Cardiology
FH	Familial hypercholesterolemia
HeFH	Heterozygous familial hypercholesterolemia
HC	Non-specific hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
ICER	Incremental cost effectiveness ratio
LDL-C	Low-density lipoprotein cholesterol
MACE	Major adverse cardiovascular event
MI	Myocardial infarction
NICE	National Institute for Health and Care Excellence
NNT	Number needed to treat
PCSK9	Proprotein convertase subtilisin/kexin type 9
QALY	Quality-adjusted life year
SBP	Systolic blood pressure

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The Institute for Clinical and Economic Review (ICER) is an independent non-profit research organization that evaluates medical evidence and convenes public deliberative bodies to help stakeholders interpret and apply evidence to improve patient outcomes and control costs. ICER receives funding from government grants, non-profit foundations, health plans, provider groups, and health industry manufacturers. Through all its work, ICER seeks to help create a future in which collaborative efforts to move evidence into action provide the foundation for a more effective, efficient, and just health care system. More information about ICER is available at http://www.icer-review.org

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The New England Comparative Effectiveness Public Advisory Council (CEPAC) is an independent, regional body of practicing physicians, methodological experts, and leaders in patient advocacy and engagement that provides objective, independent guidance on the application of medical evidence to clinical practice and payer policy decisions across New England.

Council members are selected for three-year terms, and represent a diversity of expertise and perspective; they are purposely not selected for expertise in the clinical topic under discussion in order to maintain the objectivity of the Council and to ground the conversation in the interpretation of the published evidence rather than anecdotal experience or expert opinion. Acknowledging that any judgment of evidence is strengthened by real life clinical and patient perspectives, New England CEPAC recruits subject matter experts for each meeting who provide input to Council members before the meeting to help clarify New England CEPAC's understanding of the different interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Council during their public deliberation, and help form recommendations with the New England CEPAC on ways the evidence can be applied to policy and practice.

Led by the Institute for Clinical and Economic Review, the New England CEPAC is supported by a broad coalition of state Medicaid leaders, integrated provider groups, public and private payers, patient representatives, and philanthropy. For more information about the New England CEPAC, please visit cepac.icer-review.org.

Executive Summary

Background

The goal of this report is to address the key issues that patients, providers, and payers face when making decisions about PCSK9 inhibitor therapy and to support the dialogue needed for successful action to improve the quality and value of health care for all patients.

The scope for this assessment utilizes the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, and Settings) framework. The evidence review is based on 25 clinical trials and two published systematic reviews and meta-analyses.[1,2] The results were cross-checked with the manufacturers' FDA submission documents and the FDA's briefing documents.

Topic in Context

In summarizing the contextual considerations for appraisal of a health care intervention, we seek to highlight the four following specific issues:

- Is there a particularly high burden/severity of illness?
- Do other acceptable treatments exist?
- Are other, equally or more effective treatments nearing introduction into practice?
- Would other societal values accord substantially more or less priority to providing access to this treatment for this patient population?

Elevated Cholesterol, Statin Therapy, and Cardiovascular Outcomes

Approximately one-third of American adults have cardiovascular disease (CVD), making it the most common cause of death in the United States.[3] The American Heart Association (AHA) defines cardiovascular disease as anyone with a history of myocardial infarction (MI), stroke, angina, congestive heart failure (CHF), peripheral artery disease, or hypertension. Major cardiovascular events in clinical trials usually include death due to CVD, non-fatal MI, non-fatal stroke, unstable angina requiring hospitalization, and revascularization (stenting, bypass surgery). Biological and epidemiological evidence has linked high levels of circulating low-density lipoprotein cholesterol (LDL-C) with an increased risk of MI, stroke, and death from CVD.

Multiple randomized clinical trials have demonstrated that lowering LDL-C with statin therapy reduces the risk of MI, stroke, and death from CVD. Many investigators believe that the greater the reduction in LDL -C the greater the reduction in cardiovascular events, but the topic remains controversial. However, several drugs that lower LDL-C – including hormone therapy, niacin, and

torcetrapib – have not decreased cardiovascular disease events when evaluated in randomized trials despite lowering LDL-C. On the other hand, the recently published IMPROVE-IT trial demonstrated that lowering LDL-C with ezetimibe significantly reduced cardiovascular event rates by 6% (95% CI 1 to 11%) after a median follow-up of approximately 5 years.

Guidelines for Cholesterol Lowering Therapy

In 2013 the ACC/AHA released an updated guideline for the treatment of cholesterol in order to reduce cardiovascular risk in adults.[4] The guideline includes a "strong" recommendation for high intensity statin therapy to treat individuals with cardiovascular disease who are ≤ 75 years of age; moderate intensity statin use in individuals with diabetes mellitus and LDL-C levels between 70 and 189 mg/dL who are ages 40-75 years of age; and high intensity statin use in individuals aged 40-75 with a 10-year risk for cardiovascular disease ≥ 7.5% and LDL-C levels between 70 and 189 mg/dL. The guideline also makes a "moderate" recommendation for high intensity statin therapy to treat all individuals with LDL-C levels ≥ 190 mg/dL who are ≥ 21 years of age.

The major change in this 2013 ACC/AHA guideline compared to the earlier National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guideline was its move away from recommending specific LDL-C levels as treatment targets.[5] In the prior guidelines, statin therapy was recommended to reach a target LDL-C level of < 100 mg/dL for individuals with cardiovascular disease and those with a 10-year risk ≥ 20%. For individuals with multiple risk factors and a 10-year risk < 20%, the target LDL-C level was < 130 mg/dL. The 2011 European guidelines also recommend statin therapy to reach a target LDL-C level of < 70 mg/dL for individuals with cardiovascular disease or diabetes and < 100 mg/dL for primary prevention in high risk individuals.[6] The emergence of the PCSK9 inhibitor drugs has stimulated further debate about whether clinicians should seek to achieve specific LDL-C targets when treating different kinds of patients.[7]

Unmet Clinical Need

Patient populations with elevated cholesterol in which there is an unmet clinical need include patients with a genetic condition causing highly elevated LDL-C, patients on statins and/or other cholesterol lowering drugs who are felt to have had an inadequate reduction in LDL-C, and patients who are not able to tolerate statins.[8]

Familial hypercholesterolemia (FH)

Familial hypercholesterolemia (FH) is an autosomal dominant inherited condition that causes elevated LDL-C in both the heterozygous (HeFH) and homozygous (HoFH) states.[9-12] Individuals with HoFH have LDL-C levels > 500 mg/dL and often experience cardiovascular events by age 20. It is an extremely rare condition (~1 case per 1 million people) with only 300-400 individuals in the US affected by HoFH. HeFH is more common, with estimates of affected individuals in the US varying between 500,000 to over a million, although there is considerable uncertainty in this estimate.

Individuals with HeFH often have LDL-C levels that are two to three times normal (i.e., 250-350 mg/dL).[13,14]

Statin intolerance

Statin intolerance is primarily due to muscle symptoms. These range from asymptomatic mild elevations in creatinine kinase (CK), a muscle enzyme, to muscle aches (myalgias) with or without mild elevations in CK (<4 times the upper limit of normal), to frank myositis (CK ≥ 4 time the upper limit of normal).[15,16] Precise measurement of statin intolerance is difficult because muscle symptoms arising from other causes are common, particularly in older individuals. Two studies specifically examined statin intolerance in clinical practice. The Prediction of Muscular Risk in Observational (PRIMO) trial reported a 10% incidence of mild to moderate muscle symptoms for patients on high intensity statin therapy.[17] Similarly, the Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study reported a 9.4% incidence of muscle symptoms in statin-naïve patients treated with atorvastatin 80 mg daily compared to a 4.6% incidence in patients randomized to placebo.[18]

Other Drug Therapy Options: Ezetimibe (Zetia®)

For patients unable to take statins, or for patients taking statins but not meeting their LDL-C goals, additional drugs are available, with ezetimibe (Zetia®) being the most relevant for this review. Ezetimibe inhibits the absorption of cholesterol in the intestines. Meta-analyses of randomized trials suggest that ezetimibe 10 mg lowers LDL-C by 23.6% (95% CI 21.7 to 25.6%) when added to statin therapy and by 18.6% (95% CI 17.5 to 19.7%) as monotherapy.[19,20] However, treatment with ezetimibe has been controversial because of negative findings in two trials.[21,22] These were small trials that were not designed to evaluate cardiovascular outcomes. The more recent IMPROVE-IT trial randomized 18,144 patients hospitalized for an acute coronary syndrome in the prior 10 days to the combination of simvastatin and ezetimibe or simvastatin and placebo and followed them for a median of approximately 5 years. The estimated cumulative event rate at 7 years was 32.7% in the ezetimibe group and 34.7% in the placebo group (p=0.016). The publication of the IMPROVE-IT trial in 2015 has renewed enthusiasm among many cardiologists for the use of ezetimibe to lower LDL-C beyond the reduction achieved with statin therapy.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) and cardiovascular disease

Higher levels of PCSK9 reduce the number of LDL-C receptors. If there are fewer LDL-C receptors, then LDL-C levels rise in the blood. Conversely, lower levels of PCSK9 in the blood leads higher LDL-C receptor density and lower levels of LDL-C in the blood. This biology suggests that drugs targeting PCSK9 have the potential to reduce LDL-C and cardiovascular disease.

In July and August 2015, after favorable votes from its Advisory Committee ranging from 11-4 to 15-0 for different indications, the FDA approved two new human monoclonal antibodies that target

PCSK9 in the blood and markedly reduce LDL -C levels. Alirocumab (Praluent®, Sanofi/Regeneron) is a human monoclonal antibody that inhibits PCSK9. It is administered as a subcutaneous injection once every two weeks at doses of either 75 mg or 150 mg. Evolocumab (Repatha™, Amgen) is also a human monoclonal antibody and is administered as a subcutaneous injection 140 mg once every two weeks or 420 mg once every four weeks. The annual wholesale acquisition cost for treatment with alirocumab is $14,600; the annual cost for evolocumab is $14,100.

Comparative Clinical Effectiveness

Methods

The goal of this report is to evaluate the comparative clinical effectiveness and comparative value of PCSK9 inhibitors as a class for patients with elevated LDL-C. We have attempted to identify all randomized controlled trials that evaluated the safety and efficacy of the two FDA approved PCSK9 inhibitors alirocumab and evolocumab. The published meta-analyses found that the LDL-C lowering effect of the two PCSK9 inhibitors were similar, and there are no head to head trials that compare alirocumab to evolocumab; thus, we have elected to examine the impact of PCSK9 inhibitors as a class.

Results

Our literature search identified 41 references describing eight phase 2 trials, 16 phase 3 trials, and one long-term follow-up study.[8,23-62] A high-quality meta-analysis by Navarese and colleagues was also identified and provided the basis for many of the findings in this review.[1] Most of the clinical trials were of relatively short duration. Seventeen trials had follow-up of <1 year, two trials had one year of follow-up, and five trials had follow-up longer than one year. Fourteen trials involved comparisons of PCSK9 inhibitors to placebo, seven compared PSCK9 inhibitors to ezetimibe, and three involved both comparisons. Approximately equal percentages of trial participants were male and female, 30% had a history of CVD, and 15% had diabetes. Key trials are summarized in detail in the full report.

Clinical Benefits

LDL-C reduction and other lipid parameters

Table ES1 on the following page shows the results of the Navarese meta-analysis and demonstrates that the clinical impact on LDL-C is very similar between the two drugs. Evolocumab has slightly greater LDL-C reductions than alirocumab, but the differences are very small compared to the percentage reduction achieved by either of the PCSK9 inhibitors. Furthermore, differences in the underlying populations studied may explain these relatively small differences. The evidence therefore strongly suggests that the two drugs have very similar effects, and the lack of head to

head randomized trials makes it impossible to determine whether one of the PCSK9 inhibitors lowers cholesterol more than the other.

Table ES1. Meta-analysis of the percentage reduction in LDL-C by PCSK9 inhibitors in 10,159 participants in phase 2 and 3 randomized trials by stratified by dose and type of PCSK9 inhibitor.

	Dose and type of PCSK9 inhibitor				
Comparison group	All, % (95% CI)	Alirocumab 75 mg Q2W	Alirocumab 150 mg Q2W	Evolocumab 140 mg Q2W	Evolocumab 420 mg Q4W
Placebo	58.8 (56.5 to 61.0)	52.6	56.2	63.5	57.3
Ezetimibe	36.2 (33.1 to 39.3)	31.7	*	39.3	37.5

Given these findings, the Navarese meta-analysis merged data available on both drugs to evaluate their impact on other lipid parameters.

Table ES2. Meta-analysis of the percentage reduction in LDL-C by PCSK9 inhibitors as a class in 10,159 participants in phase 2 and 3 randomized trials stratified by background statin therapy.

	Background Statin Therapy			
Comparison group	All, % (95% CI)	No statin, %	High intensity statin, %	Other statin, %
Placebo	58.8 (56.5 to 61.0)	53.6	57.9	65.2
Ezetimibe	36.2 (33.1 to 39.3)	36.2	34.4	37.5

The percentage reduction in LDL is greater when PCSK9 inhibitors are compared to placebo (58.8%) than that observed compared to ezetimibe (36.2%). The percentage reduction in LDL varies much less by background statin therapy. Detailed information on LDL-lowering by subgroup is presented in the full report. Findings from studies conducted in patients with HeFH and statin intolerance were similar to the overall results.

Patient-centered clinical outcomes

There are 5-year large outcome studies ongoing for both alirocumab and evolocumab that should present initial results in 2017. Individual studies completed to date were not powered to evaluate outcomes such as mortality or CVD adverse events. However, the meta-analysis by Navarese combined data from existing studies to examine these outcomes. The most important clinical outcomes for lipid lowering therapy include death from CVD, MI, stroke, and unstable angina requiring hospitalization. Navarese and colleagues did not report the stroke outcomes, so we performed our own meta-analysis of stroke outcomes using the same analytic methods (see Table ES3 on the next page).

Table ES3: Meta-analysis results for patient-oriented outcomes

Outcome	OR (95% CI)	P	I^2	N	Events PCSK9 group (%)	Events control group (%)
All-cause mortality	0.45 (0.23-0.86)	0.015	0%	10,159	19 (0.3%)	21 (0.5%)
CVD Mortality	0.50 (0.23-1.10)	0.084	0%	10,159	12 (0.2%)	13 (0.3%)
MI	0.49 (0.26-0.93)	0.030	0%	5,195	19 (0.6%)	19 (1.0%)
Stroke	1.97 (0.69-5.65)	0.206	0%	4,683	14 (0.5%)	3 (0.2%)
Unstable angina	0.61 (0.06-6.14)	0.676	0%	3,894	1 (0.05%)	1 (0.08%)

As shown in the table above, the findings of the meta-analysis suggest that the PCSK9 inhibitors reduce the odds of all-cause and cardiovascular mortality by about 50%, but the total number of events is low and the confidence intervals are wide. The odds ratio for stroke in the meta-analysis was twice as high in the PCSK9 group, but the confidence interval is very wide and not statistically significant. There were no significant differences in these results when stratified by comparison group (placebo, ezetimibe), by PCSK9 inhibitor (alirocumab, evolocumab) or when adjusted for length of follow-up. In sensitivity analyses, excluding the data from studies not yet published in the peer-reviewed literature, the conclusions are the same.

Harms

Nearly all studies have less than 6 months of follow-up data, but results from individual studies and from the Navarese meta-analysis have found that PCSK9 drugs are very well-tolerated; there have been no findings suggestive of significant increases in adverse event rates. There are more injection site reactions, which may lead to slightly higher rates of drug discontinuation compared to the control group. There is a slight excess of neurocognitive events with PCSK9 inhibitors, but the results are not statistically significant. There is also a trend towards more myalgias in the PCSK9 treated participants, but this is balanced by a statistically significant reduction in the number of participants with elevations in the muscle enzyme creatine kinase (CK). Detailed adverse event-rate data are provided in the full report.

Summary and Comment

Our analyses demonstrate that the existing evidence provides moderate certainty that PCSK9 treatment provides an incremental or substantial net health benefit for all of the patient subpopulations included in the scope of this review. There is no question that the drugs improve intermediate risk factors for cardiovascular disease. They substantially reduce LDL-C, total cholesterol, and lipoprotein(a), and also modestly elevate HDL-C. A high-quality meta-analysis found a 50% reduction in all-cause mortality that was statistically significant and reductions of similar magnitude (albeit not statistically significant) in death from cardiovascular disease and in MIs.

The drugs also appear to be very well-tolerated. The randomized trials do not demonstrate an increase in adverse events, serious adverse events, or drug discontinuations due to adverse events. Neurocognitive event rates are low and do not appear to be increased in patients randomized to PCSK9 inhibitors compared to the control patients.

However, there are several limitations in the evidence base that give reason for caution. There are theoretical concerns that long term exposure to very low levels of cholesterol may have unexpected adverse effects that have not been observed in the evidence base to date because the majority of the studies lasted less than six months. In addition, as noted earlier, medications such as torcetrapib that lower LDL-C, raise HDL, and have strong biological plausibility, have demonstrated in long term studies increased cardiovascular event rates and total mortality. The large randomized trials with long-term follow-up that are designed to evaluate the effect of the PCSK9 inhibitors on hard clinical endpoints have completed recruitment, but their results will not be available until 2017.

The promising evidence on patient-centered outcomes from the published meta-analysis is also limited in several ways. First, the 95% confidence intervals for the odds ratios estimating clinical benefit either include 1.0 or approach 1.0. Second, the evidence in this meta-analysis combines data from trials of two different PCSK9 inhibitors, each with two different dosing schedules, with too few events in the evidence base to attempt subgroup analyses. Another limitation of the meta-analysis is that the populations studied were quite different: young adults with homozygous FH and very high LDL-C; older adults with LDL-C < 100, but not at goal; and older adults who have already had a heart attack or stroke. A final reason for caution about the findings of the meta-analysis is that the PCSK9 inhibitors were compared to two different control arms: placebo and ezetimibe. The percentage LDL-C reduction consistently favored PCSK9 inhibitors, but the magnitude varied slightly by population and significantly by control group. It is likely that the clinical benefits will vary by dose, drug, background drug therapy, and population studied.

The evidence base provides high certainty, however, that PCSK9 inhibitors lead to superior reductions in LDL-C levels compared to both placebo and ezetimibe. The percent reduction in LDL-C with PCKS9 treatment is approximately 55-60% and appears not to differ substantially across different patient subpopulations. The potential net health benefit from this level of LDL-C reduction will be greater among patient subpopulations at higher risks of CVD. Among the subgroups, the population with HoFH is at highest risk for CVD events. Untreated, they have CVD events in the second decade of life. Differences in CVD risk are less marked between patients with HeFH and those with a prior history of CVD who have elevated LDL-C levels despite other treatment and/or who cannot take statins.

In summary, the ICER review team believes that the existing evidence suggests, with moderate certainty, that the net health benefit of the PCSK9 inhibitors is either incremental or substantial for the patients in the subpopulations within the scope of this review. Despite the uncertainty in the

actual level of net health benefit, we believe there is less than a 10% chance that ongoing trials will demonstrate a net harm from PCSK9 inhibitor treatment, and therefore our evidence rating within the ICER Integrated Evidence Rating framework is "Promising but Inconclusive."

Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include, but are not limited to:

- Methods of administration that improve or diminish patient acceptability and adherence
- A public health benefit, e.g. reducing new infections
- Treatment outcomes that reduce disparities across various patient groups
- More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
- New mechanisms of action for treatments of clinical conditions (e.g., mental illness) for which the response to currently available treatments varies significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

Currently available PCSK9 inhibitors must be injected. This is a potential disadvantage compared to most pharmaceuticals because some patients are unable to self-inject or experience anxiety associated with self-injection. On the other hand, patients rapidly learn to inject themselves with low molecular weight heparin and with insulin when needed, so the barrier may not be too high, particularly for patients motivated by FH or a history of CVD events. Furthermore, the need to inject the medication only once or twice a month may enhance adherence and be an advantage compared to medications that need to be taken on a daily basis.

There do not appear to be other benefits or disadvantages of note to PCSK9 inhibitor therapy.

Comparative Value: Incremental Costs per Outcomes Achieved

Overview

To assess the incremental costs per outcomes achieved of PCSK9 inhibitors, we conducted a cost-effectiveness analysis using the CVD Policy Model, a previously validated model of cardiovascular disease in the contemporary adult population of the United States. The CVD Policy Model is a computer-simulation, discrete-state Markov model of coronary heart disease and stroke incidence, prevalence, mortality, and costs in the U.S. population over age 35 years.[63-65] The model was created at Harvard University in 1984 and has been used for more than 30 years to provide evidence on the value of cardiovascular disease prevention approaches in U.S. adults. The CVD Policy Model team has published reports from a number of high-impact studies of public health and clinical interventions.[66-75] The last model software and input data update was completed in 2015.

For the purpose of this analysis, we estimated the degree of LDL-C reduction with PCSK9 inhibitors when used alone or in combination with statins. We assumed that the drugs were equally efficacious in all patient populations, i.e., the proportion of reduction in LDL-C from baseline was constant across all subgroups studied. We also estimated the LDL-lowering effect of ezetimibe, another second-line LDL-lowering drug, alone or in combination with statin therapy.

We assumed that the effect of these drugs on cardiovascular outcomes (non-fatal MI, stroke and cardiovascular death) is proportionate to the degree of reduction in LDL-C: for one unit decline in LDL-C, we assumed that statins, ezetimibe, and PCSK9 inhibitors reduce the risk of non-fatal MI, non-fatal stroke, and cardiovascular death by an identical amount. Since the effect of PCSK9 inhibitors on stroke is not known, we performed a sensitivity analysis that assumed no change in the risk of stroke among patients treated with PCSK9 inhibitors.

Cost-Effectiveness Model: Methods

Model Structure

We modeled the entire population of US adults aged 35 to 74 years in the year 2015. We assumed the health system perspective,[76] considering all direct and induced medical costs and relevant clinical outcomes. In the base case, we evaluated the cost-effectiveness of PCSK9 inhibitors in three target populations. Populations were chosen to approximate those described in the FDA-labeled indications for alirocumab (i.e., FH and patients with atherosclerotic cardiovascular disease (ASCVD)).[77] This is in line with the idea that because statins are both inexpensive and effective, PCSK9 inhibitors will probably be used first among patients at highest risk for adverse cardiovascular events. Because the available data sources for the model have no variables for clinically-confirmed FH, we defined this condition based on the presence of a very high LDL-C (>250 mg/dL in the absence of statin use, ≥200mg/dL with statin use). Patients with a history of CVD were stratified into those intolerant to statins (10% of the overall population) and those on statin therapy

but not at LDL-C goal (<70 mg/dL). We applied a lifetime analytic horizon, defined as until patients reach 95 years of age (because of the absence of high-quality epidemiologic data in older populations), discounting future costs and benefits by 3% a year.

Treatment Strategies

We modeled three treatment strategies in patients able to tolerate statins:

- background treatment with a statin (as treated in the population, control),
- incremental treatment with ezetimibe among patients already on a statin, or
- incremental treatment with a PCSK9 inhibitor among patients already on a statin.

In the base case, 10% of the population was deemed statin-intolerant. Where relevant, the treatment strategies available to these patients were:

- no treatment with lipid lowering therapies (control),
- treatment with ezetimibe, or
- treatment with a PCSK9 inhibitor.

In all cases, we assumed that these drugs affect cardiovascular outcomes (non-fatal MI, non-fatal stroke, and cardiovascular death) in proportion to their effect on LDL-C: for one unit decline in LDL-C, we assumed that statins, ezetimibe, and PCSK9 inhibitors reduce the risk of non-fatal MI and cardiovascular death by an identical amount.

Costs

Age- and sex-specific health care costs were estimated using national data.[71] We assumed the annual cost of ezetimibe to be $2,828, based on the wholesale acquisition cost.[78] We assumed the annual cost of PCSK9 inhibitors to be equal to the average of the recently announced annual wholesale price of alirocumab and evolocumab ($14,600 and 14,100 per patient per year, respectively).[25] Drug costs were subjected to a variety of sensitivity and threshold analyses.

Results

Familial Hypercholesterolemia

Table ES4 below demonstrates that, compared with the control arm, incremental treatment with ezetimibe would avert 115,900 Major Adverse Cardiac Events (MACE) over the lifetime horizon and produce 250,600 additional QALYs with an ICER of $135,000/QALY vs. current treatment. Adding PCSK9 inhibitors to current treatment averted 324,200 MACE and produced 665,200 additional QALYs, producing an ICER of $290,000/QALY. This higher ICER for PCSK9 inhibitors was driven largely by differences in drug costs ($14,350 per year for PCSK9 vs. $2,828 per year for ezetimibe). We did not model HoFH separately, because the expected number of patients is small (n=300-400 in the US).

Table ES4. Base Case and Clinical Outcomes among Patients with FH.

	Person-years of treatment (millions)	Total MACE averted	NNT_5†	QALYs gained^	Incremental Drug Costs^ (million $)	Incremental Costs, Other CV Care^ (million $)	ICER ($/QALY)
Statin§	*comparator*						
Statin + Ezetimibe||,¶	22.3	115,900	77	250,600	$40,359	-$6,632	$135,000
Statin + PCSK9 inhibitor,¶**	23.7	324,200	28	665,200	$210,516	-$17,304	$290,000

Abbreviations: CV, cardiovascular; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT_5, number-needed-to-treat; QALY, quality-adjusted life year.

* In the base case, all patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (10% of the population) received incremental therapy with ezetimibe or a PCSK9 inhibitor (n = 605,000 in 2015). The analytic horizon was lifetime (defined as when patients reach the age of 95 years). To reflect the precision of the model, person-years of treatment are rounded to the nearest 100,000s; MACE and QALYs are rounded to the 100s; costs are rounded to the millions; and ICERs to the 1000s.

† Number of patients that would need to be treated for 5 years to avert one MACE event.

^ All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.

§ Patients deemed to be statin-intolerant (base-case prevalence = 10% of the FH population) received no lipid-lowering therapy.

|| Patients deemed to be statin-intolerant (base-case prevalence = 10% of the FH population) received only ezetimibe.

¶ Both statin+ezetimibe and statin+PSCK9 inhibitor arms are compared with the statin-only arm.

** Patients deemed to be statin-intolerant (base-case prevalence = 10% of the FH population) received only a PCSK9 inhibitor.

Secondary Prevention Among Patients with a Prior History of CVD and Intolerant of Statins

As shown in the table below, compared with the control arm (no lipid-lowering therapy), treatment with PCSK9 inhibitors averted 1,254,400 MACE over the lifetime horizon and produced 2,366,000 additional QALYs at an ICER of $274,000/QALY. As in the FH population, ezetimibe's clinical effects were less pronounced but its incremental drug costs were approximately 20% of those for PCSK9 inhibitors, resulting in an ICER of $145,000/QALY vs. no lipid-lowering therapy.

Table ES5. Base-Case Clinical and Economic Outcomes Among Statin-Intolerant Patients with a Prior History of CVD.*

	Person-years of treatment (millions)	Total MACE averted	NNT_5†	QALYs gained^	Incremental Drug Costs^ (million $)	Incremental Costs, Other CV Care^ (million $)	ICER ($/QALY)
Control (no additional lipid-lowering therapy)	*comparator*						
Ezetimibe§	85.0	446,100	56	847,000	$138,560	-$15,961	$145,000
PCSK9 inhibitor§	85.4	1,254,400	21	2,366,000	$693,450	-$44,627	$274,000

Abbreviations: CV, cardiovascular; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT_5, number-needed-to-treat; QALY, quality-adjusted life year.

* In the base case, we assumed that 10% of the population was statin-intolerant. Patients who had a prior history of cardiovascular disease received incremental treatment with ezetimibe or a PCSK9 inhibitor (n = 1,460,000 in 2015). The analytic horizon was lifetime (defined as until patients reached the age of 95 years). To reflect the precision of the model, person-years of treatment are rounded to the 100,000s; MACE and QALYs are rounded to the nearest 100s; costs are rounded to the millions; and ICERs to the 1000s.

† Number of patients that would need to be treated for 5 years to avert one MACE event.

^ All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.

§ Both the ezetimibe and PSCK9 inhibitor arms are compared with the control (no additional lipid-lowering therapy) arm.

Secondary Prevention Among Patients with a Prior History of CVD and LDL-C ≥ 70mg/dL on Statin Therapy

Compared with the control arm, treatment with ezetimibe improved outcomes at an ICER of $135,000/QALY while PCSK9 inhibitors averted 5,621,800 MACE over the lifetime horizon and produced 10,573,800 additional QALYs at an ICER of $302,000/QALY.

Table ES6. Base-Case Clinical and Economic Outcomes Among Patients with a Prior History of CVD and LDL-C ≥ 70mg/dL on Statin Therapy.*

	Person-years of treatment (millions)	Total MACE averted	NNT_5†	QALYs gained^	Incremental Drug Costs^ (million $)	Incremental Costs, Other CV Care^ (million $)	ICER ($/QALY)
Statin	*comparator*						
Statin + Ezetimibe§	409.1	2,253,800	51	4,345,900	$673,155	-$85,520	$135,000
Statin + PCSK9 inhibitor§	416.9	5,621,800	21	10,573,800	$3,406,692	-$210,702	$302,000

Abbreviations: CV, cardiovascular; ICER, incremental cost-effectiveness ratio; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.
* In the base case, patients with pre-existing CVD and LDL-C ≥ 70mg/dL on statin therapy received incremental therapy with ezetimibe or a PCSK9 inhibitor (n = 7,271,000 in 2015). The analytic horizon was lifetime (defined as until patients reached the age of 95 years). To reflect the precision of the model, person-years of treatment are rounded to the 100,000s; MACE and QALYs are rounded to the 100s; costs are rounded to the millions; and ICERs to the 1000s.
† Number of patients that would need to be treated for 5 years to avert one MACE event.
^ All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.
§ Both the statin+ezetimibe and statin+PSCK9 inhibitor arms are compared with the statin-only arm.

Scenario Analyses

In order to explore possible subpopulations for whom the incremental cost-effectiveness ratios might be lower, we evaluated the effect of only initiating therapy immediately after an incident MI. All patients who had an incident, first-ever MI in 2015 who were receiving statin therapy if able to tolerate it received ezetimibe or a PCSK9 inhibitor. ICERs were lower than in the base case analysis for all secondary prevention ($170,000/QALY and $74,000/QALY for PCSK9 inhibitors and ezetimibe respectively) due to a greater reduction in the absolute number of MACE events.

Sensitivity Analyses

Across all subpopulations, results were most sensitive to changes in the price of PCSK9 inhibitors and the length of the time horizon (which was varied from 20 years to the lifetime). However, in none of the univariate sensitivity analyses except for price did the ICERs for PCSK9 inhibitor therapy fall below $219,000 per QALY. We varied the effect of PCSK9 inhibitors on cardiovascular event rates (from -25% to +25% relative to the base case), and found this to be a moderately sensitive parameter; in the FH population, for example, cost-effectiveness ratios ranged from $250,000 to $359,000 per QALY gained. Findings from one-way sensitivity analyses are described in further detail in the full report.

Threshold Analyses

As shown in Table ES7 below, we also evaluated the drug costs at which PCSK9 inhibitors would be considered cost-effective under conventional willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY. Across all subpopulations and thresholds of interest, these prices represented discounts of 42-78% from the full wholesale acquisition cost of $14,350. When all patient subpopulations are merged to reflect the entire eligible population, prices were $3,166, $5,404, and $7,735 to achieve thresholds of $50,000, $100,000, and $150,000 per QALY respectively.

Table ES7. Threshold analyses: Annual drug cost at which PCSK9 inhibitors would be cost-effective in subpopulations under varying willingness-to-pay thresholds.*

Patient Subpopulation	WTP threshold		
	$50,000/QALY	$100,000/QALY	$150,000/QALY
FH on statin (as treated) + statin-intolerant †	$3,400	$5,700	$8,000
Pre-existing CVD, LDL-C ≥ 70 mg/dL, and statin-intolerant ‖	$3,400	$5,800	$8,300
Pre-existing CVD, LDL-C≥ 70 mg/dL on maximally tolerated statin dose ¶	$3,100	$5,300	$7,600

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year; WTP, willingness-to-pay.

* Only drug costs and costs related to cardiovascular care were included in the ICER for these analyses. The analytic horizon was lifetime (defined as until patients reached 95 years of age), and future costs and QALYs were discounted at 3% a year. To reflect precision in the model, the reported threshold drug costs are rounded to the nearest 100s.

† Patients who met the operational definition of FH and are either already receiving statin therapy or deemed statin-intolerant (10% of the population) received incremental therapy with a PCSK9 inhibitor (n = 605,000 in 2015). Complete results of this analysis are presented in Table 14 in the full report.

‖ Ten percent of the population was assumed to be statin-intolerant (n = 1,460,000 in 2015). Complete results of this analysis are presented in Table 16 in the full report.

¶ Patients with pre-existing CVD and LDL-C ≥ 70mg/dL already receiving statin therapy received incremental therapy with a PCSK9 inhibitor (n = 7,271,000 in 2015). Complete results of this analysis are presented in Table 17 in the full report.

Comparative Value: Health System Value

Budget Impact Model: Methods

We used the same model employed for the care value analysis to estimate total budgetary impact. Budgetary impact was defined as the total incremental cost of the therapy in each population: incremental health care costs (including drug costs) minus any offsets in these costs from averted cardiovascular events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue from averted cardiovascular events. In addition to FH and patients with a history of CVD who are (a) statin intolerant or (b) not at LDL-C target on statin therapy, we also considered the budgetary impact if the treated population were limited to the higher-risk subset of patients with a history of CVD who received PCSK9 inhibitors immediately following an incident (i.e., first-ever) MI in 2015. Our calculations assume that utilization of new drugs is "unmanaged" – i.e., without payer or pharmacy benefit management controls in place – to provide an upper bound for likely patterns of drug uptake by five years after launch.

We examine six characteristics of the drug and marketplace to estimate unmanaged drug uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care vs. specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assign a new drug to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5). We then compare our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability through changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://www.icer-review.org/wp-content/uploads/2014/01/Value-Assessment-Framework-9-7.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new molecular entity approvals by the FDA each year, and the contribution of spending on retail and facility-based drugs to total health care spending. Therefore, according to

our calculations, for 2015-16, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year. In this report, each PCSK9 inhibitor is considered as an individual new drug, so the budget impact threshold for each drug is $904 million, and $1.8 billion for the two drugs combined.

We combine consideration of the potential budget impact with the prices necessary to meet commonly accepted societal willingness-to-pay thresholds in order to calculate a value-based price benchmark for each new drug. This price benchmark begins with the "care value" price range needed to achieve cost-effectiveness ratios of $100,000-$150,000 per QALY for the population being considered, but the value-based price benchmark has an upper limit determined by the price at which the new drug would exceed the potential budget impact threshold of $904 million. If the potential budget impact does not exceed $904 million, then the value-based price benchmark remains the full care value price range.

Results

Results from the budget impact model showed that if both the FH and CVD populations were treated with the uptake pattern assumptions mentioned above, 527,000 individuals would receive PCSK9 therapy in the first year. After one year of PCSK9 treatment, cost offsets due to reduced cardiovascular adverse events ranged from $592 per patient with FH to $1,010 per patient for patients with CVD who are statin-intolerant. Including this cost offset, one-year budget impact is still estimated to be quite high: approximately $7.2 billion for all patient populations.

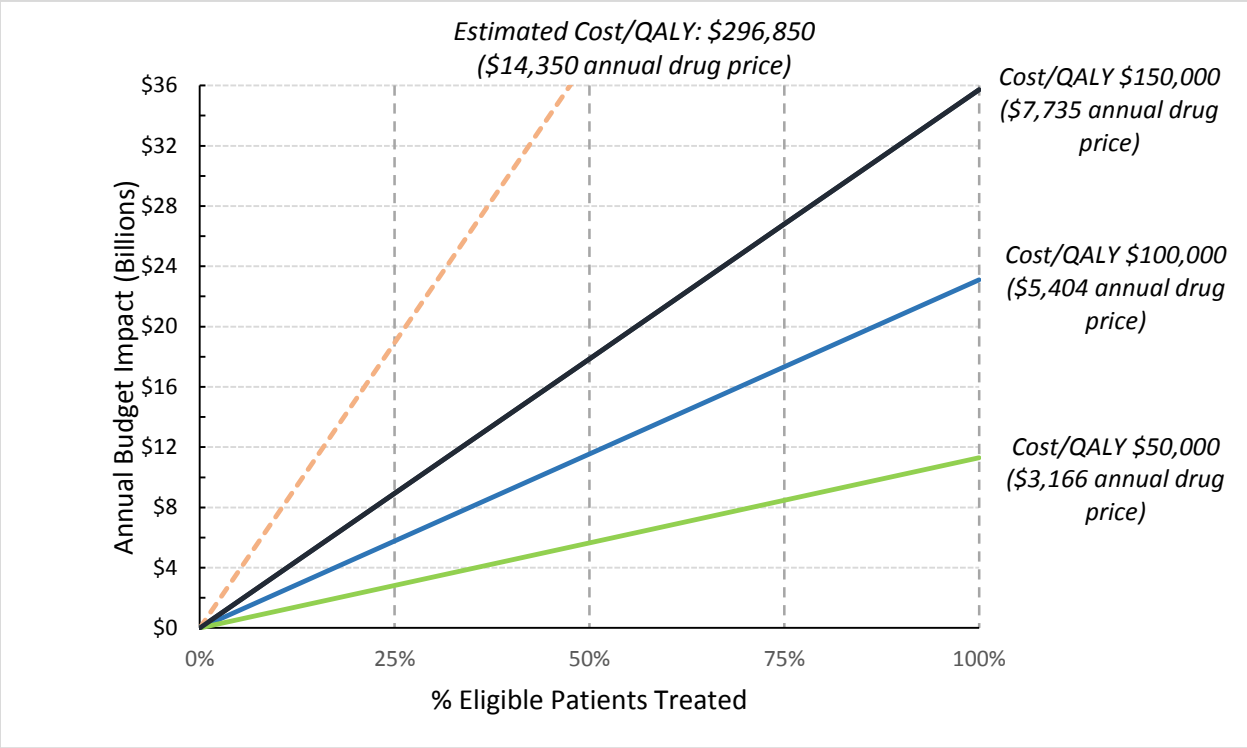
As uptake of new PCSK9 inhibitors is estimated to increase over the entire 5-year time horizon, we estimate that approximately 2.6 million persons would receive PCSK9 inhibitor therapy for one or more years by the end of that period. Total budgetary impact over five years is estimated at approximately $19 billion, $15 billion, and $74 billion for the FH, CVD statin-intolerant, and CVD not at LDL-C target subpopulations, respectively. When these 5-year budget impact figures are annualized, they equal $21.4 billion in net health care cost growth per year, which is well above the budget impact threshold of $1.8 billion for the two drugs combined. In order to not exceed this budget impact threshold, approximately 1% of eligible patients could be treated at the average list price of $14,350 per year.

Figure ES1 on the following page provides findings of multiple analyses that give perspective on the relationship between varying possible drug prices, cost-effectiveness ratios, drug uptake patterns, and potential budget impact.

As can be seen in Figure ES1, even at a drug cost of $3,166 dollars per year, the cost at which the cost/QALY = $50,000, if 50% of all eligible patients are ultimately treated over a five-year time period the annualized budget impact is approximately $5.6 billion per year. At the list price of $14,350 used for this report, if only 25% of eligible patients receive treatment, the annualized

budget impact is nearly $19 billion, meaning that over the five-year period a total of almost $100 billion would have been added to health care costs in the United States.

Figure ES1. ICER value graph combining cost-effectiveness and potential budget impact analyses. Colored lines represent the impact on annualized budget impact of different uptake patterns (eligible patients treated) at the actual list price of the drug (dashed line) and at drug prices needed to achieve common incremental cost-effectiveness ratios.



Draft Value-based Benchmark Prices

Our draft value-based benchmark prices for each key subpopulation and for the overall treated population are provided in Table ES8 on the following page. Detailed calculations for the value-based price benchmarks presented below are available in Appendix Table 15.

As shown in the table on the following page, if only the FH or the CVD statin-intolerant populations were treated, the entire care value price range is lower than the price at which the potential budget impact threshold would be exceeded. Thus, the value-based price benchmark for these two subpopulations is the care value price range. This is not surprising given the relatively small size of each of these populations. In contrast, the care value price range for the much larger population of patients with CVD not at LDL-C target is higher than the maximum price that would not exceed the budget impact threshold.

When all subpopulations are combined, the care value price range is $5,404-$7,735. However, this price range is higher than the maximum price that could be charged before exceeding the potential budget impact threshold ($2,177). Therefore, the draft ICER value-based price benchmark for each of the new PCSK9 inhibitor drugs, with all the assumptions mentioned previously regarding 5-year uptake patterns and cost offsets, is $2,177. This figure represents *an 85% discount from the full wholesale acquisition cost assumed in our analysis ($14,350).*

Table ES8. Draft value-based price benchmarks for PCSK9 inhibitor therapy.

Population	Care Value Price: $100K/QALY	Care Value Price: $150K/QALY	Max Price at Potential Budget Impact Threshold	Draft Value-Based Price Benchmark
FH (n=453,443)	$5,700	$8,000	$10,278	$5,700-$8,000
CVD statin-intolerant (n=364,948)	$5,800	$8,300	$12,896	$5,800-$8,300
CVD not at LDL target (n=1,817,788)	$5,300	$7,600	$2,976	$2,976
TOTAL (n=2,636,179)	***$5,404***	***$7,735***	***$2,177***	***$2,177***

FH: familial hypercholesterolemia; CVD: cardiovascular disease; LDL: low-density lipoprotein; QALY: quality-adjusted life year

Summary and Comment

The results of our cost-effectiveness analysis suggest that the use of PCSK9 inhibitors may produce substantial reductions in non-fatal MIs, non-fatal strokes, and cardiovascular deaths over the lifetime analytic horizon. The NNT_5 (number of patients that would be needed to be treated for 5 years to avoid one major adverse cardiovascular event) of 28 for PCSK9 inhibitors appears to be relatively low; despite this, treatment with PCSK9 inhibitors generates cost-effectiveness ratios that far exceed commonly-accepted thresholds, such as $100,000/QALY.[79] Achieving cost-effectiveness at a threshold of $100,000/QALY would require price reductions of 60% to 63% compared with current prices. And the results of our analysis of potential budget impact suggest that even deeper reductions may be required to avoid excessive cost burdens to the health care system. Our value-based price benchmark for each PCSK9 inhibitor is $2,177 annually, which represents an 85% reduction from the list price of $14,350.

1. Background

1.1 Introduction

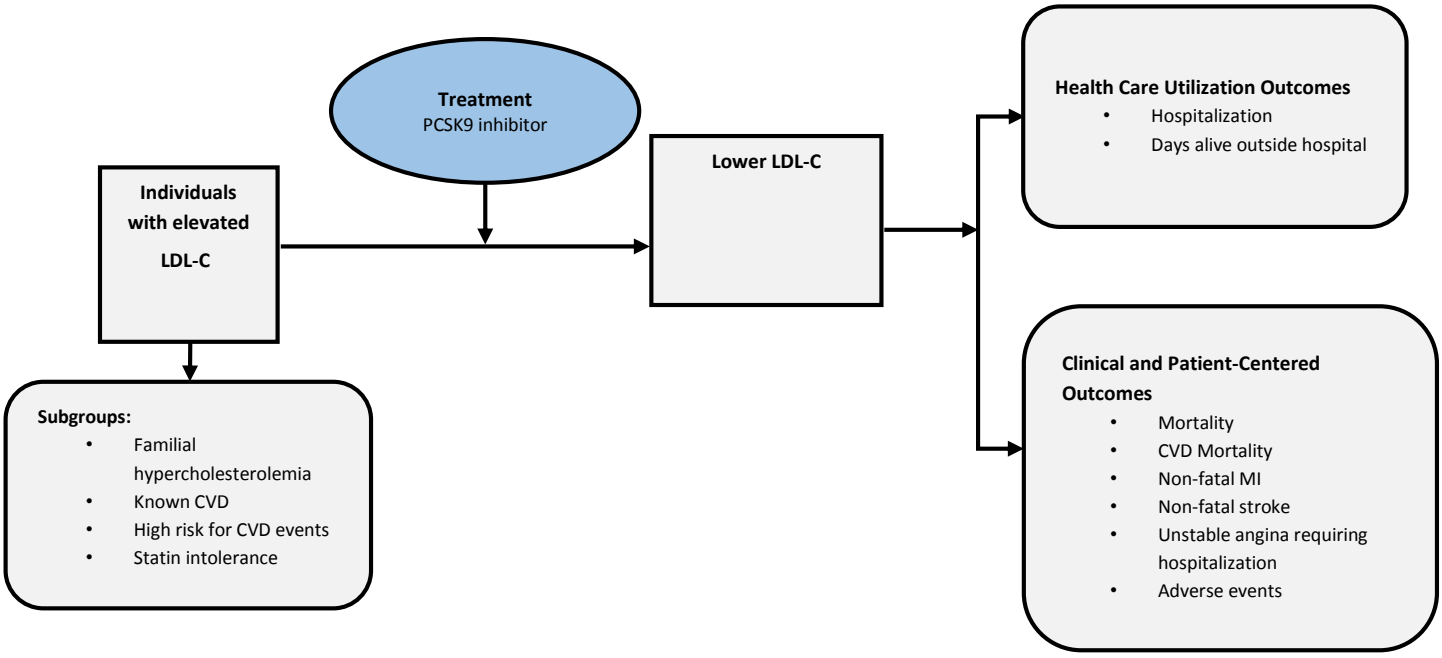
The focus for this assessment is the use of alirocumab and evolocumab for individuals with elevated LDL cholesterol. We assess the evidence on the comparative effectiveness and value of the drugs across relevant populations including:

- Patients with familial hypercholesterolemia
- Patients with established cardiovascular disease
- Patients at elevated risk for cardiovascular disease

Scope of the Assessment:

The scope for this assessment is described on the following page using the PICOTS (Population, Intervention, Comparators, Outcomes, Timing, Settings) framework. The evidence review is based on the 25 clinical trials and two published systematic reviews and meta-analyses. The results were cross-checked with the manufacturers' FDA submission documents and the FDA's briefing documents.

Figure 1: Analytic Framework for the Assessment



Population

The populations of interest include:

- Individuals with heterozygous familial hypercholesterolemia (HeFH) OR homozygous familial hypercholesterolemia (HoFH) whose cholesterol levels are not at goal
- Individuals with known cardiovascular disease (CVD) who are intolerant of statins or whose cholesterol levels are not at goal
- Individuals who are at high risk for CVD who are intolerant of statins or whose cholesterol levels are not at goal

Interventions

The interventions are the following PCSK9 inhibitors considered as a class:

- Alirocumab (Praluent®, Sanofi and Regeneron Pharmaceuticals, Inc.)
- Evolocumab (Repatha™, Amgen)

We considered the PCSK9 inhibitors as a class rather than separately for several reasons. First, there are no randomized trials comparing the two, which would allow for direct comparison of the LDL-lowering effects. Second, network meta-analytic techniques are not yet available to perform indirect comparisons for continuous outcomes such as the percentage reduction in LDL-C. Third, the magnitude of the reduction in LDL-C with PCSK9 inhibitors is much greater than any potential differences between the different drugs or their dosing. Finally, the number of clinical events for the individual PCSK9 inhibitors is too small to offer meaningful comparisons.

Comparators

The studies compare the PCSK9 inhibitors to usual care (i.e., statin therapy, lifestyle and dietary changes), placebo, and/or to ezetimibe.

Outcomes

Outcomes of interest include the impact of cholesterol-lowering interventions on:

- Mortality
- CVD mortality
- CVD events (myocardial infarction, stroke, unstable angina, revascularization)
- LDL-C reduction as an intermediate marker
- Short- and long-term complications and adverse events including neurocognitive events, myalgias, and local injection site reactions
- Economic outcomes, including payer costs, patient productivity, and cost-effectiveness

Timing

Evidence on intervention effectiveness was limited to phase 2 or 3 comparative studies with at least two months of follow-up for LDL-C reduction. Evidence on cardiovascular outcomes and harms was derived from comparative studies of any duration.

Settings

All relevant settings were considered, including inpatient, clinic, and outpatient settings.

2. The Topic in Context

Cardiovascular disease (CVD)

Cardiovascular disease is the most common cause of death in the United States and approximately one third of American adults have CVD.[3] The American Heart Association (AHA) defines cardiovascular disease as anyone with a history of myocardial infarction (MI), stroke, angina, congestive heart failure (CHF), peripheral artery disease, or hypertension. Major cardiovascular events in clinical trials usually include death due to cardiovascular disease, non-fatal MI, non-fatal stroke, unstable angina requiring hospitalization, and revascularization (stenting, bypass surgery).

Low density lipoprotein cholesterol (LDL) "lower is better" hypothesis

Low density lipoprotein cholesterol (LDL-C) is a major modifiable risk factor for myocardial infarction, stroke, and death from cardiovascular disease.[3,80] Multiple randomized clinical trials have demonstrated that lowering LDL-C with statin therapy reduces the risk of myocardial infarction, stroke, and death from cardiovascular disease.[81-83] Many investigators believe that the greater the reduction in LDL-C the greater the reduction in cardiovascular events, but the topic remains controversial.[84-88] However, several drugs that lower LDL-C – including hormone therapy, niacin, and torcetrapib – have not decreased cardiovascular disease events when evaluated in randomized trials despite lowering LDL-C.[89-93] Torcetrapib lowered LDL-C by 25%, but in the pivotal 15,000 person randomized trial, torcetrapib increased cardiovascular events by 25% and total mortality by 58%.[90] On the other hand, the recently published IMPROVE-IT trial demonstrated that the lowering of LDL-C with ezetimibe significantly reduced cardiovascular event rates by 6% (95% CI 1 to 11%) after a median follow-up of approximately 5 years.[78]

Guidelines for cholesterol lowering therapy

In 2013, the ACC/AHA released updated guidelines for the treatment of cholesterol in order to reduce cardiovascular risk in adults.[4] Diet therapy is recommended for all patients. The guidelines make strong recommendations for high intensity statin therapy to treat individuals with cardiovascular disease who are ≤ 75 years of age; moderate intensity statin use in individuals with diabetes mellitus and LDL-C levels between 70 and 189 mg/dL who are ages 40-75 years of age; and for high intensity statin use in individuals with a 10-year risk for cardiovascular disease ≥ 7.5% and LDL-C levels between 70 and 189 mg/dL who are ages 40-75 years of age. The guidelines make moderate recommendations for high intensity statin therapy to treat individuals with LDL-C levels ≥ 190 mg/dL who are ≥ 21 years of age.

Statin therapy is the primary therapy indicated for the treatment of high LDL-C. High intensity statin therapy includes atorvastatin 40 - 80 mg daily and rosuvastatin 20 - 40 mg daily. Moderate intensity statin therapy includes atorvastatin 10 - 20 mg daily, rosuvastatin 5 - 10 mg daily, simvastatin 20-40

mg daily, pravastatin 40-80 mg daily, lovastatin 40 mg daily, fluvastatin XL 80 mg daily, fluvastatin 40 mg twice daily, and pitastatin 2-4 mg daily.

The major change in the 2013 ACC/AHA guidelines compared to the earlier National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guideline[5] was moving away from recommending specific LDL-C levels as treatment targets. In the prior guidelines, statin therapy was recommended to reach a target LDL-C level of < 100 mg/dL for individuals with cardiovascular disease and those with a 10-year risk ≥ 20%. For individuals with multiple risk factors and a 10-year risk < 20%, the target LDL-C level was < 130 mg/dL. The 2011 European guidelines also recommend statin therapy to reach a target LDL-C level of < 70 mg/dL for individuals with cardiovascular disease or diabetes and < 100 mg/dL for primary prevention in high risk individuals.[6] A more complete discussion of all guidelines, as well as those from other organizations, can be found in Appendix A2.

Need for additional therapy

The use of statins to decrease LDL-C has contributed to the marked decline in death from CVD since 1950, but some patients are not able to tolerate statins and others have inadequate reductions in LDL-C.[94] Patients with familial hypercholesterolemia are the largest group of patients who may have inadequate reductions in LDL-C with statins due to their high baseline levels of LDL-C.

Familial hypercholesterolemia (FH)

Familial hypercholesterolemia (FH) is an autosomal dominant inherited condition that causes elevated LDL-C in both the heterozygous (HeFH) and homozygous (HoFH) states.[9-12] Individuals with HoFH have LDL-C levels > 500 mg/dL and experience cardiovascular events by age 20. It is an extremely rare condition (~1 case per 1million people) with only 300-400 individuals in the US affected by HoFH. HeFH is more common, with estimates of affected individuals in the US varying between 500,000 to over a million, though there is considerable uncertainty in this estimate.[9-12] Individuals with HeFH often have LDL-C levels that are approximately two to three times normal (i.e., 250-350 mg/dL).[13,14]

FH is usually diagnosed on the basis of clinical criteria because it is caused by mutations in several different genes, not all of which have been identified. The diagnostic criteria include a family history of early onset CVD, an elevated LDL-C level (>190 mg/dL in adults and >160 mg/dL in children), physical exam findings of tendon xanthomata (cholesterol deposits in tendons) or corneal arcus before the age of 45 years, and DNA analysis for known deleterious mutations causing FH.[9-12] Treatment is usually initiated early with high intensity statin therapy, with the addition of LDL apheresis in those patients with an inadequate response to aggressive lipid lowering therapy.

Statin intolerance

Statin intolerance is primarily due to muscle symptoms. These range from asymptomatic mild elevations in creatinine kinase (CK), a muscle enzyme, to muscle aches (myalgias) with or without mild elevations in CK (<4 times the upper limit of normal), to frank myositis (CK ≥ 4 time the upper limit of normal).[15,16] The muscle symptoms can include weakness, pain, stiffness and cramps. In the randomized trials of statins, the incidence of muscle symptoms was less than 5%, but these trials often excluded patients who did not tolerate statins during a run in period prior to randomization and the participants are not representative of the general population. Two studies specifically examined statin intolerance in clinical practice. The Prediction of Muscular Risk in Observational (PRIMO) trial reported a 10% incidence of mild to moderate muscle symptoms for patients on high intensity statin therapy.[17] Similarly, the Effect of Statins on Skeletal Muscle Function and Performance (STOMP) study reported a 9.4% incidence of muscle symptoms in statin-naïve patients treated with atorvastatin 80 mg daily compared to a 4.6% incidence in patients randomized to placebo.[18] Risk factors for muscle symptoms include older age, female sex, and Asian race. Strategies to manage muscle symptoms include reducing the dose of the statin, switching to a different statin, and treating vitamin D deficiency.[16,95]

The two trials of evolocumab that specifically enrolled statin intolerant patients (GAUSS, GAUSS 2) used slightly differing definitions.[61,62] For the GAUSS trial, participants were required to fail at least one statin due to intolerable muscle symptoms on the lowest dose of the statin.[62] For the GAUSS 2 trial, participants were required to fail at least two statins due to intolerable muscle symptoms on the lowest dose of the statin.[61]

Precise measurement of statin intolerance is difficult because muscle symptoms arising from other causes are common, particularly in older individuals. As an example, during the run-in period of the ODYSSEY ALTERNATIVE trial, the randomized trial of alirocumab in statin-intolerant patients, 49% of patients were reported to be intolerant of *placebo* due to musculoskeletal complaints.[43,44] Furthermore, 70% of the patients randomized to receive atorvastatin 20 mg daily (blinded) in the same trial tolerated it for the 24 week duration of the trial. Thus, many patients labeled as statin-intolerant may actually be able to tolerate a statin.

Ezetimibe (Zetia®)

Ezetimibe is a drug that inhibits the absorption of cholesterol in the intestines. The FDA approved ezetimibe 10 mg daily in October 2002 for LDL-C-lowering alone or in conjunction with other lipid lowering therapies in patients with hypercholesterolemia including homozygous familial hypercholesterolemia. Meta-analyses of randomized trials report that ezetimibe 10 mg lowers LDL-C by 23.6% (95 %CI 21.7 to 25.6%) when added to statin therapy[19] and by 18.6% (95% CI 17.5 to 19.7%) as monotherapy.[20] However, treatment with ezetimibe has been controversial because of negative findings in the ARBITER-6 and ENHANCE trials.[21,22] These were small trials that were not

designed to evaluate cardiovascular outcomes. The IMPROVE-IT trial randomized 18,144 patients hospitalized for an acute coronary syndrome in the prior 10 days to the combination of simvastatin and ezetimibe or simvastatin and placebo and followed them for a median of approximately 5 years. The hazard ratio for the reduction of all cardiovascular events was 0.936 (95% CI 0.89 to 0.99). The estimated cumulative event rate at 7 years was 32.7% in the ezetimibe group and 34.7% in the placebo group (p=0.016). The publication of the IMPROVE-IT trial in 2015 has renewed enthusiasm for the use of ezetimibe to lower LDL-C beyond the reduction achieved with statin therapy, even though the relative and absolute benefits were small.

Proprotein convertase subtilisin/kexin type 9 (PCSK9) and cardiovascular disease

PCSK9 is a protein found in the circulation that can bind to LDL-receptors. When the two undergo endocytosis, the LDL receptor is broken down and not recycled to the surface.[96] Thus higher levels of PCSK9 reduce the number of LDL receptors. If there are fewer LDL receptors, then LDL cholesterol levels rise in the blood. Conversely, lower levels of PCSK9 in the blood leads higher LDL receptor density and lower levels of LDL-C in the blood.

In 2003, a gain of function mutation was found in the PCSK9 gene that increases its activity, lowers LDL-receptor density, and causes high levels of LDL-C.[96-99] Patients with this mutation are at increased risk for premature cardiovascular disease.[96,100,101] Subsequently, loss of function mutations were identified that decrease the activity of PCSK9 and cause low levels of LDL-C.[102-104] Patients with these mutations are at decreased risk for cardiovascular disease.[103,105]

The biology described above suggests that drugs targeting PCSK9 have the potential to reduce LDL and cardiovascular disease. In June 2015, the FDA advisory panel voted to recommend approval of two human monoclonal antibodies that target proprotein convertase subtilisin/kexin type 9 (PCSK9) in the blood and markedly reduce LDL-C levels.

Alirocumab (Praluent®, Sanofi and Regeneron Pharmaceuticals, Inc.)

Alirocumab is a human monoclonal antibody that inhibits PCSK9. It is administered as a subcutaneous injection once every two weeks at doses of either 75 mg or 150 mg. It can be given as primary therapy to lower LDL-C, or it can be used in combination with statin therapy. Combination therapy is particularly efficacious, as statin therapy has been shown to up-regulate the production of PCSK9. The FDA approved alirocumab in July 2015; approved indications for alirocumab include use in addition to diet and maximally tolerated statin therapy in adult patients with (a) heterozygous familial hypercholesterolemia (HeFH); or (b) patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL cholesterol. The currently-listed wholesale acquisition cost of alirocumab is $14,600 annually, which is nearly 60 times the cost of generic statins.

Evolocumab (Repatha™, Amgen)

Evolocumab is a human monoclonal antibody that inhibits PCSK9. It is administered as a subcutaneous injection 140 mg once every two weeks or 420 mg once every four weeks. As noted for alirocumab, combination therapy with statins is particularly efficacious, as statin therapy has been shown to up-regulate the production of PCSK9. The FDA approved evolocumab in August 2015; approved indications for evolocumab include use in addition to diet and maximally tolerated statin therapy in adult patients with (a) heterozygous familial hypercholesterolemia (HeFH); (b) homozygous familial hypercholesterolemia (HoFH); or (c) patients with clinical atherosclerotic cardiovascular disease such as heart attacks or strokes, who require additional lowering of LDL-C. The currently-listed wholesale acquisition cost of evolocumab is $14,100 annually.

3. Summary of Coverage Policies

Due to their recent approval, coverage policies and authorization criteria for PCSK9 inhibitors are emerging. Below is a summary of available coverage policies as of October 2015. For completeness, we also document coverage policies in Table 1 that pertain to ezetimibe alone or in combination with simvastatin (Vytorin®) as well as rosuvastatin (Crestor®), the lone high-intensity statin available in branded form. Further explanation of these policies is available in Appendix 3.

3.1 Summary of Coverage for PCSK9 inhibitors: Praluent and Repatha

Regional Private Payers

Blue Cross Blue Shield of Vermont

http://www.bcbsvt.com/wps/wcm/connect/ae48547e-d7d9-444a-8d8b-d060db8f50fb/2015-praluent-pa-guidelines.pdf?MOD=AJPERES; http://www.bcbsvt.com/wps/wcm/connect/975504d0-cca6-41f7-8943-6c10577b8d86/2015-repatha-pa-guidelines.pdf?MOD=AJPERES

Coverage of both Praluent and Repatha is subject to prior authorization criteria. To receive a prescription, patients must have a diagnosis of HoFH, or HeFH with failure to reach LDL-C goals after trying at least one high intensity statin for 60 days. Praluent may also be covered as secondary prevention for atherosclerotic cardiovascular disease (ASCVD) or primary prevention for diabetes in patients who have not met LDL-C goals after trials of two high intensity statins for at least 60 days, or in patients who have experienced adverse effects with trials of at least two statins. Patients must be on a low fat diet and must be at least 18 years of age. A cardiologist must issue the initial request for either medication. Initial approvals will be effective for 6 months, and can be renewed if there is evidence of LDL-C reduction. Renewals are effective for 24 months and may be prescribed by another physician in consultation with a cardiologist. Dosing for Praluent should start at 75mg every two weeks subcutaneously. For HeFH, dosing for Repatha should start at 140mg once every 2 weeks, or 420mg once monthly. For HoFH, dosing should start at 420mg once monthly.

ConnectiCare

http://www.connecticare.com/globalfiles/pharmacycentral/ConnectiCare%20Formulary%20-%20Chart.pdf

Coverage of Praluent is subject to prior authorization criteria. Prescriptions must be filled by a specialty pharmacy. Repatha is not publicly listed in ConnectiCare's formulary at the time of this publication.

Harvard Pilgrim Health Care

https://www.harvardpilgrim.org/portal/page?_pageid=213,57031&_dad=portal&_schema=PORTAL

Harvard Pilgrim Health Care negotiated a discounted payment rate as well as the first pay-for-performance contract for Amgen's PCSK9 inhibitor Repatha. The drug will be included on HPHC's formulary at a reduced price. In addition, Amgen will provide additional rebates if the drug doesn't reduce cholesterol to specified target levels for eligible patients. Amgen may also pay out rebates if more patients covered by HPHC's plans end up taking the drug than was initially projected. The exact terms of the agreement including the level of discount and rebate amounts are not publicly available at this time.

National Payers

Aetna

http://www.aetna.com/products/rxnonmedicare/data/2016/MISC/PCSK9.html

Coverage of both Praluent and Repatha is subject to precertification criteria. Patients must have a documented diagnosis of HeFH or existing cardiovascular disease. In addition, patients must have LDL-C $\geq$70mg/dl after trying at least 2 different treatment regimens, including a high-potency statin at the maximally tolerated dose in combination with ezetimibe. Patients must have tried each regimen for at least 4 weeks with optimal compliance. Praluent and Repatha must be used in combination with a statin at maximally tolerated dose. Patients must be at least 18 years of age, have triglyceride levels $\leq$400mg/dl, have no history of severe renal impairment. Female patients must not be pregnant or planning to become pregnant while using either drug.

Repatha may also be covered for patients with HoFH who are at least 13 years of age. In these cases, Repatha must be used in combination with lipid-lowering therapy including a statin, ezetimibe, or lipid apheresis.

Anthem

https://www.anthem.com/ca/medicalpolicies/policies/mp_pw_c182635.htm

Praluent and Repatha are covered for patients who are at least 18 years old and at high risk for Acute Coronary Syndrome (ACS). Risk is identified by presence of HoFH, HeFH, or a history of ASCVD. To be eligible, patients with these conditions must be on high intensity statin therapy, have a condition that is a contraindication for statin therapy, or have a statin intolerance. Intolerance is defined as inability to tolerate at least 2 statin regimens, at least one of which was prescribed at the lowest starting daily dose; continued symptoms despite an attempt at dose reduction instead of

discontinuation; resolution of symptoms with discontinuation of statin therapy; and a return of symptoms after re-starting statin therapy in patients for whom re-challenge is clinically appropriate. Other possible causes of symptoms, such as hypothyroidism, drug interactions, concurrent illness, significant changes in physical activity, or underlying muscle disease, must be ruled out.

Patients meeting these criteria must also be taking ezetimibe in addition to statin therapy (for patients able to tolerate statins) and have had less than a 50% reduction in LDL-C after at least 90 days of compliant use of lipid lowering therapy and lifestyle modifications. Individuals whose initial LDL-C is unknown must have documented cardiovascular disease and LDL-C $\geq$ 70m/dL, or no documented cardiovascular disease and LDL-C $\geq$ 100mg/dL.

For continuation of therapy with a PCSK9 inhibitor after initial approval, all criteria must be met and documentation of LDL-C reduction must be provided.

In addition to the above uses, Repatha is also covered for patients 13 and older with HoFH, confirmed by presence of two mutant alleles, or confirmed by an untreated LDL-C of $\geq$500mg/dl or treated LDL-C $\geq$300mg/dl, with the presence of cutaneous or tendinous xanthoma before age 10, or untreated LDL-C levels consistent with HeFH in both parents.

United Healthcare

https://www.unitedhealthcareonline.com/ccmcontent/ProviderII/UHC/en-US/Assets/ProviderStaticFiles/ProviderStaticFilesPdf/Tools%20and%20Resources/Policies%20and%20Protocols/Medical%20Policies/Ox_MPUB_Future_Pharmacy/Med_Nec_Praluent.PDF

Both Praluent and Repatha are approved based on submission of medical records showing HeFH confirmed by pre-treatment LDL-C $\geq$190mg/dl (or >155mg/dL in patients under the age of 16) in both patient and in adult first- or second-degree relative. They are also covered for patients with ASCVD. Medical records must document that the patient has received at least 12 weeks or high-intensity statin therapy and will continue to receive a high-intensity statin. In patients unable to tolerate high-intensity statin due to documented myalgia or myositis, a moderate- or low-intensity statin may be used. If the patient is unable to tolerate all doses of statin therapy, and the patient has undergone a statin re-challenge with a different low-intensity statin with a documented return of muscle pain, has a contraindication to statin use, or has experienced rhabdomyolysis with statin treatment with CK elevations <10 times ULN, a PSCK9 inhibitor may be covered. Patients must also have tried Zetia in combination with statin therapy, or have a contraindication to Zetia. The drugs are also covered for patients with LDL-C $\geq$100mg/dL with ASCVD while on maximally tolerated lipid lowering therapy, or LDL-C $\geq$130mg/dL without ASCVD. The drugs must be used in addition to a low-fat diet and exercise and must be prescribed by a cardiologist, endocrinologist, or lipid specialist. They cannot be used in combination with any other PCSK9 inhibitor.

Initial authorization is valid for 6 months, after which point the prescription may be renewed. To meet criteria for renewal, patients must continue to received maximally tolerated statin therapy, continue to receive Zetia in addition to statin therapy, continue a low-fat diet and exercise program, and be prescribed by one of the aforementioned specialists. Medical records indicating an LDL-C reduction must be submitted. Re-authorization is valid for 12 months.

Repatha is also covered for HoFH confirmed by medical records documenting a pre-treatment LDL-C $\geq$500mg/dL or a treated LDL-C $\geq$300mg/dL and presence of either xanthoma before age 10 or evidence of HeFH in both parents. Patients should be on a low-fat diet and exercise program and be on other lipid-lowering therapies. Prescriptions must come from a specialist as described above. Repatha should not be used in combination with Juxtapid or Kynamro. The same re-authorization criteria as above apply.

3.2 Summary of Coverage for Existing Lipid-Lowering Therapies

Table 1 on the following page summarizes coverage policies for other key lipid-lowering therapies. As displayed in the table, nearly all regional public payers as well as regional and national private payers impose coverage restrictions on Crestor®, Vytorin®, and Zetia®. Detailed descriptions of these coverage policies can be found in Appendix 3.

Table 1: Coverage Policies for Crestor, Vytorin, and Zetia

	Crestor®	Vytorin®	Zetia®
Public Payers			
Connecticut	Covered	--	--
Maine	Covered	Covered	Covered. PA required as add-on to Lipitor. No PA for statin intolerance or patients at maximally tolerated statin dose.
Massachusetts	Covered for patients with inadequate response to atorvastatin dose of at least 80mg/day (or another equipotent statin), or adverse reaction or contraindication to atorvastatin	Covered for patients with inadequate response to atorvastatin dose of at least 80mg/day (or another equipotent statin), or adverse reaction or contraindication to atorvastatin	PA required. Covered for patients with inadequate response to atorvastatin 80mg/day or another statin with equipotent dosing, or for statin-intolerant patients
New Hampshire	Non-preferred	Non-preferred	Non-preferred agent. Must fail with 2 high-potency statins and combination products.
Rhode Island	PA and ST required	PA required.	PA required.
Vermont	QL apply.	PA required.	PA required.
Regional Private Payers			
BCBS MA	Tier 2, QL apply and ST required	ST required and QL apply	Tier 3, ST required.
BCBS RI	Tier 2	Tier 3	Tier 2
BCBS VT	Covered, no restrictions listed	--	--
ConnectiCare	Tier 2; ST required and QL apply	Tier 3, ST required and QL apply	Tier 2, QL apply
HPHC	Tier 2 Deductible exemption through Preventative Drug Benefit	Tier 3, QL; ST required for 10/10mg or 10/20mg formulations. Deductible exemption through Preventative Drug Benefit	Tier 2, ST required. Deductible exemption through Preventative Drug Benefit
NHPRI	Tier 3, ST required	Tier 3, PA required	Tier 3, PA required
THP	Tier 3, PA required	Tier 2	Tier 3
National Private Payers			
Aetna	Tier 2, QL	Tier 3, ST required and QL apply	Tier 2, QL apply
Anthem	Covered	--	--
Cigna	Tier 2, PA and ST required for 5mg and 10mg; 30mg and 40mg covered without restriction Deductible exemption through Preventative Drug Benefit	Tier 3, PA and ST required	Tier 2 Deductible exemption through Preventative Drug Benefit
Humana	Tier 2, QL	Tier 2 or 3 depending on plan, QL apply	Tier 2, QL apply
UHC	Tier 2, QL	Tier 3 or 4 depending on plan, QL apply	Tier 3 or 4 depending on plan, QL apply

QL=Quantity Limits ST=Step Therapy PA=Prior Authorization --- = Not listed in formulary

4. Comparative Clinical Effectiveness

4.1 Methods

The goal of this report is to evaluate the comparative clinical effectiveness and comparative value of PCSK9 inhibitors as a class for patients with elevated LD-C. We have attempted to identify all randomized controlled trials that evaluated the safety and efficacy of the two FDA approved PCSK9 inhibitors alirocumab and evolocumab. The published meta-analyses found that the LDL-C lowering effect of the two PCSK9 inhibitors were similar and there are no head to head trials that compare alirocumab to evolocumab; accordingly, we have elected to examine the impact of PCSK9 inhibitors as a class.

We searched the Medline database, Embase, Cochrane clinical trials database, Cochrane reviews database, and the Database of Abstracts of Reviews of Effects (DARE), using the key words "alirocumab" OR "evolocumab" OR "PCSK9 antibody." The search was performed for the period from 1945 through August 7, 2015. No language restriction was used. Full details of the search are in Appendix A1. The bibliographies of systematic reviews and key articles were manually searched for additional references. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full.

We included all phase 2 and 3 randomized trials evaluating either alirocumab or evolocumab that reported adverse events, LDL-C outcomes, or cardiovascular events. We excluded animal studies and phase 1 studies.

We abstracted data from each trial on the number of patients randomized, the duration of follow-up, age, sex, diabetes, heart disease, lipid levels, lipid therapy, trial quality measures, and the experimental and control interventions. We extracted data for intervention groups that evaluated the FDA approved doses for alirocumab and evolocumab. Key outcomes included changes in LDL-cholesterol levels, cardiovascular events, liver and muscle enzyme changes, neurocognitive outcomes, total adverse events, serious adverse events, discontinuations due to adverse events, and common adverse events.

The quality of individual studies was assessed by considering the domains listed below, which are adapted from the methods guide of the Agency for Healthcare Research & Quality (AHRQ[106]):

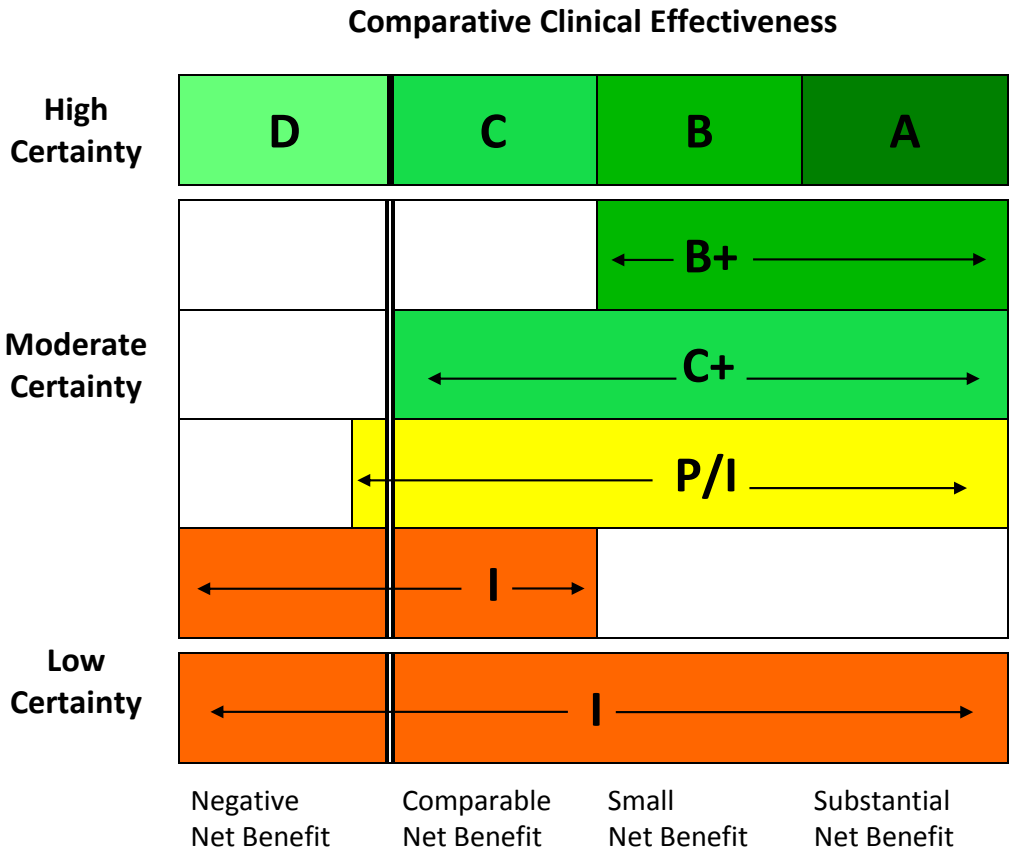
- Similarity of baseline characteristics and prognostic factors between comparison groups
- Well-described methods for randomization and concealment of treatment assignment
- Use of valid, well-described primary outcomes
- Blinding of subjects, providers, and outcome assessors
- Intent-to-treat analysis (all randomized subjects included)
- Limited and non-differential loss to follow-up
- Disclosure of any conflicts of interest

We also adopted the approach of the ICER Evidence Rating Matrix (see Figure 2 on the following page) to evaluate the overall strength of evidence for each therapy (ICER Evidence Rating Matrix: http://www.icer-review.org/wp-content/uploads/2008/03/Rating-Matrix-User-Guide-FINAL-v10-22-13.pdf)

The evidence rating reflects a joint judgment of two critical components:

1. The magnitude of the difference between a therapeutic agent and its comparator in "net health benefit" – the balance between clinical benefits and risks and/or adverse effects AND
2. The level of certainty in the best point estimate of net health benefit.

Figure 2. ICER Evidence Rating Matrix



A = "Superior" - High certainty of a substantial (moderate-large) net health benefit
B = "Incremental" - High certainty of a small net health benefit
C = "Comparable"- High certainty of a comparable net health benefit
D="Negative"- High certainty of an inferior net health benefit
B+="Incremental or Better" – Moderate certainty of a small net health benefit, with high certainty of at least incremental net health benefit
C+="Comparable or Better" - Moderate certainty of a comparable net health benefit, with high certainty of at least comparable net health benefit
P/I = "Promising but Inconclusive" - Moderate certainty of a small or substantial net health benefit, small (but nonzero) likelihood of a negative net health benefit
I = "Insufficient" – Either moderate certainty that the best point estimate of comparative net health benefit is comparable or inferior; or any situation in which the level of certainty in the evidence is low

Our search identified the same 25 trials that form the basis of two published systematic reviews and meta-analyses of the safety and efficacy of PCSK9 inhibitors.[1,2] We verified the data for their meta-analyses and primarily used the results of their meta-analyses to summarize the results from the trials. When not available elsewhere, we used data from the publicly-available FDA briefing documents and manufacturer submissions to the FDA for additional adverse event reporting.

For the meta-analyses, we followed the methodology reported in the meta-analysis by Navarese and colleagues.[1] Heterogeneity was assessed using the Cochran q test and the I^2 statistic. If the inconsistency was high ($I^2 \geq 50\%$), then the results were combined using a random effects model. Otherwise a fixed effects model was used. We assessed for publication bias using funnel plots and Egger's statistic.

We focused our analyses on the effect of PCSK9 inhibitors as a class because the LDL-C lowering effects are similar, there are no head to head trials comparing them, and because of currently limited data on their effects on key clinical outcomes, such as stroke, MI, and cardiovascular death. Where possible, we looked at important subgroups of patients who might benefit from PCSK9 inhibitors. These include patients with HoFH, those with HeFH, those who have already experienced CVD events, those without CVD events who are at high risk for events, and patients eligible for statin therapy who are intolerant of statins. Unfortunately, most of the trials included a mix of patients with and without prior CVD and did not report the results by those subgroups. The large outcomes trials currently in progress (ODYSSEY OUTCOMES, FOURIER) are specifically enrolling only patients with recent CVD events as this population is at highest risk for future events and thus will be most likely to benefit from PCSK9 inhibitor therapy.

4.2 Results

Study selection and Patient Population

The search identified 41 references describing 8 phase 2 trials, 16 phase 3 trials and one long-term follow-up study.[8,23-62] There are 13 trials (3 phase 2 trials) of alirocumab, including a total of 5,137 patients. Five of the trials of alirocumab have only been presented at conferences.[23,31,34,44] There are 10 trials (5 phase 2 trials) of evolocumab including a total of 5,022 patients. In addition, the OSLER trial re-randomized 4,465 participants from the phase 2 and 3 trials of evolocumab and followed them for 52 weeks.[56] The OSLER results are not included in the primary meta-analyses because the participants are already included in the results of the primary trials. However, the OSLER results (combined OSLER 1 and OSLER 2 trials) will be summarized because of the relatively long duration of follow-up and large size of the trial. All of the trials of evolocumab have been published in the peer-reviewed literature.

Appendix 6 Table 1 provides an overview of the studies. The TESLA Part B trial (evolocumab) is the only trial that specifically enrolled patients with HoFH.[47] The remaining trials enrolled patients with either HeFH or non-specific hypercholesterolemia. The Gauss and Gauss 2 trials[61,62] (evolocumab) and the Odyssey Alternative trial [43] only enrolled patients with statin intolerance. There were no trials that only enrolled patients with known CVD, although most of the trials had a significant portion of participants with CVD. Follow-up was longer than one year for 5 trials, one year for 2 trials and less than one year for the remaining 17 trials. PCSK9 inhibitor therapy was compared to placebo in 14 trials, to ezetimibe in 7 trials, and to both placebo and ezetimibe in the remaining 3 trials.

The average age of the participants was 51 to 66 years with the exception of the TESLA Part B trial (HoFH patients) in which the participants had an average age of 31. About half of the participants were female, approximately 30% had prior CVD, and approximately 15% had diabetes mellitus. High intensity statin therapy was used in 17 of the 24 trials.

Quality of individual studies

The assessment of the quality of individual studies is summarized in Appendix 6 Table 2. For the unpublished studies, peer reviewed publications[27,35,43] of the study design and rationale were used to supplement the abstracts and slide presentations. There was low risk of bias in all of the trials except the OSLER 1 and 2 trials. Randomization was done appropriately with allocation concealment and blinding of the participants, the investigators, and the staff performing outcome adjudication. Follow-up retention was high and analyses were performed adhering to intention-to-treat principles. All of the studies were funded by the manufacturers. In the OSLER trials, appropriate randomization and allocation concealment was performed, but there was no blinding of patients, investigators, or staff, so there was increased risk of bias.

Key Studies

Alirocumab

The ODYSSEY LONG TERM trial is the largest randomized trial of alirocumab.[50] The eligible population included adults with known coronary heart disease (69%) or a coronary heart disease (CHD) risk equivalent (peripheral artery disease, ischemic stroke, chronic kidney disease, or diabetes with at least two additional risk factors). Patients also had an LDL-C level ≥ 70 mg/dL on statin therapy. All participants continued to take high intensity statin therapy (47%) or the highest tolerated dose (53%). The investigators randomized 2,341 participants in a 2:1 ratio to alirocumab 150 mg every two weeks (n=1530) or to identical placebo (n=780) and followed them for 78 weeks. At 24 weeks LDL-C levels declined from 122.8 to 48.3 mg/dL in the alirocumab group and from 122.0 to 118.9 in the placebo group. The reduction in LDL-C was greater in the alirocumab group at 24 weeks (-61.0% vs. 0.8%, p<0.001) and at 78 weeks (-52.4% vs. 3.6%, p<0.001).

Overall, there was no trend towards more AEs, serious AEs, diabetes, liver enzyme elevation, or muscle enzyme elevation in the alirocumab group (see Table 2 on the following page). There was a trend towards more discontinuations due to AEs, more neurocognitive AEs, and more injection site reactions, but these were not statistically significant, particularly if adjustment is made for multiple comparisons. For the major cardiovascular adverse events, there were trends towards fewer deaths from CHD (0.3% vs. 0.9%, p=0.26), fewer non-fatal MIs (0.9% vs. 2.3%, p=0.01), and less unstable angina requiring hospitalization (0% vs. 0.1%, p=0.34), but more fatal and non-fatal ischemic strokes (0.6% vs. 0.3%, p=0.35). There was a significant reduction in the sum of these four major adverse cardiovascular events (MACE 1.7% vs. 3.3%, p=0.02). In the alirocumab group, the 575 participants (37%) with LDL-C levels < 25 mg/dL on two or more consecutive measurements had similar rates of adverse events as the overall alirocumab group.

The trial unequivocally demonstrates that alirocumab lowers LDL-C levels compared with placebo. The study is underpowered to evaluate uncommon AEs but selected AEs can be found in Table 2 on the next page. Given the large number of AEs evaluated, even those achieving statistical significance at a p-value of 0.05 may be due to chance. For example, at 52 weeks follow-up in the other large RCT of alirocumab[26] (ODYSSEY COMBO II trial, n=720), there were more non-fatal MIs in the alirocumab group (2.5% vs. 1.2%) and fewer patients reporting myalgias (4.4% vs. 5.0%), both in the opposite direction of the ODYSSEY LONG TERM results. Larger clinical trials with longer follow-up are needed to adequately address the balance of benefits and harms for the PCSK9 inhibitors.

Table 2: Selected adverse events in the ODYSSEY LONG TERM trial

Adverse event (AE)	Alirocumab (%)	Placebo (%)	P value
Any AE	81.0	82.5	0.40
Serious AE	18.7	19.5	0.66
AE leading to drug discontinuation	7.2	5.8	0.26
Death from CHD	0.3	0.9	0.26
Non-fatal myocardial infarction (MI)	0.9	2.3	0.01
Stroke	0.6	0.3	0.35
Myalgias	5.4	2.9	0.006
Neurocognitive AE	1.2	0.5	0.17
New diabetes	1.8	2.0	0.84
Alanine Aminotransferase (ALT) elevation	1.8	2.1	0.75
Creatine kinase (CK) elevation	3.7	4.9	0.18
Injection site reaction	5.9	4.2	0.10

Evolocumab

TESLA Part B

The TESLA Part B trial is unique among the trials because it randomized 49 participants ≥ 12 years old who were diagnosed with HoFH.[47] All participants were taking statins (94% high intensity) and most were also taking ezetimibe (92%). Despite maximal lipid lowering therapy, the baseline LDL-C level was 9.0 mmol/L (348 mg/dL). The participants were randomized to evolocumab 420 mg or placebo every 4 weeks for 12 weeks. LDL-C decreased by 23.1% in the evolocumab group and increased by 7.9% in the placebo group (between group difference: 30.9%, $p<0.0001$). The percentage change in LDL-C is relatively low in this study, but 92% of patients were taking ezetimibe. There were no deaths, no serious adverse events, and no discontinuations due to AEs. Overall AEs were less common in the evolocumab group (36% vs. 63%). The trial was too small and follow-up too short to evaluate clinical outcomes.

DESCARTES

The DESCARTES trial is the only primary randomized trial of evolocumab with greater than 12 weeks of follow-up. The eligible population included adults with an LDL-C level ≥ 75 mg/dL. Approximately 15% of the participants had prior CVD and 12% had diabetes. The investigators randomized 901 participants in a 2:1 ratio to evolocumab 420 mg every four weeks (n=599) or to identical placebo (n=302) and followed for 52 weeks. At 52 weeks LDL-C levels declined 50.6% from a baseline of

100.4 mg/dL in the evolocumab group and increased 8.7% from 100.2 mg/dL in the placebo group (between group difference: 57.0%, p<0.001).

Overall, there were no more AEs in the evolocumab group, as seen in Table 3 below. There were nominally more serious AEs, discontinuations due to AEs, atherosclerotic events, myalgias, injection site reactions and CK elevations, though the absolute differences were small. Neurocognitive AEs were not reported.

Table 3: Selected adverse events in the DESCARTES trial

Adverse event (AE)	Evolocumab (%)	Placebo (%)	P value
Any AE	74.8	74.2	NR
Serious AE	5.5	4.3	NR
AE leading to drug discontinuation	2.2	1.0	NR
Death	0	0.3	NR
Atherosclerotic event	1.0	0.7	NR
Myalgias	4.0	3.0	NR
ALT elevation	0.8	1.0	NR
CK elevation	1.2	0.3	NR
Injection site reaction	5.7	5.0	NR

NR Not reported

OSLER 1 and 2

The OSLER trials were open label randomized trials of the participants in the all of the Phase 2 trials of evolocumab (OSLER 1) and all of the Phase 3 trials (OSLER 2) who agreed to be re-randomized for extended follow-up.[56] The results of the two trials were combined in the published results as the OSLER trial. The investigators randomized 4,465 participants (74.1% of eligible participants) in a 2:1 ratio to evolocumab either 140 mg every two weeks or 420 mg once a month (n=2,976) or to standard therapy without placebo (n=1489) and followed for 52 weeks. The baseline LDL-C level was 120 in the evolocumab group and 121 in the standard therapy group. At 48 weeks the between group difference in LDL-C was 58.4% (p<0.001).

Transient evolocumab-binding antibodies were detected in 0.3% of patients in both groups, but were not neutralizing. As in the prior trials, the AEs are similar in the two groups (Table 4 on the following page), though may be more subject to reporting bias because of the lack of blinding in the OSLER trials.

Table 4: Selected adverse events in the OSLER 1 AND 2 trials

Adverse event (AE)	Alirocumab (%)	Placebo (%)	P value
Any AE	69.2	64.8	NR
Serious AE	7.5	7.5	NR
AE leading to drug discontinuation	2.4	NA	NR
Death from CHD	0.1	0.2	NR
Non-fatal MI	0.3	0.3	NR
Stroke	0.1	0.1	NR
Myalgia	3.0	2.9	NR
Neurocognitive AE	0.9	0.3	NR
New diabetes	1.1	0.7	NR
ALT elevation	1.0	1.2	NR
CK elevation	0.6	1.1	NR
Injection site reaction	4.3	NA	NR

NR Not reported NA Not applicable

Clinical Benefits

The section that follows evaluates the effectiveness of PCSK9 inhibitors as a class, including the percentage LDL-C lowering effects of PCSK9 inhibitors versus placebo and versus ezetimibe, and differences by individual drug dose. Background lipid therapy may be important because statin therapy raises PCSK9 levels in the blood, so the percentage reduction of LDL-C tends to be greater in individuals taking statin therapy compared to those not receiving such therapy. Clinical outcomes, including total mortality, CVD mortality, non-fatal MI, and stroke are then discussed. We have elected to not apply any limits to the PCSK9 inhibitor evidence base used for this analysis. This decision was made because no trials were designed with clinical events as the primary outcome, the number of events is low, and the lipid lowering effects are similar for the approved doses of PCSK9 inhibitors. The meta-analysis results of Navarese and colleagues are used unless otherwise noted.[1]

LDL-C reduction

The summary estimate for percentage reduction in LDL-C is 47.5% (95% CI: 25.4 to 69.6). There was no evidence for publication bias for the meta-analysis of LDL-C reduction (Egger's p-value 0.99). However, there was significant heterogeneity observed (I^2 = 93%, p<0.001). As noted in the Methods, an I^2 > 50% is considered high. Sources of heterogeneity likely include differences in the patient populations studied (baseline lipid levels, background statin therapy), differences in the dose and type of PCSK9 inhibitor, and differences in the comparison group. These are explored further in stratified analyses in the table below.

Table 5: Meta-analysis of the percentage reduction in LDL-C by PCSK9 inhibitors as a class in 10,159 participants in phase 2 and 3 randomized trials stratified by background statin therapy

	Background Statin Therapy			
Comparison group	All, % (95% CI)	No statin, %	High intensity statin, %	Other statin, %
Placebo	58.8 (56.5 to 61.0)	53.6	57.9	65.2
Ezetimibe	36.2 (33.1 to 39.3)	36.2	34.4	37.5

The percentage reduction in LDL-C is greater when PCSK9 inhibitors are compared to placebo (58.8%) than that observed compared to ezetimibe (36.2%). The percentage reduction in LDL-C varies much less by background statin therapy.

Findings are stratified by dose and type of PCSK9 inhibitor in Table 6 below. Evolocumab may have slightly greater LDL-C reductions than alirocumab, but the differences are small compared to the percentage reduction achieved by either of the PCSK9 inhibitors. Furthermore, differences in the underlying populations studied may explain the relatively small differences in the percentage reduction in LDL-C. The lack of head to head randomized trials makes it impossible to conclude that one of the PCSK9 inhibitors lowers cholesterol more than the other.

Table 6: Meta-analysis of the percentage reduction in LDL-C by PCSK9 inhibitors in 10,159 participants in phase 2 and 3 randomized trials by stratified by dose and type of PCSK9 inhibitor

	Dose and type of PCSK9 inhibitor				
Comparison group	All, % (95% CI)	Alirocumab 75 mg Q2W	Alirocumab 150 mg Q2W	Evolocumab 140 mg Q2W	Evolocumab 420 mg Q4W
Placebo	58.8 (56.5 to 61.0)	52.6	56.2	63.5	57.3
Ezetimibe	36.2 (33.1 to 39.3)	31.7	*	39.3	37.5

** Insufficient data*

The PCSK9 inhibitors also improved other lipid parameters. HDL cholesterol increased by 6.1% compared with placebo and 6.8% compared with ezetimibe (P<0.001 for both). There were also significant reductions in total cholesterol (39% vs. placebo, 24% vs. ezetimibe, p<0.001 for both) and in lipoprotein (a) (28% vs. placebo, 24% vs. ezetimibe, p<0.001 for both).

The evidence clearly shows that the PCSK9 inhibitors improve all lipid parameters significantly compared to placebo or ezetimibe therapy. These findings are consistent whether the population studied is taking high intensity statin therapy, lower intensity statin therapy, or no statin therapy at baseline.

LDL-C lowering by patient subpopulation

HoFH: As described earlier, the TESLA Part B trial[47] is the only trial that randomized patients with known HoFH. The percentage LDL-C reduction of evolocumab compared to placebo was lower in

this trial (30.9%) than seen in other trials. This may reflect the much higher pre-treatment LDL in this population (356 mg/dL), or it may reflect lower efficacy of PCSK9 inhibitors in patients with one or more of the mutations represented in the trial. In addition, 92% of the participants were taking ezetimibe: the observed difference is similar to that observed in the studies that randomized patients to either a PCSK9 inhibitor or ezetimibe. Even though the relative reduction in LDL was lower than in the other trials, the absolute reduction (74 mg/dL) is similar to that reported in populations with HeFH or non-specific hypercholesterolemia.

HeFH: 10 studies randomized primarily participants with HeFH. The LDL-C reduction in this subpopulation ranged from 39.1% to 63.9% compared to placebo and from 34% to 35.8% compared to ezetimibe. These subgroup findings are quite similar to the overall results.

Non-specific hypercholesterolemia (HC): 13 studies randomized primarily participants with non-specific hypercholesterolemia. The LDL-C reduction in this subpopulation ranged from 45.9% to 70.9% compared to placebo and from 27.2% to 43.4% compared to ezetimibe. Again, these subgroup findings are quite similar to the overall results.

Statin intolerant: Three studies randomized statin intolerant patients (GAUSS, GAUSS 2, ODYSSEY ALTERNATIVE).[44,61,62] In the GAUSS trial, there was a 47.3% LDL-C reduction with evolocumab treatment compared to placebo, and a 35.9% reduction compared to ezetimibe. In the GAUSS 2 trial, the LDL-C reduction was 38.1% with every 2 week dosing and 37.6% with every 4 week dosing both compared to ezetimibe. Finally, in the ODYSSEY ALTERNATIVE trial, the LDL-C reduction with alirocumab treatment was 30.4% compared to ezetimibe.

The percentage LDL-C reduction in the statin intolerant patient population was similar to that of both the FH and HC populations. There do not appear to be large differences between the LDL-C lowering effects of PCSK9 inhibitors in HeFH, HC, or statin intolerant patient populations. The HoFH population, which is a small population with extraordinarily high LDL-C levels, appears to have a lower percentage reduction in LDL-C than the other populations. The study results were not presented in subgroups defined by a prior history of CVD events, so no pooled estimates could be made.

Clinical outcomes

There are large long-term (5-year or more) outcomes studies ongoing for both alirocumab (ODYSSEY OUTCOMES, n=18,000, >5 years) and evolocumab (FOURIER, n=22,500, 5 years) that should present initial results in 2017. The clinical outcomes below from the meta-analysis by Navarese represent CVD events in trials designed with LDL-C lowering as the primary outcome and are reported as adverse events. The most important clinical outcomes for lipid lowering therapy include death from cardiovascular disease, MI, stroke, and unstable angina requiring hospitalization. There was little statistical heterogeneity for each of the outcomes (I^2 = 0%), so fixed

effects models were used. Navarese and colleagues did not report the stroke outcomes, so we performed our own meta-analysis for this outcome using the same analytic methods (Table 7, below). Publication bias was not apparent for any outcome, either by examining funnel plots or Egger's p statistic.

Table 7: Meta-analysis results for patient-oriented outcomes

Outcome	OR (95% CI)	p	I^2	N	Events PCSK9 group (%)	Events control group (%)
All-cause mortality	0.45 (0.23-0.86)	0.015	0%	10,159	19 (0.3%)	21 (0.5%)
CVD Mortality	0.50 (0.23-1.10)	0.084	0%	10,159	12 (0.2%)	13 (0.3%)
MI	0.49 (0.26-0.93)	0.030	0%	5,195	19 (0.6%)	19 (1.0%)
Stroke	1.97 (0.69-5.65)	0.206	0%	4,683	14 (0.5%)	3 (0.2%)
Unstable angina	0.61 (0.06-6.14)	0.676	0%	3,894	1 (0.05%)	1 (0.08%)

The findings of the meta-analysis suggest that the PCSK9 inhibitors reduce the odds of all-cause and cardiovascular mortality by about 50%; however the total number of events is low and the confidence intervals are wide. The odds ratio for stroke in the meta-analysis was twice as high in the PCSK9 group, but the confidence interval is very wide and not statistically significant. There were no significant differences in these results when stratified by comparison group (placebo, ezetimibe), by PCSK9 inhibitor (alirocumab, evolocumab), or when adjusted for length of follow-up. In sensitivity analyses excluding the data from studies not yet published in the peer-reviewed literature, the conclusions are the same.

Harms

As seen in the earlier section that described the largest trials of PCSK9 inhibitors, there were no large differences in the overall adverse event rates between these agents and their comparators. Meta-analyses of selected adverse event rates are summarized in Table 8 on the following page. We focused on serious adverse events including those leading to drug discontinuation, adverse events associated with other lipid lowering drugs (myalgias, neurocognitive events, liver and muscle enzyme elevations), and those associated with monoclonal antibody injections (injection site reactions, hypersensitivity reactions).

Table 8: Meta-analysis results for selected harms

Outcome	OR (95% CI)	P	I^2	N	Events PCSK9 group (%)	Events control group (%)
Serious AE	1.01 (0.87-1.18)	0.879	0%	10,159	573 (9.3)	307 (7.7%)
AE leading to drug discontinuation	1.03 (0.84-1.26)	0.773	0%	9424	270 (4.7%)	167 (4.5%)
Myalgias	1.16 (0.91-1.49)	0.236	37%	6269	199 (5.1%)	108 (4.5%)
Neurocognitive AE	1.08 (0.57-2.06)	0.816	13	6601	27 (0.6%)	14 (0.6%)
ALT elevation	0.82 (0.54-1.24)	0.350	0%	9108	55 (1.0%)	39 (1.1%)
CK elevation	0.72 (0.54-0.96)	0.026	0%	10,159	121 (2.0%)	92 (2.3%)
Injection site reaction	1.30 (1.03-1.65)	0.029	4.5%	9028	222 (4.1%)	106 (3.0%)
Hypersensitivity reactions	0.69 (0.23-2.08)	0.510	3.5%	1062	7 (1.2%)	7 (1.4%)

These meta-analysis results do not suggest that the PCSK9 inhibitors lead to elevations in serious adverse event rates. There are more injection site reactions, which may lead to slightly higher rates of drug discontinuation compared to the control group. There is a slight excess of neurocognitive events with PCSK9 inhibitors, but the results are not statistically significant. There is also a trend towards more myalgias in the PCSK9 treated participants, but this is balanced by a statistically significant reduction in the number of participants with elevations in the muscle enzyme CK.

The results were generally consistent, and there was little evidence for publication bias except for the neurocognitive adverse events, which were not consistently reported in the published studies. Excluding data from the unpublished studies did not significantly impact the results.

Although these results do not identify any worrisome or unexpected adverse events, many of the trials were 6 months or less in duration. Serious adverse events may be identified in the large 5-year outcome trials that are currently in progress (ODYSSEY OUTCOMES, FOURIER).

4.3 Summary and Comment

Our analyses demonstrate that the existing evidence provides moderate certainty that PCSK9 treatment provides an incremental or substantial net health benefit for all of the patient subpopulations included in the scope of this review. There is no question that the drugs improve intermediate risk factors for cardiovascular disease. They substantially reduce LDL-C, total cholesterol, and lipoprotein (a), and also modestly elevate HDL-cholesterol. A high-quality meta-analysis found a 50% reduction in all-cause mortality that was statistically significant and reductions of similar magnitude (albeit not statistically significant) in death from cardiovascular disease and in MIs.

The drugs also appear to be very well-tolerated. The randomized trials do not demonstrate an increase in AEs, serious AEs, or drug discontinuations due to AEs. Neurocognitive event rates are

low and do not appear to be increased in patients randomized to PCSK9 inhibitors compared to the control patients.

However, there are several limitations in the evidence base that give reason for caution. There are theoretical concerns that long term exposure to very low levels of cholesterol may have unexpected adverse effects that have not been observed in the evidence base to date because the majority of the studies lasted less than 6 months. In addition, as noted earlier, medications such as torcetrapib that lower LDL-C, raise HDL, and have strong biological plausibility, have demonstrated increased cardiovascular event rates and total mortality in long term studies. The large randomized trials with long-term follow-up that are designed to evaluate the effect of the PCSK9 inhibitors on hard clinical endpoints have completed recruitment, but their results will not be available until 2017.

The promising evidence on patient-centered outcomes from the published meta-analysis is also limited in several ways. First, the 95% confidence intervals for the odds ratios estimating clinical benefit either include 1.0 or approach 1.0. Second, the evidence in this meta-analysis combines data from trials of two different PCSK9 inhibitors, each with two different dosing schedules, with too few events in the evidence base to attempt subgroup analyses. Another limitation of the meta-analysis is that the populations studied were quite different: young adults with homozygous FH and very high LDL-C; older adults with LDL-C < 100, but not at goal; and older adults who have already had a heart attack or stroke. A final reason for caution about the findings for the meta-analysis is that the PCSK9 inhibitors were compared to two different control arms: placebo and ezetimibe. The percentage LDL-C reduction consistently favored PCSK9 inhibitors, but the magnitude varied slightly by population and significantly by control group. It is likely that the clinical benefits will vary by dose, drug, background drug therapy, and population studied.

Despite these limitations, the evidence base provides high certainty that PCSK9 inhibitors lead to superior reductions in LDL-C levels compared to both placebo and ezetimibe. The percent reduction in LDL-C with PCKS9 inhibitor treatment is approximately 55-60% and appears not to differ substantially across different patient subpopulations. The potential net health benefit from this level of LDL-C reduction will be greater among patient subpopulations at higher risks of CVD. Among the subgroups, the population with HoFH is at highest risk for CVD events. Untreated, they have CVD events in the second decade of life. Differences in CVD risk are less marked between patients with HeFH and those with a prior history of CVD who have elevated LDL-C levels despite other treatment and/or who cannot take statins.

In summary, the ICER review team believes that the existing evidence suggests, with moderate certainty, that the net health benefit of the PCSK9 inhibitors is either incremental or substantial for the patients in the subpopulations within the scope of this review. Despite the uncertainty in the actual level of net health benefit, we believe there is less than a 10% chance that ongoing trials will demonstrate a net harm from PCSK9 inhibitor treatment, and, therefore, our evidence rating within the ICER Integrated Evidence Rating framework is “Promising but Inconclusive.”

5. Other Benefits or Disadvantages

Our reviews seek to provide information on other benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples include, but are not limited to:

- Methods of administration that improve or diminish patient acceptability and adherence
- A public health benefit, e.g. reducing new infections
- Treatment outcomes that reduce disparities across various patient groups
- More rapid return to work or other positive effects on productivity (if not considered a benefit as part of comparative clinical effectiveness)
- New mechanisms of action for treatments of clinical conditions (e.g., mental illness) for which the response to currently available treatments varies significantly among patients for unknown reasons (substantial heterogeneity of treatment effect)

Currently available PCSK9 inhibitors must be injected. This is a potential disadvantage compared to most pharmaceuticals because some patients are unable to self-inject or experience anxiety associated with self-injection. On the other hand, patients rapidly learn to inject themselves with low molecular weight heparin and with insulin when needed, so the barrier may not be too high, particularly for patients motivated by FH or a history of CVD events. Furthermore, the need to inject the medication only once or twice a month may enhance adherence and be considered an advantage compared to medications that need to be taken on a daily basis.

There do not appear to be other benefits or disadvantages of note to PCSK9 inhibitor therapy.

6. Comparative Value

6.1 Overview

In order to assess the incremental costs per outcomes achieved of PCSK9 inhibitors, we conducted a cost-effectiveness analysis using a previously validated model of cardiovascular disease in the contemporary adult population of the United States (see section 6.2).[63-65] We modeled the addition of ezetimibe and PCSK9 inhibitors to background statin therapy as currently being used in the population and examined the impact on MI, stroke, and cardiovascular death. We estimated drug costs based on current prices, predicted population-level reductions in clinical outcomes, and cardiovascular disease costs (hospitalizations, procedures, and chronic disease care costs) due to the LDL-C lowering effects of the drugs to estimate the incremental cost-effectiveness of PCSK9 inhibitors and their anticipated budgetary impact. Clinical trials suggest only minor differences in effectiveness between alirocumab and evolocumab based on frequency of dosing and impact on LDL-C; therefore, we model PCSK9 inhibitors as a class for the purpose of this analysis.

Outputs from this model were also used to inform a population-based analysis of the one- and five-year budgetary impact of PCSK9 inhibitors, by key subpopulation and on an overall basis (see section 6.3). Budgetary impact was assessed using assumed levels of uptake over these timeframes, and included assessment of drug costs as well as cost savings from averted cardiovascular events. We also define a "value-based price benchmark" for PCSK9 inhibitors based on a calculated threshold for policy intervention to manage the costs of new pharmaceuticals.

6.2 Incremental Costs per Outcomes Achieved

Cost-Effectiveness Model: Methods

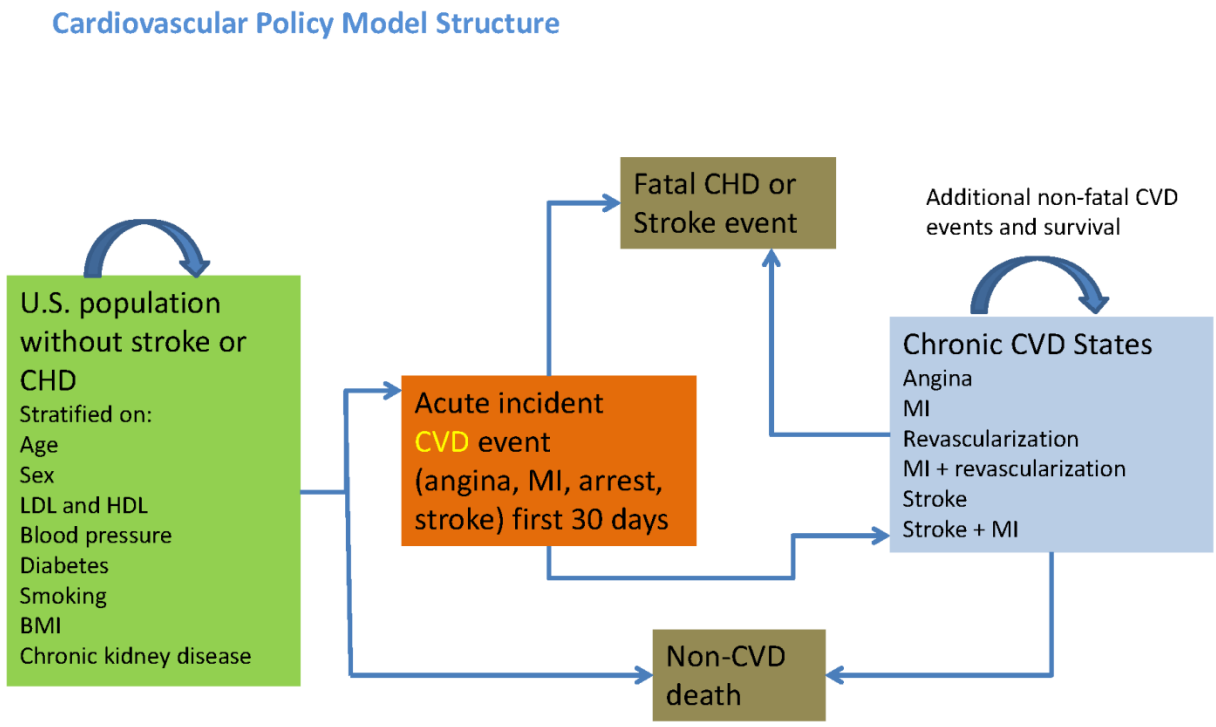
Model Structure

The CVD Policy Model is a computer-simulation, discrete-state Markov model of coronary heart disease and stroke incidence, prevalence, mortality, and costs in the U.S. population over age 35.[63-65] The model was created at Harvard University in 1984 and has been used for more than 30 years to provide evidence on the value of cardiovascular disease prevention approaches in U.S. adults. The CVD Policy Model team has published reports from a number of high-impact studies of public health and clinical interventions.[66-75] The last model software and input data update was completed in 2015.

The Demographic-Epidemiologic Sub model predicts coronary heart disease and stroke incidence and non-CVD mortality among subjects without CVD, stratified by age, sex, and up to 8 additional categorized risk factors estimated from weighted United States National Health and Nutrition

Examination Surveys data from 2007-2010 (Figure 3). Risk factors include: systolic blood pressure (<130, 130-139.9, ≥140 mm Hg), smoking status (active smoker, non-smoker with exposure to environmental tobacco smoke, non-smoker without environmental exposure), high density lipoprotein (HDL) cholesterol (<1.0, 1.0-1.5, ≥1.6 mmol/L; <40, 40-59.9, ≥60 mg/dL), low-density lipoprotein cholesterol (LDL-C) (<2.6, 2.6-3.3, ≥3.4 mmol/L; <70, 70-99.9, ≥100 mg/dL), body mass index (<25, 25-29.9, ≥30 kg/M^2), diabetes mellitus (Type 1 or Type 2; yes or no), statin use (yes or no). After CVD develops, the Bridge Sub model characterizes the initial stroke or coronary heart disease event (cardiac arrest, MI, or angina) and its sequelae (including CVD mortality) for 30 days. Then, the Disease History Sub model predicts subsequent CVD events, coronary revascularization procedures, CVD mortality, and non-CVD mortality among patients with CVD, stratified by age, sex, and history of events. The general chronic CVD categories are coronary heart disease only, stroke only, and combined prior coronary heart disease and prior stroke. Each state and event has an annual cost and quality-of-life adjustment, as well as an annual probability of a repeat event and/or transition to a different CVD state. All population distributions, risk factor levels, coefficients, event rates, case fatality rates, costs, and quality-of-life adjustments can be modified for forecasting simulations.

Figure 3: Cardiovascular Disease Policy Model structure and disease states.



We modeled the entire population of U.S. adults aged 35 to 74 years in the year 2015. We assumed the health system perspective,[76] considering all direct and induced medical costs and relevant clinical outcomes over a lifetime analytic horizon (defined as until patients reach 95 years of age due to the absence of high-quality epidemiologic data in older populations). Utilities and costs were assigned to each clinical event in annual cycles and discounted at 3% annually.[107] We conducted extensive deterministic and scenario-based sensitivity analyses to account for uncertainty in the input parameters. We adhered to the recommendations of the Panel on Cost -Effectiveness in Health and Medicine where practicable.[108] Additional modeling details, including sources of input parameters and model calibration, are presented in Appendix A7.

With regards to the impact of statin therapy on LDL-C, we assumed a "flat" beta across age-groups as demonstrated in clinical trials: i.e., that risk reduction in cardiovascular events per unit reduction in cholesterol is identical in all age groups.[109] The effect of LDL-C lowering on CHD prevention assumed by the CVD Policy Model (relative risk per mg/dL LDL-C reduction) was validated in a simulation of West of Scotland Coronary Prevention Study.[71,110] Simulations of the US population aged 45-64, imposing the pre- and post-intervention LDL-C and HDL cholesterol levels recorded in the West of Scotland Study 9[110] produced estimates of key clinical outcomes, i.e., cumulative CHD mortality or first MI, and ratio of events in participants treated with statins or placebo, within 1% of the numbers observed in the trial (Appendix 7 Table 2).

Importantly, while categorical definitions of LDL-C are used for the purpose of stratifying patients without a CVD history into risk factor groups, continuous measures of LDL-C were used to assess levels of risk reduction for the treatments of interest in our model.

The CVD Policy Model is written in Lahey Fortran 95. Processing of modeled outcomes was carried out using QuickBasic64 and Excel 2011 (Microsoft, Redmond, Washington); statistical analyses were performed using SAS 9.4 (SAS, Inc., Cary, North Carolina) and Stata 13 (StataCorp, College Station, Texas).

Target Population

In the base case, we evaluated the cost-effectiveness of PCSK9 inhibitors in three target populations. Populations were chosen to approximate those described in the FDA-labeled indications for alirocumab, which was approved in July 2015.[77] This is in line with the idea that because statins are both inexpensive and effective, PCSK9 inhibitors will probably be first used among patients at highest risk for adverse cardiovascular events (Table 9 on the following page).

Three target populations:

1. **Familial Hypercholesterolemia (FH)**

   At least three different definitions of FH are used in clinical practice; all clinical definitions relate to high baseline levels of LDL-C and personal or family history of premature coronary heart disease. [111,112] For the purpose of this analysis, we defined FH as a baseline LDL-C level greater than or equal to 250mg/dL (6.465 mmol/L) among patients not on statin therapy, and an LDL-C level greater than or equal to 200mg/dL (5.172 mmol/L) among patients receiving statin therapy. We were unable to specifically identify patients with a family history of premature coronary disease because of limitations of available epidemiological data. For the purpose of this analysis, we assumed that 10% of the population would be statin-intolerant, defined as being unable to tolerate even low-dose statins, and varied this proportion between 3% and 20% in sensitivity analyses.[113-115]

2. **Patients with pre-existing CVD (defined as a prior history of angina, MI, or stroke) whose LDL-C level is greater than or equal to 70mg/dL (1.810 mmol/L) and who are unable to tolerate statin therapy.**

   For the purpose of this analysis, we assumed that 10% of the population with pre-existing CVD is statin-intolerant, defined as being unable to tolerate even low-dose statins. We varied the prevalence of statin intolerance in sensitivity analyses between 3% and 20%.

3. **Patients with pre-existing CVD (defined as a prior history of angina, MI, or stroke) whose LDL-C level is greater than or equal to 70mg/dL (1.810 mmol/L) despite receiving maximally tolerated statin therapy.**

Demographic and key clinical characteristics of the target populations are shown in Appendix 7 Table 3.

Table 9. Treatment Strategies Evaluated in this Report.

	Target Population											
	FH (Base Case = As Treated)			FH (Base Case = Full Treatment)			CVD, Statin-Intolerant			CVD, Statin-Tolerant		
	Control Arm	Ezetimibe Arm	PCSK9 Inhibitor Arm	Control Arm	Ezetimibe Arm	PCSK9 Inhibitor Arm	Control Arm	Ezetimibe Arm	PCSK9 Inhibitor Arm	Control Arm	Ezetimibe Arm	PCSK9 Inhibitor Arm
Statin Intolerant (10% of population)	-	Ezetimibe	PCSK9 inhibitor	-	Ezetimibe	PCSK9 inhibitor	-	Ezetimibe	PCSK9 inhibitor	-	-	-
Statin Tolerant on Statins	Statin	Statin + Ezetimibe	Statin + PCSK9 inhibitor	Statin	Statin + Ezetimibe	Statin + PCSK9 inhibitor	-	-	-	Statin	Statin + Ezetimibe	Statin + PCSK9 inhibitor
Statin Tolerant not already on statins	-	-	-	Statin*	Statin* + Ezetimibe	Statin* + PCSK9 inhibitor	-	-	-	-	-	-

Treatment Strategies

We modeled three treatment strategies in patients able to tolerate statins, as shown in Table 9, above:

- background treatment with a statin (as treated in the population, control),
- incremental treatment with ezetimibe among patients already on a statin, or
- incremental treatment with a PCSK9 inhibitor among patients already on a statin.

In the base case, 10% of the population was deemed statin-intolerant. Where relevant, the treatment strategies available to these patients were:

- no treatment with lipid lowering therapies (control),
- treatment with ezetimibe, or
- treatment with a PCSK9 inhibitor.

In other words, the FH and CVD populations included patients who were receiving statin therapy, those who could tolerate statins but were not receiving them, and patients who were intolerant of statins ("background therapy with statins as tolerated"). In the base-case analyses for each population, only patients who were either already receiving statin therapy or deemed statin intolerant (10% of the population) received incremental therapy with either ezetimibe or a PCSK9 inhibitor (Table 10).

We estimated the degree of LDL-C reduction with maximally tolerated doses of ezetimibe and PCSK9 inhibitors (when used alone or in combination with statins) from the published literature (Tables 10 and 11). We assumed that the drugs were equally efficacious in all patient populations, i.e., the proportion of reduction in LDL-C from baseline was constant across all subgroups studied.

Our review of the literature yielded the following estimates of the effect of ezetimibe and PCSK9 inhibitors on LDL-C (Table 10):

Table 10. Effect of ezetimibe and PCSK9 inhibitors on serum LDL-C when used alone or incremental effect when added to statins.

Medication	Background statin use	%LDL-C reduction (incremental to statin effect in statin-treated)	95% CI for sensitivity analysis	Reference
PCSK9 inhibitor	None	53.65	47.78 – 5 9.51	[1]
	Mixed low- and high-intensity	65.24	60.02 – 70.46	
	High-intensity	57.93	54.91 – 60.95	
Ezetimibe	None	18.56	17.44 – 19.68	[116]
	Mixed low- and high-intensity	23.60	21.70-25.60	
	High-intensity	23.60	21.70-25.60	

Abbreviations: Abbreviations: CI, confidence interval; LDLC, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

Our review suggested the following effect of treatment with statin use on cardiovascular outcomes (Table 11):

Table 11. Effect of ezetimibe and PCSK9 inhibitors on Clinical Outcomes (MI, stroke, and CV death) per 1mmol/L reduction in LDL-C.

Medication	Risk Ratio for MI and CV death per 1 mmol/L reduction in LDL-C	Risk ratio for stroke per 1 mmol/L reduction in LDL-C	Comment	Reference
Statins	0.76	0.85	We assumed a "flat" beta across age-groups as demonstrated in clinical trials: i.e., that risk reduction in cardiovascular events per unit reduction in cholesterol is identical in all age groups.	[109]
Ezetimibe	0.76	0.85	-	[109]
PCSK9 inhibitors	0.76	0.85*	Since the effect of PCSK9 inhibitors on stroke risk is not known, we performed a sensitivity analysis that assumed no effect on stroke.	[1,109]

Abbreviations: CI, confidence interval; CV, cardiovascular; LDLC, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9.

* Assumed in the base-case analysis.

We assumed that these drugs affect cardiovascular outcomes (non-fatal MI, non-fatal stroke, and cardiovascular death) in proportion to their effect on LDL-C: for one unit decline in LDL-C, we assumed that statins, ezetimibe, and PCSK9 inhibitors reduce the risk of non-fatal MI and cardiovascular death by an identical amount. In the absence of long-term effectiveness data, it is uncertain whether LDL-C reduction with PCSK9 inhibitors produces similar reductions in clinical events compared with statins. On the one hand, results of short-term clinical trials suggest greater reductions in CV mortality and MI rates compared with statin treatment trials or observational cohort studies for the same unit difference in LDL-C, so that theoretically, PCSK9 inhibitors may have better clinical outcomes than with statins. On the other hand, statins have been ascribed "pleiotropic" effects that may stabilize an atherosclerotic plaque and lower risk beyond that expected for the same unit difference in LDL-C in observational cohort studies—and it may be that PCSK9 inhibitors do not provide these additional benefits. In light of this uncertainty, we performed a one-way sensitivity analysis in which we assessed the impact of a 25% greater or lesser effect of PCSK9 inhibitors on MACE compared with equivalent LDL-C reduction observed in statin treatment trials.

In the base-case, we assumed that statins, ezetimibe, and PCSK9 inhibitors also reduce the risk of stroke (mediated by their effect on ischemic stroke but incorporated in the model as the adjusted effect on total stroke). Previous studies examining the impact of lipid-lowering agents on stroke have yielded mixed results (see discussion below). Furthermore, as noted in the review of clinical evidence presented above, the effect of PCSK-9 inhibitors on stroke is uncertain. We therefore performed a sensitivity analysis that assumed that treatment with PCSK9 inhibitors does not lower the risk of stroke.

In clinical trials, serious adverse events with treatment with ezetimibe or PCSK9 inhibitors were infrequent and did not statistically differ across treatment arms.[50,56,78] For this analysis, we did not model costs or disutilities associated with these minor adverse events such as injection site reactions.

Note, however, that long-term effectiveness or safety data are not presently available for PCSK9 inhibitors.

Costs

Age- and sex-specific health care costs were estimated using national data.[71] Hospitalized stroke and coronary heart disease costs and acute stroke rehabilitation costs were estimated using California hospital data[117] and deflated using cost-to-charge ratios[118] and the ratio of the U.S. national average costs to the California average.[119] Chronic outpatient CVD costs additional to average background health care costs for the first year after an event and for subsequent years were estimated for patients with a stroke or coronary heart disease diagnosis surveyed in the U.S. Medical Expenditure Panel Surveys (MEPS) pooled from 1998-2008. Average annual non-

cardiovascular (background) costs were also estimated from the MEPS.[120] All model costs were indexed to the year 2015 using the medical component of the U.S. Consumer Price Index.[94] We assumed the annual cost of ezetimibe to be $2,828, based on the wholesale acquisition cost (WAC);[50] costs of atorvastatin 80 mg (used in one of the scenario analyses) were estimated to total $812 per year, based on median WAC across brand and generic versions.[78] We assumed the annual cost of PCSK9 inhibitors to be equal to the average of the recently announced annual wholesale prices of alirocumab ($14,600 per patient per year) and evolocumab ($14,100 per patient per year).[25] Drug costs were subjected to a variety of sensitivity and threshold analyses.

Utilities

Health-related quality-of-life weights and severity distributions for CVD disease states were based on the Global Burden of Disease disability weights study.[121-123]

Outcome Measures

We report results in 2015 U.S. dollars, quality-adjusted life years (QALYs), and incremental cost-effectiveness ratios (ICERs).[108] We assessed the cost-effectiveness of both PCSK9 inhibitors and ezetimibe relative to comparator treatment (i.e., statin therapy in those who could tolerate it and no therapy in those who could not).

$$\text{ICER} = \frac{\text{Cost}_{\text{Therapy being evaluated}} - \text{Cost}_{\text{Next most effective therapy}}}{\text{Effectiveness}_{\text{Therapy being evaluated}} - \text{Effectiveness}_{\text{Next most effective therapy}}}$$

In the base case, we only included costs related to drug therapy and all costs related to the management of cardiovascular disease. In a sensitivity analysis, we also included the costs related to management of other conditions. We assumed a willingness-to-pay threshold of $100,000/QALY. We also report the number of patients that would need to be treated for five years (NNT_5) to avert one major adverse cardiovascular event (MACE, defined as cardiovascular death, nonfatal MI, or nonfatal stroke).

Sensitivity Analyses

Sensitivity analyses examine the impact of uncertainty in various input parameters on the estimates of cost-effectiveness of the therapies being examined in the model.

We performed various one-way sensitivity analyses for each of the target subpopulations (Table 12) by varying one input parameter at a time while holding all other parameters constant at their base-case values. In particular, there is uncertainty in extrapolating the impact of statins on stroke to PCSK9 inhibitors because of the following:

- Observational studies demonstrated no association between LDL-C and stroke

- Randomized trials of statins show a decrease in stroke rates with statins compared with placebo, for high intensity statins vs. low intensity statins, and for ezetimibe relative to placebo [78,109,124]

- Randomized trials of other cholesterol-lowering agents have demonstrated either no impact on stroke (fibrates, resins, diet) or an increase in stroke (hormone therapy/estrogens).

In light of this uncertainty, we performed a sensitivity analysis that assumed that treatment with PCSK9 inhibitors has no effect on the risk of stroke (Table 12).

Table 12. Upper and lower bounds of inputs explored in one-way sensitivity analyses.

Target Subpopulation	One-Way Sensitivity Analyses	Source
Familial Hyper-cholesterolemia	LDL-C lowering by PCSK9 (base case and range as reported in Table 10)	[1]
	PCSK9 inhibitor effect on CV outcomes relative to statins per mmol/L reduction in LDL-C (base case = 1 [equivalent to statins], range: 0.25-1.25)	Assumed
	Stroke benefit for PCSK9 (base case RR = 0.85 per mmol/L reduction in LDL-C, range: 0.85-1.00)	[1,109]
	Inclusion of non-cardiovascular costs into the ICER (base case = 0% of non-cardiovascular costs included; range: 0-100%)	Assumed
	Prevalence of statin-intolerance (base case = 10%, range: 3-20%)	[113-115]
	Analytic horizon (base case = lifetime, range: 20 years - lifetime)	Assumed
	Drug cost for PCSK9 inhibitors (base case = $14,350 per patient per year; range: 50-200% of base-case)	[25], Range Assumed
History of CVD, statin intolerant	LDL-C lowering by PCSK9 (base case and range as reported in Table 10)	[1]
	PCSK9 inhibitor effect on CV outcomes relative to statins per mmol/L reduction in LDL-C (base case = 1 [equivalent to statins], range: 0.75-1.25)	Assumed
	Stroke benefit for PCSK9 (base case RR = 0.85 per mmol/L reduction in LDL-C, range: 0.85-1.00)	[1,109]
	Inclusion of non-cardiovascular costs into the ICER (base case = 0% of non-cardiovascular costs included; range: 0-100%)	Assumed
	Analytic horizon (base case = lifetime, range: 20 years - lifetime)	Assumed
	Drug cost for PCSK9 inhibitors (base case = $14,350 per patient per year; range: 50-200% of base-case)	[25], Range Assumed
History of CVD, on statin therapy	LDL-C lowering by PCSK9 (base case and range as reported in Table 10)	[1]
	PCSK9 inhibitor effect on CV outcomes relative to statins per mmol/L reduction in LDL-C (base case = 1 [equivalent to statins], range: 0.75-1.25)	Assumed
	Stroke benefit for PCSK9 (base case RR = 0.85 per mmol/L reduction in LDL-C, range: 0.85-1.00)	[1,109]
	Inclusion of non-cardiovascular costs into the ICER (base case = 0% of non-cardiovascular costs included; range: 0-100%)	Assumed
	Analytic horizon (base case = lifetime, range: 20 years - lifetime)	Assumed
	Drug cost for PCSK9 inhibitors (base case = $14,350 per patient per year; range: 50-200% of base-case)	[25], Range Assumed

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

We also performed several scenario analyses, varying combinations of parameters in a clinically meaningful manner (Table 13).

Table 13. Scenario Analyses.

Target Subpopulation	Scenario Analyses
FH	In the base case, only patients who met the operational definition of FH and were either already receiving statin therapy or were deemed statin intolerant (10% of the population) received incremental therapy with ezetimibe or a PCSK9 inhibitor. In a scenario analysis, we evaluated the impact of "full treatment" in which all statin-tolerant patients who were not already receiving statins were first treated with high-intensity statins, after which the entire FH subpopulation was incrementally treated with ezetimibe or a PCSK9 inhibitor.
History of CVD, high-risk	In the base case, all patients with pre-existing CVD and LDL-C ≥70mg/dL on statin therapy received incremental treatment with ezetimibe or a PCSK9 inhibitor. In a scenario analysis, we evaluated the effect of only initiating therapy after an incident MI. In this analysis, all patients who had an incident (first-ever) MI in 2015 received incremental PCSK9 inhibitor therapy and were followed over their lifetime.

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolemia; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9.

Finally, in pre-specified threshold analyses, we evaluated the price at which PCSK9 inhibitors would be considered cost-effective at willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY.

Cost-Effectiveness Model: Results

Familial Hypercholesterolemia

The operational definition of FH in our model (baseline LDL-C level greater than or equal to 250mg/dL [6.465 mmol/L] among patients not on statin therapy and an LDL-C level greater than or equal to 200mg/dL [5.172 mmol/L] among patients receiving statin therapy) identified 605,000 patients with FH, equating to 13.3 million patient-years of treatment over twenty years. The risk of MACE in this population was 2.2-3.4 fold higher than an age- and gender-matched population that does not meet the definition of FH and does not have pre-existing CVD. Key results are reported in Table 14, one-way sensitivity analyses are shown in Figure 3, and additional results are shown in Appendix 7 Table 5.

Compared with the control arm, incremental treatment with ezetimibe would avert 115,900 MACE over the lifetime analytic horizon and produce 250,600 additional QALYs with an ICER of $135,000/QALY compared with current treatment. Compared with the control arm, adding PCSK9 inhibitors to current treatment averted 324,200 MACE and produced 665,200 additional QALYs, producing an ICER of $290,000/QALY. This higher ICER for PCSK9 inhibitors was driven by

differences in drug costs ($14,350 per year for PCSK9 compared with $2,828 per year for ezetimibe). We did not model HoFH separately, because the expected number of patients is small (n=300-400 in the US).

Table 14. Base-Case Clinical and Economic Outcomes Among Patients with FH.*

	Person-years of treatment (millions)	Total MACE averted	NNT_5†	QALYs gained^	Incremental Drug Costs^ (million $)	Incremental Costs, Other CV Care^ (million $)	ICER ($/QALY)
Statin§	*comparator*						
Statin + Ezetimibe||,¶	22.3	115,900	77	250,600	$40,359	-$6,632	$135,000
Statin + PCSK9 inhibitor,¶**	23.7	324,200	28	665,200	$210,516	-$17,304	$290,000

Abbreviations: CV, cardiovascular; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT_5, number-needed-to-treat; QALY, quality-adjusted life year.

* In the base case, all patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (10% of the population) received incremental therapy with ezetimibe or a PCSK9 inhibitor (n = 605,000 in 2015). The analytic horizon was lifetime (defined as when patients reach the age of 95 years). To reflect the precision of the model, person-years of treatment are rounded to the nearest 100,000s; MACE and QALYs are rounded to the 100s; costs are rounded to the millions; and ICERs to the 1000s.

† Number of patients that would need to be treated for 5 years to avert one MACE event.

^ All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.

§ Patients deemed to be statin-intolerant (base-case prevalence = 10% of the FH population) received no lipid-lowering therapy.

|| Patients deemed to be statin-intolerant (base-case prevalence = 10% of the FH population) received only ezetimibe.

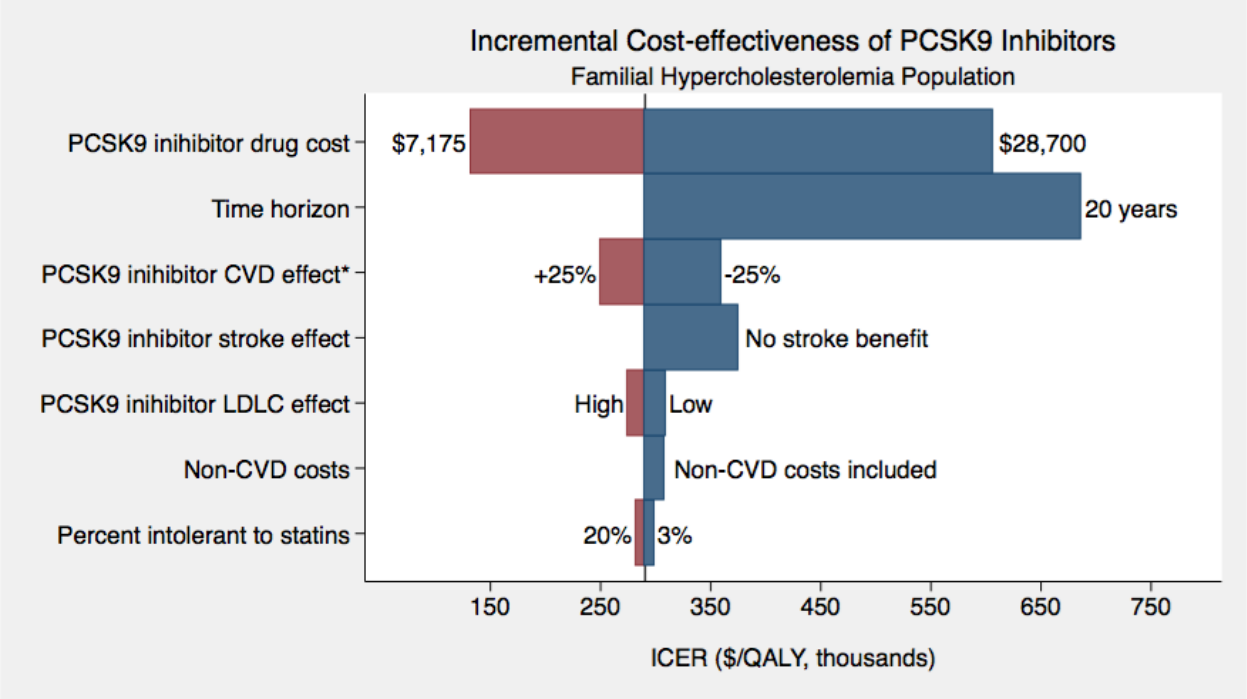
¶ Both statin+ezetimibe and statin+PSCK9 inhibitor arms are compared with the statin-only arm.

** Patients deemed to be statin-intolerant (base-case prevalence = 10% of the FH population) received only a PCSK9 inhibitor.

One-Way Sensitivity Analyses:

In one-way sensitivity analyses, we examined the impact of varying individual input parameters while holding all others constant (Figure 4 below). The ICER was very sensitive to changes in drug cost and the analytic horizon, with higher drug costs and shorter analytic horizons reducing the cost-effectiveness of the therapy.

Figure 4. One-way sensitivity analyses among patients with FH.



Base-case ICER = = $290,000/QALY. The ICER was very sensitive to changes in drug cost and the analytic horizon, with higher drug costs and shorter analytic horizons lowering the cost-effectiveness of the therapy. Abbreviations: CVD, cardiovascular disease; ICER, incremental-cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In this sensitivity analysis, we vary the effect of LDL-C reduction by a PCSK9 inhibitor relative to an equivalent reduction in LDL-C by a statin. The base case assumes that a 1mmol/dL reduction in LDL-C by a PCSK9 inhibitor produces the same effect on CVD outcomes as a 1mmol/dL reduction in LDL-C by a statin; this one-way analysis increases or decreases the relative effect of PCSK9 inhibitors on CVD outcomes by 25%.

Scenario Analysis: Initiating Therapy with Ezetimibe or PCSK9 After "Full Treatment" with Statins in the FH population.

In a scenario analysis, we evaluated the impact of "full treatment" in which all patients who could tolerate statins but were not already receiving statins at baseline were first treated with high-intensity statins, after which the entire FH subpopulation was incrementally treated with ezetimibe or a PCSK9 inhibitor. Key results are presented in Table 15 below; additional details are presented in Appendix 7 Table 6. ICERs for the addition of ezetimibe or PCSK9 inhibitors are higher in this analysis than in the base case due to the clinical benefit of moving untreated FH patients onto high-intensity statin therapy; in fact, the "full treatment" strategy is cost-saving relative to the base case as-treated approach.

Table 15. Scenario Analysis: Clinical and Economic Outcomes Assuming "Full Treatment" of FH Patients with Statins Prior to Incremental Treatment with Ezetimibe or a PCSK9 inhibitor.*

	Person-years of treatment (millions)	Total MACE averted	NNT_5†	QALYs gained^	Incremental Drug Costs^ (million $)	Incremental Costs, Other CV Care^ (million $)	ICER ($/QALY)
Statin (as treated)§	*comparator*						
Statin (full treatment)§,||	3.7	84,300	25	160,500	$1,889	-$3,286	Cost-Saving ¶
Statin + Ezetimibe,††**	26.1	140,500	71	303,300	$47,217	-$7,709	$130,000
Statin + PCSK9 inhibitor^^,††	27.5	335,300	33	680,800	$245,111	-$17,833	$334,000

Abbreviations: CV, cardiovascular; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT_5, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In a scenario analysis, we evaluated the impact of "full treatment" in which all statin-tolerant patients who were not already receiving statins were first treated with high-intensity statins, after which the entire FH subpopulation (n = 748,000 patients in 2015) was incrementally treated with ezetimibe or a PCSK9 inhibitor. The analytic horizon was lifetime (defined as when patients reach 95 years of age). To reflect the precision of the model, person-years of treatment are rounded to the 100,000s; MACE and QALYs are rounded to the 100s; costs are rounded to the millions; and ICERs to the 1000s.

† Number of patients that would need to be treated for 5 years to avert one MACE event.

^ All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.

§ Patients deemed to be statin-intolerant (base-case prevalence = 10% of the FH population) received only ezetimibe.

|| The statin (full treatment) arm was compared with the statin (as treated) arm.

¶ Compared with the statin (as treated) arm, the statin (full treatment) arm costs $1.9 billion less and generates 160,500 additional QALYs. It is, therefore, an economically "dominating" option.

**Patients deemed to be statin-intolerant (base-case prevalence = 10%) received only ezetimibe.

†† The statin+ezetimibe and statin+PCSK9 inhibitor arms are compared with the statin (full treatment) arm.

^^ Patients deemed to be statin-intolerant (base-case prevalence = 10% of the FH population) received only a PCSK9 inhibitor.

Secondary Prevention Among Patients with a Prior History of CVD and Intolerant of Statins

The base-case analysis modeled 1,460,000 statin-intolerant patients with a history of CVD. This equated to approximately 85 million patient-years of treatment over the lifetime horizon. Key results are reported in Table 16, and additional results are shown in Appendix 7 Table 7. Compared with the control arm (no lipid-lowering therapy), treatment with PCSK9 inhibitors averted 1,254,400 MACE and produced 2,366,000 additional QALYs at an ICER of $274,000/QALY. As in the FH population, ezetimibe's clinical effects were less pronounced, but its incremental drug costs were approximately 20% of those for PCSK9 inhibitors, resulting in an ICER of $145,000/QALY versus no lipid-lowering therapy.

Table 16. Base-Case Clinical and Economic Outcomes Among Statin-Intolerant Patients with a Prior History of CVD.*

	Person-years of treatment (millions)	Total MACE averted	NNT_5†	QALYs gained^	Incremental Drug Costs^ (million $)	Incremental Costs, Other CV Care^ (million $)	ICER ($/QALY)
Control (no additional lipid-lowering therapy)	*comparator*						
Ezetimibe§	85.0	446,100	56	847,000	$138,560	-$15,961	$145,000
PCSK9 inhibitor§	85.4	1,254,400	21	2,366,000	$693,450	-$44,627	$274,000

Abbreviations: CV, cardiovascular; ICER, incremental cost-effectiveness ratio; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT_5, number-needed-to-treat; QALY, quality-adjusted life year.

* In the base case, we assumed that 10% of the population was statin-intolerant. Patients who had a prior history of cardiovascular disease received incremental treatment with ezetimibe or a PCSK9 inhibitor (n = 1,460,000 in 2015). The analytic horizon was lifetime (defined as until patients reached the age of 95 years). To reflect the precision of the model, person-years of treatment are rounded to the 100,000s; MACE and QALYs are rounded to the nearest 100s; costs are rounded to the millions; and ICERs to the 1000s.

† Number of patients that would need to be treated for 5 years to avert one MACE event.

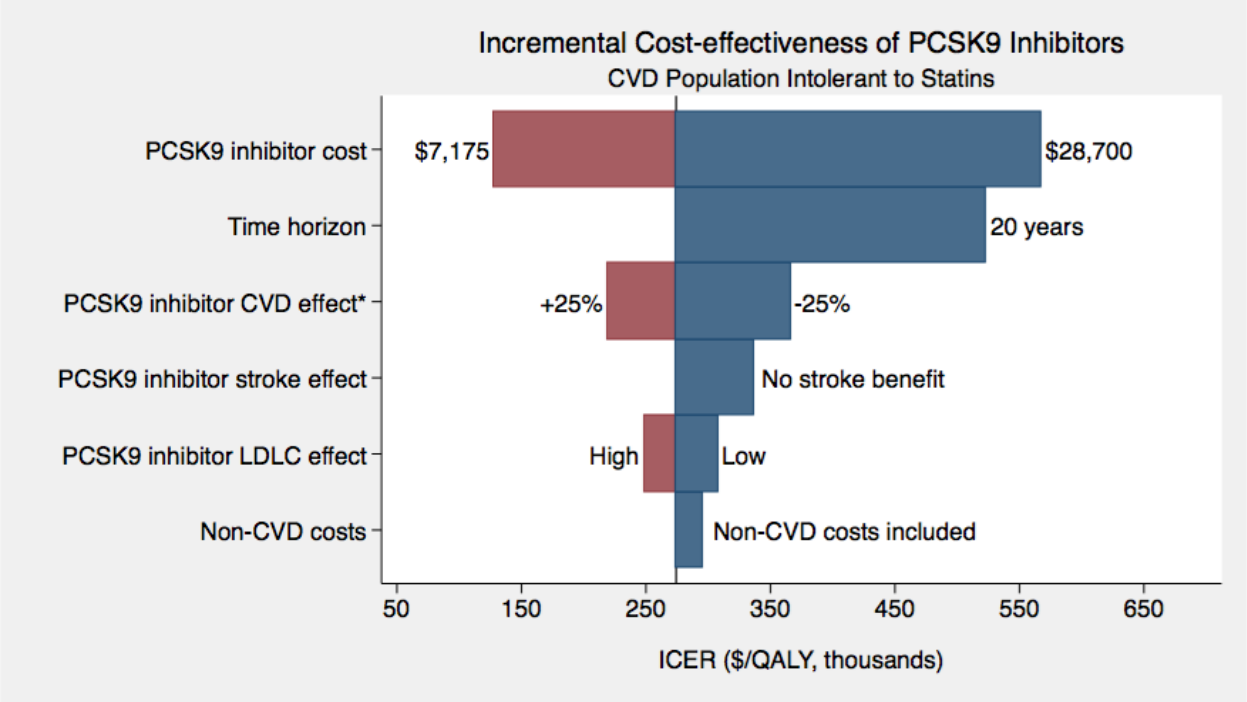
^ All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.

§ Both the ezetimibe and PSCK9 inhibitor arms are compared with the control (no additional lipid-lowering therapy) arm.

One-Way Sensitivity Analyses:

In one-way sensitivity analyses, we examined the impact of varying individual input parameters while holding all others constant (Figure 5). The ICER was very sensitive to changes in drug cost and the analytic horizon, with higher drug costs and shorter analytic horizons worsening the cost-effectiveness of the therapy.

Figure 5. One-way sensitivity analyses among statin-intolerant patients with a history of CVD.



Base-case ICER = $274,000/QALY. The ICER was very sensitive to changes in drug cost and the analytic horizon, with lower drug costs and longer analytic horizons improving the cost-effectiveness of the therapy. Abbreviations: CVD, cardiovascular disease; ICER, incremental-cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In this sensitivity analysis, we vary the effect of LDL-C reduction by a PCSK9 inhibitor relative to an equivalent reduction in LDL-C by a statin. The base case assumes that a 1mmol/dL reduction in LD-LC by a PCSK9 inhibitor produces the same effect on CVD outcomes as a 1mmol/dL reduction in LDL-C by a statin; this one-way analysis increases or decreases the relative effect of PCSK9 inhibitors on CVD outcomes by 25%.

Secondary Prevention Among Patients with a Prior History of CVD and LDL-C ≥ 70mg/dL on Statin Therapy

The base-case analysis modeled 7,271,000 patients with a history of CVD and an LDL-C level ≥ 70mg/dL despite statin therapy, equating to approximately 410 million patient-years of treatment over the lifetime horizon. Key results are reported in Table 17, and additional results are shown in Appendix 7 Table 8.

Compared with the control arm, treatment with PCSK9 inhibitors averted 5,621,800 MACE and produced 10,573,800 additional QALYs at an ICER of $302,000/QALY.

Table 17. Base-Case Clinical and Economic Outcomes Among Patients with a Prior History of CVD and LDL-C ≥ 70mg/dL on Statin Therapy.*

	Person-years of treatment (millions)	Total MACE averted	NNT_5 †	QALYs gained^	Incremental Drug Costs^ (million $)	Incremental Costs, Other CV Care^ (million $)	ICER ($/QALY)
Statin	*comparator*						
Statin + Ezetimibe§	409.1	2,253,800	51	4,345,900	$673,155	-$85,520	$135,000
Statin + PCSK9 inhibitor§	416.9	5,621,800	21	10,573,800	$3,406,692	-$210,702	$302,000

Abbreviations: CV, cardiovascular; ICER, incremental cost-effectiveness ratio; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In the base case, patients with pre-existing CVD and LDL-C ≥ 70mg/dL on statin therapy received incremental therapy with ezetimibe or a PCSK9 inhibitor (n = 7,271,000 in 2015). The analytic horizon was lifetime (defined as until patients reached the age of 95 years). To reflect the precision of the model, person-years of treatment are rounded to the 100,000s; MACE and QALYs are rounded to the 100s; costs are rounded to the millions; and ICERs to the 1000s.

† Number of patients that would need to be treated for 5 years to avert one MACE event.

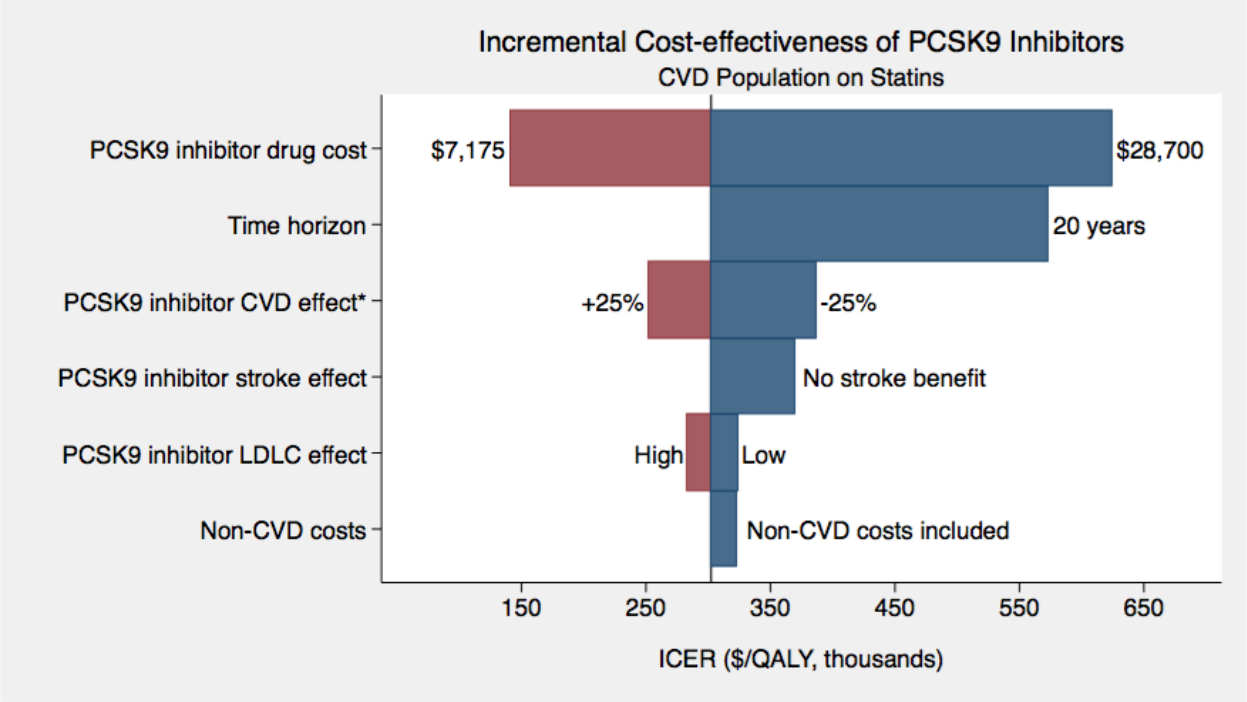
^ All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.

§ Both the statin+ezetimibe and statin+PSCK9 inhibitor arms are compared with the statin-only arm.

One-Way Sensitivity Analyses:

In the one-way sensitivity analyses, we examined the impact of varying individual input parameters while holding all others constant (Figure 6). As with the sensitivity analyses reported above, the ICER for adding PCSK9 therapy to background statin therapy was very sensitive to changes in drug cost and the analytic horizon, with higher drug costs and shorter analytic horizons worsening the cost-effectiveness of the therapy.

Figure 6. One-way sensitivity analyses among patients with cardiovascular disease but LDL-C≥ 70mg/dL on statin therapy.



Base-case ICER = $302,000/QALY. The ICER was very sensitive to changes in drug cost and the analytic horizon, with lower drug costs and longer analytic horizons improving the cost-effectiveness of the therapy. Abbreviations: CVD, cardiovascular disease; ICER, incremental-cost-effectiveness ratio; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In this sensitivity analysis, we vary the effect of LDL-C reduction by a PCSK9 inhibitor relative to an equivalent reduction in LDL-C by a statin. The base case assumes that a 1mmol/dL reduction in LDL-C by a PCSK9 inhibitor produces the same effect on CVD outcomes as a 1mmol/dL reduction in LDL-C by a statin; this one-way analysis increases or decreases the relative effect of PCSK9 inhibitors on CVD outcomes by 25%.

Scenario Analysis: Initiating Therapy with Ezetimibe or PCSK9 After Incident (First-Ever) MI

In a scenario analysis, we explored the effect of only initiating therapy immediately after an incident MI. All patients who had an incident, first-ever MI in 2015 who were receiving statin therapy, if able to tolerate it, received ezetimibe or a PCSK9 inhibitor (n =169,000). Results are shown in Table 18 below. ICERs are lower than in the base case analysis for all secondary prevention ($170,000/QALY and $74,000/QALY for PCSK9s and ezetimibe respectively) due to a greater reduction in the absolute number of MACE events. NNT_5 estimates for PCSK9 inhibitors and ezetimibe were 15 and 37 in this analysis.

Table 18. Scenario Analyses: Clinical and Economic Outcomes Among Patients Initiating Ezetimibe or a PCSK9 Inhibitor After Incident (First-Ever) MI.*

	Person-years of treatment (millions)	Total MACE averted	NNT_5†	QALYs gained^	Incremental Drug Costs^ (million $)	Incremental Costs, Other CV Care^ (million $)	ICER ($/QALY)
Statin§	*comparator*						
Statin + Ezetimibe||,¶	3.3	16,800	37	64,200	$5,844	-$1,075	$74,000
Statin + PCSK9 inhibitor,¶**	3.5	43,200	15	159,200	$29,751	-$2,692	$170,000

Abbreviations: CV, cardiovascular; ICER, incremental cost-effectiveness ratio; LDL-C, low-density lipoprotein; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT_5, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In this scenario analysis, all patients who had an incident (first-ever) MI in 2015, were receiving statin therapy if tolerated, received incremental treatment with ezetimibe or a PCSK9 inhibitor (n = 169,000). Ten percent of the population was assumed to be statin-intolerant. The analytic horizon was lifetime (defined as when patients reach the age of 95 years). To reflect the precision of the model, person-years of treatment are rounded to the 100,000s; MACE and QALYs are rounded to the 100s; costs are rounded to the millions; and ICERs to the 1000s.

† Number of patients that would need to be treated for 5 years to avert one MACE event.

^ All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.

§ Patients deemed to be statin-intolerant (base-case prevalence = 10%) received no lipid-lowering therapy.

|| Patients deemed to be statin-intolerant (base-case prevalence = 10%) received only ezetimibe.

¶ Both the statin+ezetimibe and statin+PSCK9 inhibitor arms are compared with the statin-only arm.

** Patients deemed to be statin-intolerant (base-case prevalence = 10%) received only a PCSK9 inhibitor.

Threshold Analyses:

We evaluated the drug costs at which PCSK9 inhibitors would be considered cost-effective under conventional willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $150,000/QALY. For these analyses, we only considered total cardiovascular costs in the incremental cost-effectiveness ratio, employed a lifetime analytic horizon and discounted future costs at 3% a year. Results are presented in Table 19 on the following page.

When weighted by the size of the three major subpopulations of interest (i.e., FH, CVD statin-intolerant, CVD not at LDL-C target), threshold prices were $3,166, $5,404, and $7,735 for $50,000, $100,000, and $150,000 per QALY respectively.

Table 19. Threshold analyses: Annual drug cost at which PCSK9 inhibitors would be cost-effective in high-risk subpopulations under varying willingness-to-pay thresholds.*

Patient Subpopulation	WTP threshold		
	$50,000/QALY	$100,000/QALY	$150,000/QALY
FH on statin (as treated) + statin-intolerant †	$3,400	$5,700	$8,000
FH will full treatment with statin or statin-intolerant §	$3,000	$5,000	$7,000
Pre-existing CVD, LDL-C ≥ 70 mg/dL, and statin-intolerant ||	$3,400	$5,800	$8,300
Pre-existing CVD, LDL-C ≥ 70 mg/dL on current statin regimen ¶	$3,100	$5,300	$7,600
After first-ever MI	$4,300	$7,600	$10,800
ALL SUBPOPULATIONS	*$3,166*	*$5,404*	*$7,735*

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolemia; LDL, low-density lipoprotein; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year; WTP, willingness-to-pay.

* Only drug costs and costs related to cardiovascular care were included in the ICER for these analyses. The analytic horizon was lifetime (defined as until patients reached 95 years of age), and future costs and QALYs were discounted at 3% a year. To reflect precision in the model, the reported threshold drug costs are rounded to the nearest 100s.

† Patients who met the operational definition of FH and are either already receiving statin therapy or deemed statin-intolerant (10% of the population) received incremental therapy with a PCSK9 inhibitor (n = 600,000 in 2015). Complete results of this analysis are presented in Table 14 above.

§ All statin-tolerant patients who met the operational definition of FH but were not already receiving statins were first treated with high-intensity statins, after which the entire FH subpopulation was incrementally treated with a PCSK9 inhibitor (n = 748,000 patients in 2015). Complete results of this analysis are presented in Table 15 above.

|| Ten percent of the population was assumed to be statin-intolerant (n = 1,460,000 in 2015). Complete results of this analysis are presented in Table 16 above.

¶ Patients with pre-existing CVD and LDL-C ≥ 70mg/dL already receiving statin therapy received incremental therapy with a PCSK9 inhibitor (n = 7,271,000 in 2015). Complete results of this analysis are presented in Table 17 above.

** Patients who had an incident (first-ever) MI in 2015 and were receiving statin therapy if able to tolerate it received incremental therapy with a PCSK9 inhibitor (n = 169,000). Complete results of this analysis are presented in Table 18 above.

6.3 Health System Value

In addition to the incremental cost-effectiveness of PCSK9 inhibitors, we sought to estimate the total budgetary impact of PCSK9 inhibitors in each of the three target populations defined above. Assessment of budget impact as well as comparison to defined thresholds for policy intervention and presentation of "value-based price benchmarks" are described in further detail below.

Budget Impact Model: Methods

We used the same model employed for the care value analysis to estimate total budgetary impact. Budgetary impact was defined as the total incremental cost of the therapy in each population which equals the incremental health care costs (including drug costs) minus any offsets in these costs from averted cardiovascular events. All costs were undiscounted and estimated over one- and five-year time horizons. The five-year timeframe was of primary interest, given the potential for cost offsets to accrue from averted cardiovascular events. In addition to FH and patients with a history of CVD who are (a) statin intolerant or (b) not at LDL-C target on statin therapy, we also considered the budgetary impact if the treated population were limited to the higher-risk subset of patients with a history of CVD who received PCSK9 inhibitors immediately following an incident (i.e., first-ever) MI in 2015.

ICER's methods for estimating budget impact and calculating benchmark prices are described in detail at (http://www.icer-review.org/impact-and-outcomes/value-assessment-project/). Briefly, our calculations assume that utilization of new drugs is "unmanaged" – i.e., without payer or pharmacy benefit management controls in place – to provide an upper bound for likely patterns of drug uptake by five years after launch. We examine six characteristics of the drug and marketplace to estimate unmanaged drug uptake. These characteristics are listed below:

- Magnitude of improvement in clinical safety and/or effectiveness
- Patient-level burden of illness
- Patient preference (ease of administration)
- Proportion of eligible patients currently being treated
- Primary care vs. specialty clinician prescribing/use
- Presence or emergence of competing treatments of equal or superior effectiveness

Based on our assessment of these criteria, we assign a new drug to one of four categories of unmanaged drug uptake patterns: 1) very high (75% uptake by year 5); 2) high (50% uptake by year 5); 3) intermediate (25% uptake by year 5); and 4) low (10% uptake by year 5).

For patients with FH, we assumed a "very high" uptake pattern (75% at five years) for the two drugs, combined, driven largely by the perceived acuity of the need for treatment of this population. We assigned an "intermediate" uptake pattern (25% at five years) for the two drugs, combined, in the secondary prevention population, given the availability of two new agents of comparable effectiveness, as well as alternative treatments. For consistency, uptake was assumed to occur in equal proportions across the five-year timeframe, and we adjusted both drug costs and cost offsets accordingly. For example, in populations estimated to have a 25% 5-year uptake, 5% of patients would be assumed to initiate therapy each year. Patients initiating therapy in year 1 would accrue all drug costs and cost offsets over the full five years, but those initiating in other years would only accrue a proportional amount of 5-year costs.

Using this approach to estimate potential budget impact, we then compared our estimates to a budget impact threshold that represents a potential trigger for policy mechanisms to improve affordability through changes to pricing, payment, or patient eligibility. As described in ICER's methods presentation (http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf), this threshold is based on an underlying assumption that health care costs should not grow much faster than growth in the overall national economy. From this foundational assumption, our potential budget impact threshold is derived using an estimate of growth in US gross domestic product (GDP) +1%, the average number of new molecular entity approvals by the FDA each year, and the contribution of spending on retail and facility-based drugs to total health care spending. Calculations can be found in Table 20 below.

Table 20. Calculation of Potential Budget Impact Threshold.

Item	Parameter	Estimate	Source
1	Growth in US GDP, 2015-2016 (est.) +1%	3.75%	World Bank, 2015
2	Total health care spending ($)	$3.08 trillion	CMS NHE, 2014
3	Contribution of drug spending to total health care spending (%)	13.3%	CMS NHE, Altarum Institute, 2014
4	Contribution of drug spending to total health care spending ($) (Row 2 x Row 3)	$410 billion	Calculation
5	Annual threshold for net health care cost growth for ALL new drugs (Row 1 x Row 4)	$15.4 billion	Calculation
6	Average annual number of new molecular entity approvals, 2013-2014	34	FDA, 2014
7	Annual threshold for average cost growth per individual new molecular entity (Row 5 ÷ Row 6)	$452 million	Calculation
8	Annual threshold for estimated potential budget impact for each individual new molecular entity (doubling of Row 7)	$904 million	Calculation

For 2015-16, therefore, the five-year annualized potential budget impact threshold that should trigger policy actions to manage affordability is calculated to total approximately $904 million per year. In this report, each PCSK9 inhibitor is considered as an individual new drug, so the budget impact threshold for each drug is $904 million and $1.8 billion for the two drugs combined.

Potential Budget Impact and the Value-based Price Benchmark

We combine consideration of the potential budget impact with the care value threshold prices presented in Section 6 above to calculate a value-based price benchmark for each new drug. This price benchmark begins with the care value price range to achieve cost-effectiveness ratios of $100,000-$150,000 per QALY for the population being considered but has an upper limit determined by the price at which the new drug would exceed the potential budget impact threshold of $904 million. If the potential budget impact does not exceed $904 million, then the value-based price benchmark remains the full care value price range.

Budget Impact Model: Results

The following tables present the budgetary impact of one year and five years of PCSK9 inhibitor therapy in the populations studied, assuming the uptake patterns previously described. Detailed information on cost offsets and clinical events averted can be found in the Appendix 7 Tables 10-15.

Findings based on the assumption that 75% of FH and 25% of CVD patients would initiate PCSK9 therapy by five years (i.e., 15% and 5% of these eligible populations each year), with drug costs and cost offsets adjusted accordingly, are presented in Table 21 on the following page. Calculations for adjustment of drug costs and cost offsets are provided in Appendix 7 Table 16. Results are presented for both one-year and five-year time horizons.

Results from the budget impact model showed that if both the FH and CVD populations are treated with the uptake pattern assumptions mentioned above, 527,000 individuals would receive PCSK9 therapy in the first year. After one year of PCSK9 treatment, cost offsets due to reduced cardiovascular adverse events range from $592 per patient with FH to $1,010 per patient for patients with CVD who are statin-intolerant. Including this cost offset, one-year budget impact is still estimated to be quite high: approximately $7.2 billion for all patient populations.

Over the entire 5-year time horizon, we estimate that approximately 2.6 million persons would receive PCSK9 inhibitor therapy for one or more years. Drug cost and cost-offset adjustments for the full 5-year time horizon are described in detail in Appendix 7; across this timeframe the weighted budgetary impact (i.e., adjusted for differing periods of drug utilization and associated cost-offsets for different patients) ranges between $40,000 and $41,000 per patient for each subpopulation. Total budgetary impact over five years is approximately $19 billion, $15 billion, and $74 billion for the FH, CVD statin-intolerant, and CVD not at LDL-C target subpopulations. When

these 5-year budget impact figures are annualized, they equal $21.4 billion in net health care cost growth per year. This annualized potential budget impact is well above the budget impact threshold of $1.8 billion for the two drugs combined. In order to not exceed this budget impact threshold, approximately 1% of eligible patients could be treated at the average list price of $14,350 per year.

Table 21. Total Budgetary Impact of PCSK9 Inhibitors based on Assumed Patterns of Uptake, by Subpopulation.

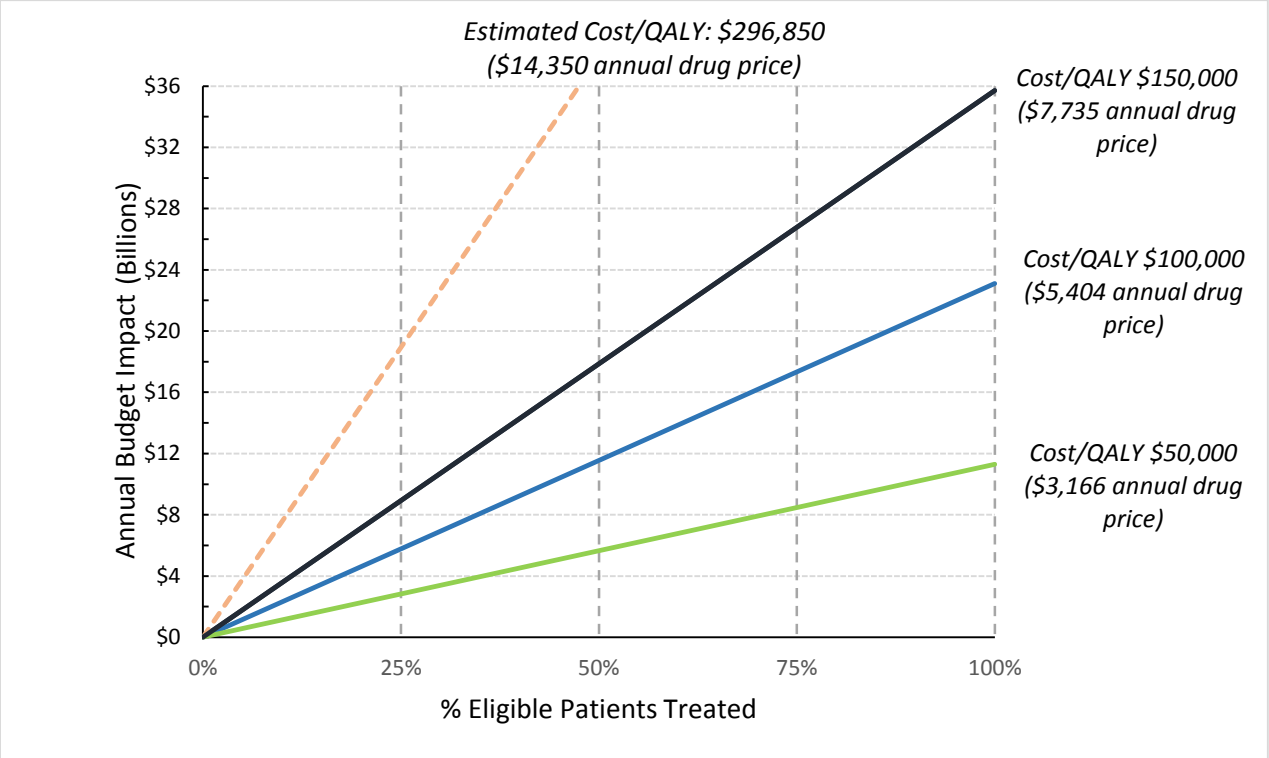
	Analytic Horizon = 1 Year				Analytic Horizon = 5 Years		
	Eligible Population (thousands)	Number Treated (thousands)	Weighted BI per Patient ($)*	Total BI, $ (billions)	Number Treated (thousands)	Weighted BI per Patient ($)*	Total BI per yr, $ (billions)
FH	605	91	$13,824	$1.3B	453	$41,345	$3.7B
CVD, statin-Intolerant	1,460	73	$13,496	$1.0B	365	$40,446	$3.0B
CVD, not at LDL-C target	7,271	364	$13,529	$4.9B	1,818	$40,562	$14.7B
TOTAL	**9,335**	**527**	**$13,576**	**$7.2B**	**2,636**	**$40,681**	**$21.4B**
CVD, first-ever MI only	*169*	*9*	*$13,391*	*$0.1B*	*42*	*$39,931*	*$0.3B*

NOTE: Subpopulation figures may not sum to total due to rounding
BI: Budget impact
*Weighted budget impact calculated by subtracting cost offsets from drug costs for one-year horizon. For five-year horizon, drug costs and cost offsets apportioned assuming 20% of patients in uptake target initiate therapy each year. Those initiating in year 1 receive full drug costs and cost offsets, those initiating in year 2 receive 80% of drug costs and cost offsets, etc.

Figure 7 on the following page provides findings of multiple analyses that give perspective on the relationship between varying possible drug prices, cost-effectiveness ratios, drug uptake patterns, and potential budget impact. The vertical axis shows the annualized budget impact, and the horizontal axis represents the percentage of eligible patients treated over a five-year period. The colored lines demonstrate how quickly the annual budget impact increases with increasing percentages of patients treated at four different drug prices: those at which the cost/QALY = $50,000, $100,000 and $150,000; and the list price used in this analysis ($14,350).

As can be seen in Figure 7, even at a drug cost of $3,166 dollars per year, the cost at which the cost/QALY = $50,000, if 50% of all eligible patients are ultimately treated over a five-year time period the annualized budget impact is approximately $5.6 billion per year. At the list price of $14,350 used for this report, if only 25% of eligible patients receive treatment, the annualized budget impact is nearly $19 billion, meaning that over the five-year period a total of almost $100 billion would have been added to health care costs in the United States.

Figure 7. ICER value graph combining cost-effectiveness and potential budget impact analyses. Colored lines represent the impact on annualized budget impact of different uptake patterns (eligible patients treated) at the actual list price of the drug (dashed line) and at drug prices needed to achieve common incremental cost-effectiveness ratios.



6.4 Draft Value-based Benchmark Prices

Our draft value-based benchmark prices for each key subpopulation and for the overall treated population are provided in Table 22 on the following page. As noted in the ICER methods document (http://www.icer-review.org/wp-content/uploads/2014/01/Slides-on-value-framework-for-national-webinar1.pdf), the draft value-based benchmark price for a drug is defined as the care value price range that would achieve cost-effectiveness ratios between $100,000 and $150,000 per QALY gained, limited, if the results require, by the price at which the $904 million budgetary impact threshold would be exceeded. Detailed calculations for the value-based price benchmarks presented below are available in Appendix 7 Table 17.

As shown in the table on the following page, if only the FH or the CVD statin-intolerant populations were treated, the entire care value price range is lower than the price at which the potential budget impact threshold would be exceeded. Thus, the value-based price benchmark for these two subpopulations is the care value price range. This is not surprising given the relatively small size of each of these populations. In contrast, the care value price range for the much larger population of

patients with CVD not at LDL-C target is higher than the maximum price that would not exceed the budget impact threshold.

When all subpopulations are combined, the care value price range is $5,404-$7,735. But this price range is higher than the maximum price that could be charged before exceeding the potential budget impact threshold ($2,177). Therefore, the draft ICER value-based price benchmark for each of the new PCSK9 drugs, with all the assumptions mentioned previously regarding 5-year uptake patterns and cost offsets, is $2,177. This figure represents *an 85% discount from the full wholesale acquisition cost assumed in our analysis ($14,350).*

Table 22. Draft value-based price benchmarks for PCSK9 inhibitor therapy.

Population	Care Value Price: $100K/QALY	Care Value Price: $150K/QALY	Max Price at Potential Budget Impact Threshold	Draft Value-Based Price Benchmark
FH (n=453,443)	$5,700	$8,000	$10,278	$5,700-$8,000
CVD statin-intolerant (n=364,948)	$5,800	$8,300	$12,896	$5,800-$8,300
CVD not at LDL target (n=1,817,788)	$5,300	$7,600	$2,976	$2,976
TOTAL (n=2,636,179)	$5,404	$7,735	$2,177	$2,177

Abbreviations: FH: familial hypercholesterolemia; CVD: cardiovascular disease; LDL: low-density lipoprotein; QALY: quality-adjusted life year

6.5 Summary and Comment

The results of our cost-effectiveness analysis suggest that the use of PCSK9 inhibitors may produce substantial reductions in non-fatal MIs, non-fatal strokes, and cardiovascular deaths over the lifetime analytic horizon. The NNT_5 (number of patients that would be needed to be treated for 5 years to avoid one major adverse cardiovascular event) of 28 for PCSK9 inhibitors appears to be relatively low; despite this, however, treatment with PCSK9 inhibitors generates cost-effectiveness ratios that far exceed commonly-accepted thresholds such as $100,000/QALY.[79] Achieving cost-effectiveness at a threshold of $100,000/QALY would require price reductions of 60% to 63% compared with current prices. And the results of our analysis of potential budget impact suggest that even deeper reductions may be required to avoid excessive cost burdens to the health care system. Our value-based price benchmark for each PCSK9 inhibitor is $2,177 annually, which represents an 85% reduction from the list price of $14,350.

The high costs of specialty drugs – including novel chemotherapeutic agents for cancer and treatments for Hepatitis C – have generated considerable debate about their societal value.[125-127] The opportunity cost of these high drug prices is a function of the incidence and prevalence of the

targeted disease, as well as the indicated duration of treatment.[127] An expensive therapy for a rare disease that affects a small number of patients may only have a small impact on the health care budget. On the other hand, PCSK9 inhibitors are meant to be lifelong therapy for a large and growing population with pre-existing CVD, and their high price may have a sizeable effect on total health care spending.

The key strengths of this analysis are the modeling of a nationally representative cohort, long-term follow-up, and real world cost estimates. Extensive one-way and scenario-based sensitivity analyses were used to examine the impact of uncertainty about the input parameters on the results. We found that across all subpopulations, results were most sensitive to changes in the price of PCSK9 inhibitors and the length of the time horizon. However, in none of the one-way sensitivity analyses (other than those on price) did the ICERs for PCSK9 inhibitor therapy fall below $219,000 per QALY. As expected, PCSK9 inhibitors were most cost-effective in the patients at highest risk of adverse events, i.e., patients after their first-ever MI. Future studies should examine the role of risk stratification in improving the effectiveness and cost-effectiveness of PCSK9 inhibitors.

Our analysis has several key limitations that merit attention. First, there are no long-term effectiveness data for PCSK9 inhibitors, although short-term studies suggest that they lower the risk of MI and cardiovascular death. While modeling the lifetime analytic horizon as we have done in this analysis captures all potential benefits and costs related to the intervention based on our current knowledge, extrapolating to several decades the results of trials that are 3-6 months long increases the uncertainty in the results. For instance, if short-term LDL-C reductions observed in the trials are not sustained, we will have over-estimated CVD risk reduction benefits. There is even greater uncertainty about their impact on stroke. In line with the "LDL hypothesis," our base case assumed that a 1 mmol/L reduction in LDL-C levels would produce an identical reduction in MI, stroke, and cardiovascular death, irrespective of whether this reduction was achieved using a PCSK9 inhibitor or a statin. We varied the effect of PCSK9 inhibitors on cardiovascular event rates (from -25% to +25% relative to the base case), and found this to be a moderately sensitive parameter; in the FH population, for example, cost-effectiveness ratios ranged from $250,000 to $359,000 per QALY gained. Future long-term studies will address whether the beneficial effects of statins on cardiovascular events can truly be extrapolated to PCSK9 inhibitors.

Second, given lack of evidence of clinically significant harms in short-term PCSK9 trials, we did not model drug-related adverse events. Injection-site reactions were common in PCSK9 inhibitor trials, but we assumed these are mild and transient and did not affect patients' quality of life. Although the incidence of these events was not significantly different among patients receiving PCSK9 inhibitors and patients receiving an injectable placebo used in clinical trials, injection-site reactions may in fact represent a small increase in costs and disutility relative to the orally administered comparators in this analysis. If future studies reveal more serious or more frequent adverse events, or substantial disutility arising from the need for parenteral administration of PCSK9 inhibitors, we

will have overestimated the cost-effectiveness of PCSK9 inhibitors, and this analysis would need to be updated to account for this new safety information.

Third, this analysis was performed assuming that patients continued taking the medication strategy assigned at baseline for years afterward, and did not directly account for decrements in medication adherence, stopping the assigned medication strategy, or switching to another strategy over time. Our model partially accounts for medication non-adherence to the extent that its effect on clinical efficacy is already captured in the observed risk reduction seen in clinical trials and our population-based approach accounted for background statin therapy in the population. However, real-world adherence may vary from that observed in clinical trials based on age, educational status, co-morbidities, and cost-sharing.[128] It is plausible that adherence to PCSK9 inhibitors – which have to be self-injected and may have higher co-pays – may be lower in the real world compared with that observed in clinical trial populations. At the same time, a monthly or biweekly regimen may improve adherence over a once-daily dose. Future studies must examine the impact of non-adherence on effectiveness and safety.

Fourth, our model incorporated the entire cohort of US adults aged 35 to 74 years in the year 2015 and followed them until the age of 95 years. Treatment of FH often begins in childhood or adolescence with premature coronary disease often manifesting in the third decade of life; we therefore may not have captured the entire clinical and economic burden of FH in the population or the benefits of LDL-C lowering in childhood or young adulthood. However, there are currently no data about the efficacy or safety of PCSK9 inhibitors in children, and until such data become available, any assumptions about the benefits and risks of PCSK9 inhibitors in children would be purely speculative. We assumed that the elevated cardiovascular risk among patients with FH is entirely mediated by their high serum levels of LDL-C along with characteristics measured in the NHANES risk factor survey. If an FH patient with a certain LDL cholesterol level is at a higher risk for a cardiovascular event compared with an otherwise identical patient with the same LDL-C level but without FH (perhaps due to onset of exposure to high LDL-C earlier in life, leading to accelerated atherosclerosis), we will have underestimated the clinical and economic burden of FH, and possibly the cost-effectiveness of PCSK9 inhibitors in this population. On the other hand, it is likely that our operational definition of FH (with LDL-C level ≥250mg/dL off statins or ≥200mg/dL on statin therapy) identifies a subgroup of patients at a relatively higher risk of events given that the clinical diagnosis of FH can be made in adults with an LDL-C level greater than or equal to 190mg/dL who have a family history of FH. We chose our operational definition to increase specificity in the absence of family history data in the model and to approximate the previously published population prevalence of FH (1 in 500). But the higher LDL-C threshold may have produced a study cohort at higher-than-average risk of cardiovascular events. Applying a lower LDL-C threshold to define FH (e.g., LDL-C ≥ 190mg/dL) would substantially increase the number of individuals eligible for additional lipid-lowering therapy and hence amplify the budget impact. At the same time, lowering

the LDL-C threshold would lower the average risk of cardiovascular events in the eligible population, thus reducing the cost-effectiveness of PCSK9 inhibitors in this subpopulation.

Fifth, our model assumes a constant drug cost over the analytic horizon, but long-term changes in drug prices may be impacted by patent expiration, availability of generics or biosimilars, or development of novel therapies. If drug-prices decrease over time, we will have underestimated long-term cost-effectiveness and over-estimated budget impact.

Finally, our assumed levels of PCSK9 inhibitor uptake in the marketplace by five years were based on reasoned assumptions, but actual uptake may vary from these estimates. We also present potential budget impact across a range of uptake possibilities in sensitivity analyses.

7. Summary of the Votes and Considerations for Policy

7.1 About the New England CEPAC Process

During public meetings of the New England CEPAC, the Council deliberates and votes on key questions related to the systematic review of the clinical evidence, an economic analysis of the applications of the medical technologies or treatments under examination, and the supplementary information presented. Council members are selected for three year terms and are intentionally selected to represent a range of expertise and diverse perspectives. To maintain the objectivity of New England CEPAC and ground the conversation in the interpretation of the published evidence, members are not pre-selected based on the topic being addressed. Acknowledging that any judgment of evidence is strengthened by real-life clinical and patient perspectives, clinical representatives with expertise in the subject matter are recruited for each meeting topic and provide input to Council members before the meeting to help clarify their understanding of the interventions being analyzed in the evidence review. The same clinical experts serve as a resource to the Council during their deliberation, and they help form recommendations with the Council on ways the evidence can be applied to policy and practice.

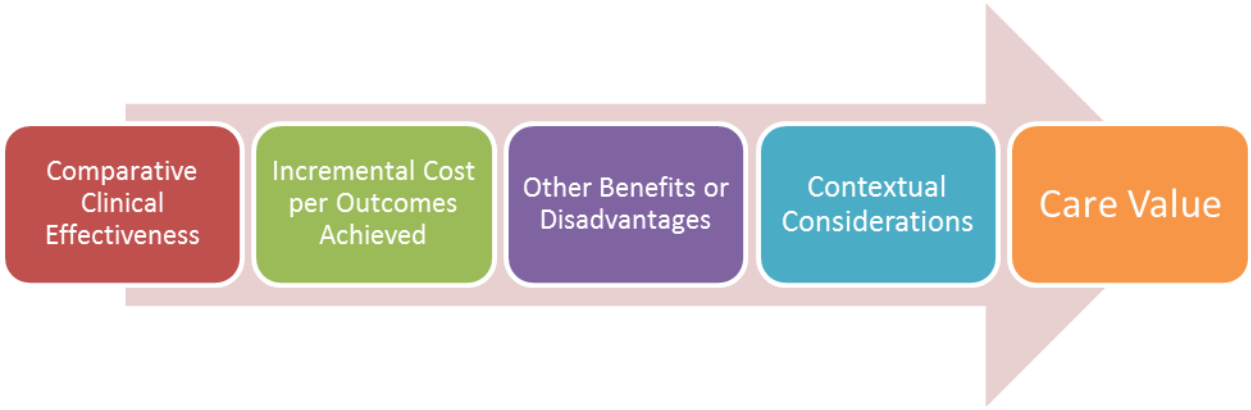
At each meeting, after the Council votes, a Policy Roundtable discussion is held with the Council, clinical experts, and representatives from provider groups, payers, and patient groups. This is intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient education, clinical practice, and coverage and public policies. Participants on Policy Roundtables are selected for their expertise on the specific meeting topic, are different for each meeting, and do not vote on any questions.

At the October 27, 2015 meeting, the Council discussed issues regarding the application of the available evidence to help patients, providers, and payers address the important questions related to the management of high cholesterol. Following an evidence presentation and public comments, the Council voted on key questions concerning the clinical effectiveness and value of PCSK9 inhibitors alirocumab and evolocumab. These questions are developed by the ICER research team for each assessment, with input from the New England CEPAC Advisory Board to ensure that the questions are framed to address the issues that are most important in applying the evidence to support clinical practice and medical policy decisions. The voting results are presented in the section below, along with comments reflecting considerations mentioned by the Council members during the voting process.

In its deliberations and voting related to value, the Council made use of a value assessment framework with four different components of *care value*, a concept which represents the long-term perspective, at the individual patient level, on patient benefits and the incremental costs to achieve those benefits. The four components of care value are comparative clinical effectiveness, incremental cost per outcomes achieved, additional benefits or disadvantages, and contextual considerations regarding the illness or therapy.

Once they made an overall assessment of care value as low, intermediate, or high considering these four components, the New England CEPAC then explicitly considered the affordability of PCSK9 inhibitors in assessing *provisional* health system value as low, intermediate, or high (see Figure 8 below and Figure 9 on the next page, as well as the detailed explanation that follows).

Figure 8. Care Value Framework



There are four elements to consider when deliberating on care value:

1. ***Comparative clinical effectiveness*** is a judgment of the overall difference in clinical outcomes between two interventions (or between an intervention and placebo), tempered by the level of certainty possible given the strengths and weaknesses of the body of evidence. The Council uses the ICER Evidence Rating Matrix as its conceptual framework for considering comparative clinical effectiveness.

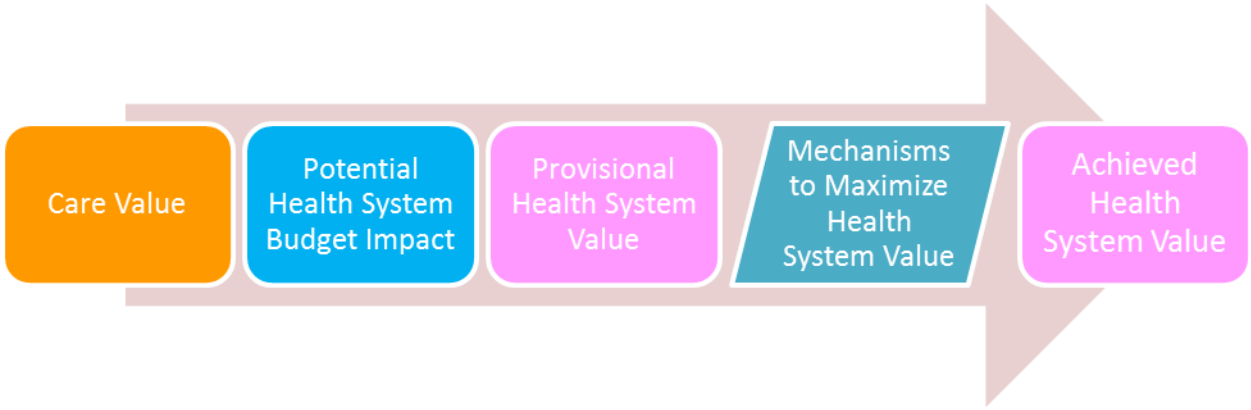
2. ***Incremental cost per outcomes achieved*** is the average per-patient incremental cost of one intervention compared to another to achieve a desired "health gain," such as an additional stroke prevented, case of cancer diagnosed, or gain of a year of life. Alternative interventions are compared in terms of cost per unit of effectiveness, and the resulting comparison is presented as a ratio: a "cost per outcome achieved." Relative certainty in the cost and outcome estimates continues to be a consideration. As a measure of incremental costs per outcomes achieved, ICER follows common academic and World Health Organization (WHO) standards by using cost per quality-adjusted life years (QALYs) and adopting thresholds at $100,000 per QALY and $150,000 per QALY as guides to reasonable ratios of incremental costs per outcomes achieved.

3. ***Other benefits or disadvantages*** refers to any significant benefits or disadvantages offered by the intervention to the individual patient, caregivers, the delivery system, other patients, or the public that would not have been considered as part of the evidence on comparative clinical effectiveness. Examples of additional benefits include mechanisms of treatment delivery that require many fewer visits to the clinician's office, treatments that reduce disparities across various patient groups, and new potential mechanisms of action for treating clinical conditions that have demonstrated low rates of response to currently available therapies. Additional disadvantages could include increased burden of treatment on patients or their caregivers. For each intervention evaluated, it will be open to discussion whether additional benefits or disadvantages such as these are important enough to factor into the overall judgment of care value. There is no quantitative measure for additional benefits or disadvantages.

4. ***Contextual considerations*** include ethical, legal, or other issues (but not cost) that influence the relative priority of illnesses and interventions. Examples of contextual considerations include whether there are currently any existing treatments for the condition, whether the condition severely affects quality of life or not, and whether the condition affects priority populations. There is no quantitative measure for the role of contextual considerations in an overall judgment of care value.

In assessing provisional health system value, the Council was asked to vote whether interventions represent a "high," "intermediate," or "low" value.

Figure 9. Health System Value Framework



1. ***Potential Health System Budget Impact*** is the estimated *net* change in *total* health care costs over a 5-year time-frame.
2. ***Provisional "Health System Value"*** represents a judgment integrating consideration of the long-term care value of a new intervention with an analysis of its potential short-term budget impact if utilization is unmanaged. The Council votes reflect a judgement on the provisional health system value of an intervention.
3. ***Mechanisms to Maximize Health System Value*** is an action step, ideally supported by enhanced early dialogue among manufacturers, payers, and other stakeholders.

4. ***Achieved Health System Value*** is the real-world result of health care stakeholder efforts to maximize the value of a given intervention.

Usually, the care value and the provisional health care system value of an intervention or approach to care will align, whether it is "high," "intermediate," or "low." For example, a treatment that is judged to represent high care value from the perspective of per-patient costs and benefits will almost always represent a high health system value as well. But health system value also takes into consideration the short-term effects of the potential budget impact of a change in care across the entire population of patients. Rarely, when the additional per-patient costs for a new care option are multiplied by the number of potential patients treated, the short-term budget impact of a new intervention of intermediate or even high care value could be so substantial that the intervention would be "unaffordable" unless the health system severely restricts its use, delays or cancels other valuable care programs, or undermines access to affordable health insurance for all patients by sharply increasing health care premiums. Under these circumstances, unmanaged change to a new care option could cause significant harm across the entire health system, in the short-term possibly even outweighing the good provided by use of the new care option itself.

Provisional health system value builds upon the judgment of care value by integrating consideration of the potential short-term budget impact of a new intervention, a figure highly dependent upon an estimation of the potential uptake of the new drug across the entire population. In the ICER framework, the theoretical basis for the budget impact threshold is based on societal willingness to pay. This foundation rests upon the assumption that society would prefer health care costs to grow at a rate that does not exceed growth in the overall national economy. ICER has used estimates based on data from the World Bank, the Centers for Medicare & Medicaid Services (CMS), and other public sources to calculate a budget impact threshold for individual new drugs or devices that would identify those whose potential budget impact would contribute significantly to excessive health care cost growth.

It should be noted that if, after considering potential budget impact, a health intervention judged to have high care value receives a judgment of "low" provisional health system value from the Council, this does not imply that the health system should not adopt the intervention; rather, the vote indicates that policy makers should consider implementing mechanisms related to patient selection, step therapy, pricing, and/or financing to ensure that the short-term budget impact of a high care value intervention does not lead to more harm than good. New England CEPAC votes on provisional health system value will therefore serve an important function by highlighting situations when policymakers need to take action and work together to align care value with health system value.

7.2 Comparative Clinical Effectiveness Voting Results

1. Is the evidence adequate to distinguish between the overall net health benefits of the PCSK9 inhibitors Praluent® and Repatha™, excluding use in homozygous familial hypercholesterolemia for which only Repatha has an indication?

   Council Vote: 0 Yes (0%) **12 No (100%)**

   Sub populations include:
   - Individuals with heterozygous familial hypercholesterolemia (HeFH) who are not at goal (LDL <160mg/dL)
   - Individuals with a history of atherosclerotic cardiovascular disease who cannot take statins or who take statins but are not at goal (LDL < 70mg/dL)

For individuals with heterozygous familial hypercholesterolemia (HeFH) who are statin intolerant or who take statins but are not at goal (<160mg/dL):

2. Is the evidence adequate to demonstrate that adding PCSK9 inhibitors to treatment improves net health benefits?

   Council Vote: **7 Yes (58%)** 5 No (42%)

   Comments: Council members voting yes noted that their votes assumed that lower LDL-C is a sufficient indicator for improved outcomes. It was also noted that the higher risk in FH populations was an important consideration and that this vote is based only on evidence available at present. Members voting no suggested that while the early evidence looks promising, more data is needed before conclusions can be drawn. They also expressed concerns that lower LDL-C may not be a sufficient endpoint to indicate improved outcomes.

For individuals with a history of atherosclerotic cardiovascular disease who are statin intolerant:

3. Is the evidence adequate to demonstrate that adding PCSK9 inhibitors to treatment improves net health benefits?

   Council Vote: 4 Yes (33%) **8 No (67%)**

   Comments: CEPAC members voting no pointed primarily to the uncertainty around the LDL hypothesis (whether a lower LDL-C leads to improved outcomes) given that this population may not have risks as high as patients who have FH and therefore high cholesterol from birth. Uncertainty was also discussed surrounding possible harms of the drugs given that LDL-C levels as low as those produced by these drugs have not been seen before and may have unknown long-term consequences.

For individuals with a history of atherosclerotic cardiovascular disease who take statins but are not at goal (LDL < 70mg/dL):

4. Is the evidence adequate to demonstrate that adding PCSK9 inhibitors to treatment improves net health benefits?

   Council Vote: 3 Yes (25%) **9 No (75%)**

   Comments: Similar to the previous question, Council members voting no cited a lack of evidence that lowering LDL-C below 70mg/dL ultimately improves outcomes. Without this evidence, many Council members felt unable to conclusively vote that PCSK9 inhibitors improve net health benefit for this population. Council members voting yes noted the LDL is a central mechanism of disease, and efforts should be taken to lower it when possible.

7.3 Care Value Voting Results

For individuals with heterozygous familial hypercholesterolemia (HeFH) who are statin intolerant or who take statins but are not at goal (LDL <160mg/dL):

5. Given the available evidence, what is the *care value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

   Council Vote: 0 High (0%) **8 Intermediate (67%)** 4 Low (33%)

   Comments: A majority of the council found PCSK9 inhibitors to have an intermediate care value for patients with HeFH. Members of the Council voting for an intermediate care value acknowledged the high incremental cost-effectiveness ratios but were persuaded not to vote "low" value because of the perceived increased risk and limited treatment options for patients with FH in whom statins have not been sufficiently effective. It was suggested that PCSK9 inhibitors help to fill a critical unmet need for this population. Members voting for a low value were persuaded by the high cost-effectiveness ratios in light of the residual uncertainty about clinical benefits.

For individuals with a history of atherosclerotic cardiovascular disease who are statin intolerant:

6. Given the available evidence, what is the *care value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

   Council Vote: 0 High (0%) 5 Intermediate (42%) **7 Low (58%)**

   Comments: CEPAC found PCKS9 inhibitors to present a low to intermediate care value for this population. Members felt that this population is not at as high of a risk as those with FH.

For individuals with a history of atherosclerotic cardiovascular disease who take statins but are not at goal (LDL < 70mg/dL):

7. Given the available evidence, what is the *care value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

   Council Vote: 0 High (0%) 2 Intermediate (17%) **10 Low (83%)**

   Comments: Rationale for a majority "low" vote was similar to that for the previous question; council members also noted that this population has several alternative treatment options at their disposal.

For the combined population of all patients in these groups

8. Given the available evidence, what is the *care value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

   Council Vote: 0 High (0%) 3 Intermediate (25%) **9 Low (75%)**

   Comments: Council members questioned the utility of lumping all patient populations together into a single group; however, it was recognized that in real-world situations, policy makers may not be able to tease out each sub-population.

7.4 Provisional Health System Value Voting Results

For individuals with heterozygous familial hypercholesterolemia (HeFH) who are statin intolerant or who take statins but are not at goal (LDL <160mg/dL):

9. Given the available evidence, what is the provisional *health system value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

   Council Vote: 0 High (100%) 2 Intermediate (17%) **10 Low (83%)**

   Comment: Council members voting for a low provisional health system value emphasized the need to consider the high short-term costs from a societal perspective. Council members emphasized that paying high prices for PCSK9 inhibitors will create the need for cuts in other areas.

For Individuals with a history of atherosclerotic cardiovascular disease who are statin intolerant:

10. Given the available evidence, what is the provisional *health system value* of adding ***PCSK9 inhibitors vs. no additional treatment***?
    Council Vote: 0 High (100%) 0 Intermediate (0%) **12 Low (100%)**

For Individuals with a history of atherosclerotic cardiovascular disease who take statins but are not at goal (LDL < 70mg/dL):

11. Given the available evidence, what is the provisional *health system value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

    Council Vote: 0 High (100%) 0 Intermediate (0%) **12 Low (100%)**

For the combined population of all patients in these groups

12. Given the available evidence, what is the provisional *health system value* of adding ***PCSK9 inhibitors vs. no additional treatment***?

    Council Vote: 0 High (100%) 0 Intermediate (0%) **12 Low (100%)**

7.5 Roundtable Discussion and Key Policy Recommendations

Following New England CEPAC's deliberation on the evidence and subsequent voting, ICER convened a Policy Roundtable intended to bring stakeholders into the discussion on how best to apply the evidence to guide patient education, clinical practice, and coverage policies. The Roundtable was composed of clinical experts, a patient, a representative from a national pharmacy benefit management company, a regional insurer, a purchaser of state based health insurance, and a representative from an academic medical center. Participants on Policy Roundtables are selected for their expertise or experience related to the specific meeting topic, are different for each meeting, and do not vote on any questions. The Policy Roundtable participants are displayed below.

Table 23. Policy Roundtable Participants

Policy Roundtable Participants
Leslie Fish, PharmD Vice President of Pharmacy, Fallon Health
Jonathan Karas Patient Representative
Dolores Mitchell, Executive Director, Group Insurance Commission
Patrick O'Gara, MD Senior Physician, Brigham and Women's Hospital Professor of Medicine, Harvard Medical School
William Shrank, MD, MSHS Senior Vice President, Chief Scientific Officer and Chief Medical Officer, Provider Innovation and Analytics, CVS Health
Thomas Siepka, RPh, MS FACHE Vice President, System Pharmacy and Outreach, Dartmouth Hitchcock
Paul Thompson, MD Chief of Cardiology, Hartford Hospital Professor of Medicine, University of Connecticut

The Roundtable discussion explored the implications of New England CEPAC's votes for clinical practice and medical policy, considered real life issues critical to developing best practice recommendations in this area, and identified potential avenues for applying the evidence to improve patient care. The main themes and recommended best practices from the conversation are summarized below. The Policy Roundtable discussion reflected multiple perspectives and opinions; therefore, none of the recommendations below should be taken as a consensus view held by all participants.

1. **Professional societies should take prompt action to update clinical guidance, including a likely need to return to treatment goals based on target LDL-C levels.**

Members of the Roundtable highlighted the need to link the dialogue surrounding PCSK9 inhibitors to a broader discussion about clinical guidelines made by professional societies. Physicians rely on clinical guidelines when making decisions about a particular diagnostic or therapeutic procedure. Guidelines are intended to direct everyday clinical decision-making and reinforce the practice of evidence based medicine. Roundtable participants noted that the emergence of PCSK9 inhibitors has unveiled an urgent need for action from professional societies. As mentioned earlier in this report, guidelines for the treatment of cholesterol have changed in recent years. In 2013, the ACC/AHA released a guideline that moved away from recommending specific LDL-C levels as treatment targets.[5] While both the 2013 guideline and previous guidelines include strong recommendations for use of statin therapy to treat individuals with cardiovascular disease, the updated guideline does not recommend specific LDL-C targets. This guideline was developed when little clinical evidence was available for treatment with PCSK9 inhibitors. Clinical participants on the Roundtable voiced that LDL-C goals serve as a mechanism to measure patient progress.

Without specific treatment goals, clinicians may face challenges when prescribing statin therapy as a preferred treatment. They may feel pressured to prescribe PCSK9 inhibitors to yield lower LDL-C levels despite a lack of evidence supporting the hypothesis that lower LDL-C leads to improved outcomes. An updated guideline that stratifies patients by their cardiovascular risk, includes treatment goals based on target LDL-C levels, and titrates medication use to reach a specified target would provide clinicians with a basis for discussion when examining treatment options with patients. In order to remain relevant and effective within the context of a changed treatment landscape, professional societies should produce updated guidelines that recommend specific LDL-C targets based on patient characteristics.

2. **Payers should use prior authorization to enhance health system value by limiting treatment to patients for whom extended trials of high-dose statins combined with ezetimibe have been unsuccessful.**

Due to the high cost of PCSK9 inhibitors, payers will likely administer utilization management techniques to control aggregate health care costs. Specifically, prior authorization and step therapy are used to stratify patients by risk and previous treatment in order to ensure that coverage policies align with prudent clinical practice options. These coverage policies typically require patients to first try a lower-cost, evidence based therapy to achieve a clinical goal. If a patient is unable to achieve a goal with a specified therapy, a physician may escalate a patient to a more intensive and costly option.

For high cost drugs, prior authorization criteria are generally based on an FDA indication, and treatment is limited to patients for whom the evidence demonstrates greatest benefit. In addition to the FDA indications, PCSK9 inhibitors will likely be limited to patients who have not reached appropriate LDL-C after extended trials (likely 60-90 days) of high-dose statins combined with ezetimibe. Clinical expert participants on the Roundtable felt that it was practical and reasonable for patients to fail at least 2 statins, with one at the lowest dose, prior to use of PCSK9 inhibitors. Statin non-adherence was also raised as a point of concern; one clinical expert expressed that providers do not always know when a patient is taking statins as prescribed. Another participant expressed that as part of coverage policies, payers may want to consider using results of lab tests to demonstrate that 2 statins have been tried. If executed appropriately, these measures will enhance the health system value of PCSK9 inhibitors. As noted earlier, unless the current treatment guideline is updated, payers will likely face challenges when developing criteria and will be limited in their ability to administer these tools. Discussion also turned to managing use of PCSK9 inhibitors in key subpopulations as described below:

Patients with FH

There was consensus throughout the meeting that there is a significant unmet need among patients with FH who are unable to lower cholesterol sufficiently using statins or ezetimibe. The patient participant on the Roundtable shared his experience in dealing with FH as a patient and as a parent of a child with FH, noting that some patients with FH must endure intensive and expensive treatment like apheresis. Other Roundtable participants mentioned that for those patients with clearly identified unmet need (e.g., homozygous FH or very high LDLs on treatment) the discussed criteria could be relaxed. Roundtable participants also stated that identifying patients with FH can be difficult. The clinical experts acknowledged that LDL-C measures are most useful for understanding risk; specifically noting that they would consider a patient to have clinical FH if they presented with an LDL > 190 mg/dL without any treatment. Measures such as genetic testing were deemed unnecessary for most patients, as these tests can be costly and there are 1700 genetic mutations that can cause FH.

Primary Prevention and Off-Label Use

In the discussion of off-label use, there was general consensus that PCSK9 inhibitors should not be used for primary prevention or for patients with comorbidities such as diabetes; participants considered off-label use to be a slippery slope within the context of this discussion.

3. Prior authorization criteria may need to require most patients who believe they are statin intolerant to be re-tried on statins.

Many patients report adverse effects associated with statin therapy; however, the field lacks consensus on a definition of statin intolerance. Based on feedback from the clinical expert participants and a review of existing definitions, it may be considered reasonable by some to operationalize the recent National Lipid Association (NLA) definition of statin intolerance when making treatment decisions. In June 2014 National Lipid Association Expert Panel on Statin Intolerance suggested the following definition for statin intolerance:

> Statin intolerance is a clinical syndrome characterized by the inability to tolerate at least 2 statins: one statin at the lowest starting daily dose AND another statin at any daily dose, due to either objectionable symptoms (real or perceived) or abnormal lab determinations, which are temporally related to statin treatment and reversible upon statin discontinuation, but reproducible by re-challenge with other known determinants being excluded (such as hypothyroidism, interacting drugs, concurrent illnesses, significant changes in physical activity or exercise, and underlying muscle disease). Specifically, the lowest starting statin daily dose, is defined as rosuvastatin 5 mg, atorvastatin 10 mg, simvastatin 10 mg, lovastatin 20 mg, pravastatin 40 mg, fluvastatin 40 mg, and pitavastatin 2 mg[1].

This definition may prove useful in clinical practice, but it is important to note that there are limitations to understanding statin intolerance. The prevalence of true statin intolerance is uncertain and 'perceived symptoms' are not always related to statin therapy. One clinical expert participant shared that many people who think they have statin intolerance actually can tolerate the medications. Two studies referenced in this report examined statin intolerance; one found a 10% incidence of mild to moderate muscle symptoms for patients on high intensity statin therapy[17] and the second a 9.4% incidence of muscle symptoms in statin-naïve patients treated with atorvastatin 80 mg daily compared to a 4.6% incidence in patients randomized to placebo.[18]

[1] An assessment by the Statin Intolerance Panel: 2014 update
John R. Guyton, MD, FNLA correspondence email, Harold E. Bays, MD, FNLA, Scott M. Grundy, MD, PhD, FNLA, Terry A. Jacobson, MD, FACP, FNLA Received: March 3, 2014; Accepted: March 4, 2014;

Also of note, the precise measurement of statin intolerance is difficult. As noted earlier in our report, often statin intolerance is primarily associated with muscle pain, which can arise from a number of other causes, particularly in older individuals. This was echoed by one clinical expert participant of the Roundtable who conveyed that statin intolerance is primarily a clinical diagnosis; there is no genetic marker to identify it.

4. **Management of patients with possible statin intolerance and other complexities of decision-making regarding PCSK9 inhibitors suggest that it is reasonable to restrict prescribing of PCSK9 inhibitors to specialists in lipid management.**

   Currently, there is variation in how payers define statin intolerance; it will likely take work to define the concept. One way to ensure that possible statin intolerance and other complexities are appropriately managed would be to limit prescribing authority of PCSK9 inhibitors to specialists in lipid management. This was emphasized during the Roundtable when one participant noted that it is difficult to account for grey areas when releasing a very expensive drug; even among specialists there is great variability in expertise. Given that cardiologists are likely to see the majority of the high risk patients it may be reasonable to restrict prescribing of PCSK9 inhibitors to specialists.

5. **If the pricing for PCSK9 inhibitors were to fall 50%-85% to a level that aligns with the benefit to patients and with a reasonable short term affordability, payers would likely consider lifting many elements of proposed prior authorization requirements.**

   During the Policy Roundtable, there was a focused discussion on the price of PCSK9 inhibitors as it relates to other public health expenditures. One participant vocalized that other services are being starved to pay for these and other drugs. The participant included pointed statements towards the morality associated with prices charged for new treatments and society's willingness to pay. There was an urge for stakeholders to understand how to apply balance between the cost of care versus other services that must be financed such as public health, education, safety, and other public programs. When the pharmacy benefit management representative was asked about the price he responded that if PCSK9 inhibitors were priced lower, the conversation about cost and value would not be taking place.

   The high cost of the pharmaceuticals was also noted by participants both on the payer and provider side when discussing the administrative burden associated with prior authorization and other utilization management techniques. These mechanisms are necessary to reduce the budgetary impact of PCSK9 inhibitors at the current price. However, Roundtable participants noted that if the drugs were priced near ICER's value-based price benchmark, the focus on utilization management, and perhaps the entire discussion surrounding the value and budgetary impact of PCSK9 inhibitors, would not be taking place. In the future, pharmaceutical companies should join a broader discussion with payers and other stakeholders about how the current approach to the pricing of drugs can change to help address the negative impact of rising health care costs on patients and on other important societal goals.

6. **Future research needs will be strongly influenced by the results of current clinical outcomes studies, but additional research in adherence and long-term safety will be important to guide practice and policy in the future.**

Discussion during the October 27, 2015 meeting highlighted the need for more information about efficacy and safety of PCSK9 inhibitors. It was evident that there is an unmet need among patients with FH, but evidence pertaining to other sub-populations is less clear. When voting on the evidence, the majority of the council concluded that there was not adequate evidence to demonstrate that PCSK9 inhibitors improve net health benefits in patients with a history of cardiovascular disease. In addition to general uncertainty around long-term effectiveness and safety, most Council members were unable to completely accept the so-called "LDL hypothesis". This hypothesis assumes that any lowering of LDL cholesterol would also lower the risk of heart attacks and strokes. Council members were reluctant to embrace the hypothesis likely because this has been demonstrated for some drugs (statins, ezetimibe) but not for others (niacin, fibrates). It will be necessary to revisit the discussion surrounding the direct effects of PCSK9 inhibitors on rates of heart attack and stroke when results of ongoing trials are released in 2017.

There may also be a need to examine real world data related to difference in treatment adherence between PCSK9 inhibitors and statins. As noted earlier, it is difficult to measure treatment adherence among patients who have been prescribed statins. It remains unclear whether treatment adherence would improve if a patient were to switch from an oral statin to a less frequent, but injectable, PCSK9 inhibitor. PCSK9 inhibitor adherence was referenced during the evidence review in the context of clinical trial data. Some felt that there may be differences between adherence rates observed in RCTs versus those experienced by patients that are not participating in trials. Some argue rates of adherence found outside of clinical trials will most certainly be lower than those reported during clinical trials. Adherence rates for PCSK9 inhibitors versus statins will likely need to be studied further.

There appeared to be consensus among participants of the Roundtable that clinicians should try multiple statin options before seeking alternative treatments for patients with elevated LDL-C. There may be opportunity in this area to develop tools to help physicians educate patients about statin intolerance. One physician shared that patients are often afraid that any experienced muscle pain while taking statins will be permanent and therefore discontinue use of the medication. As direct to consumer marketing campaigns are executed for the new LDL-C lowering therapies, statin intolerance-related muscle pain will likely be used as means of attracting patients to PCSK9 inhibitors. In this environment, it is imperative that patients be equipped with accurate information pertaining to evidence based therapies in order to make well informed treatment decisions.

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APPENDICES

A1. Search Strategies

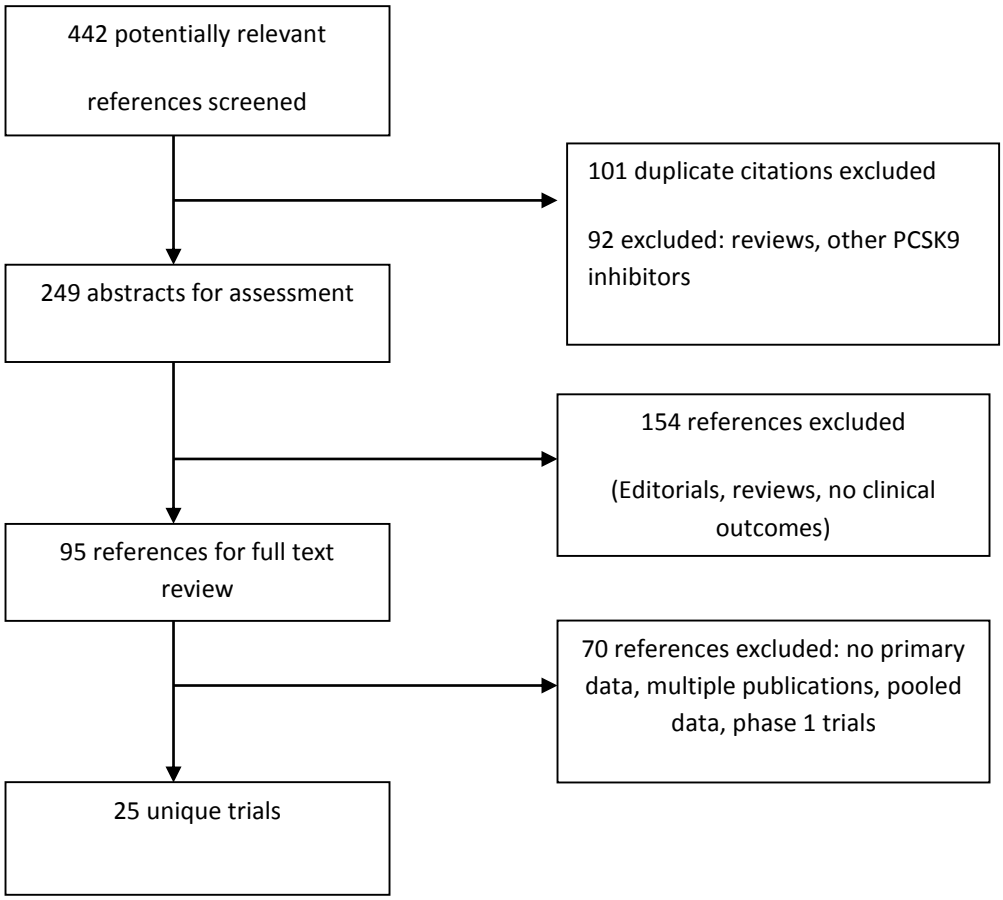
PubMed

((((((alirocumab) OR evolocumab) OR pcsk9 inhibitor) OR pcsk9 antibody) OR amg 145) OR regn727) OR sar236553

Cochrane

((((((alirocumab) OR evolocumab) OR pcsk9 inhibitor) OR pcsk9 antibody) OR amg 145) OR regn727) OR sar236553

Figure 1. Selection of Studies for Inclusion in Review



A2. Clinical Guidelines

For the purposes of this review, this section outlines available clinical guidelines for the management of high cholesterol. It is important to note that that the use of target or goal lipid levels is no longer universal across all guideline statements. As noted in the Background section, this has been the subject of debate in many policy settings and the academic literature. At the time of review, existing guidelines did not include reference to PCSK9 inhibitors for treatment of cholesterol. Websites for this review were accessed on August 17, 2015.

Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) Final Report 2001

http://circ.ahajournals.org/content/106/25/3143.full.pdf

In 2001 the National Cholesterol Education Program (NCEP) produced a report updated recommendations for cholesterol testing and management (ATP III). Many of the guidelines included in this section build upon this report. ATP III targets the clinical approach to prevention of coronary heart disease (CHD) and identifies low-density lipoprotein (LDL-C) as the primary target of cholesterol-lowering therapy. Statins are noted as the primary option for attainment of the LDL-C goal in higher-risk individuals as they are most effective, well tolerated and easy to administer. Combination therapy with other agents (e.g., bile acid sequestrants) may be needed to provide additional reduction of LDL-C, to achieve the goal for non-HDL cholesterol, to treat severe hypertriglyceridemia, and if it seems advisable, to raise HDL cholesterol levels.

The report Identifies LDL-C of <100 mg/dL as optimal and notes that prospective epidemiological studies show that when LDL–C levels are below 100 mg/dL an individual's CHD risk likewise is low, even in the presence of other risk factors. However, in 2004, the National Cholesterol Education Program (NCEP) Adult Treatment Program (ATP) III updated its guidelines to include an "optional" LDL-C goal less than 70 mg/dL for patients at very high risk. The 2004 NCEP ATP III update further indicated that it is always prudent to initiate therapy at a level sufficient to achieve a 30% to 40% LDL-C reduction.[i]

Guidelines from Clinical Societies

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults

http://circ.ahajournals.org/content/early/2013/11/11/01.cir.0000437738.63853.7a

The previous ACC/AHA guideline recommended that clinicians treat patients to a specific LDL-C target by stratifying patients according to their cardiovascular risk, assigning an LDL-C target, and titrating medication use to reach that target. **The updated guideline does not contain recommendations for or against specific LDL-C or non–HDL-C targets for the primary or secondary prevention of ASCVD.** The Expert Panel was unable to find sufficient RCT evidence to support continued use of specific LDL-C or non–HDL-C treatment targets.

The guideline describes 4 statin benefit groups that focus efforts to reduce ASCVD events in secondary and primary prevention. The appropriate intensity of statin therapy should be used to reduce ASCVD risk in those most likely to benefit.

Primary Prevention

Adults ≥21 years of age with primary, severe elevations of LDL–C (≥190 mg/dL) have a high lifetime risk for ASCVD events and should receive high-intensity statin therapy if they have not already been diagnosed and treated before this age. For individuals with LDL-C 70–189 mg/dL moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes. High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes with a ≥7.5% estimated 10-year ASCVD risk unless contraindicated. Adults 40 to 75 years of age with LDL-C 70–189 mg/dL, without clinical ASCVD or diabetes, and with an estimated 10-year ASCVD risk ≥7.5% should be treated with moderate- to high-intensity statin therapy. It is reasonable to offer treatment with a moderate-intensity statin to adults 40 to 75 years of age, with LDL-C 70–189 mg/dL, without clinical ASCVD or diabetes, and with an estimated 10-year ASCVD risk of 5% to <7.5%.

Secondary Prevention

The guideline recommends that secondary prevention high-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have clinical ASCVD, unless contraindicated. Moderate-intensity statin should be used as the second option if tolerated in individuals with clinical ASCVD in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present. Individuals with clinical ASCVD >75 years of age should be evaluated for potential ASCVD risk-reduction benefits and for adverse effects and drug

interactions; patient preferences should also be considered when initiating a moderate- or high-intensity statin.

Non statin therapies, as compared to statin therapy, do not provide acceptable ASCVD risk-reduction benefits relative to their potential for adverse effects in the routine prevention of ASCVD. If considering non-statin therapies, the guideline recommends that adherence to lifestyle and to statin therapy re-emphasized before the addition of a non-statin drug. High-risk patients who have a less-than-anticipated response to statins, who are unable to tolerate a less-than-recommended intensity of a statin, or who are completely statin intolerant may require a non-statin cholesterol-lowering therapy. Non statin therapies referenced in the guideline include niacin, bile acid sequestrants, cholesterol-absorption inhibitors, fibrates, and omega-3 fatty acids.

The American Association of Clinical Endocrinologists' (AACE) Guidelines for Management of Dyslipidemia and Prevention of Atherosclerosis (March and April 2012)

https://www.aace.com/sites/default/files/LipidGuidelines.pdf

For patients with average or elevated LDL-C, the AACE recommends aggressive lipid-modifying therapy to lower LDL-C to less than 100 mg/dL.

The AACE identifies statins as the drug of choice for LDL-C reduction due to the efficacy and safety profile of the drug class. Other pharmacologic therapy referenced in the guidelines include fibrates, niacin, bile acid sequestrants, cholesterol absorption inhibitors (ezetimibe), and combination therapy.

Cholesterol Absorption Inhibitors (ezetimibe) are noted as an effective monotherapy in reducing LDL-C and apo B or as part of combination therapy with statins. Current research indicates that combining statins with ezetimibe may yield enhanced benefits by furthering the impact of statins on triglycerides and HDL-C, but it is uncertain whether ezetimibe has a direct benefit on reducing cardiovascular events.

In adults of both sexes, AACE recommends a target LDL-C concentration less than 100 mg/dL and less than 70 mg/dL in patients at very high risk, including those with one or more additional risk factors, such as established CVD or CAD. For patients with diabetes mellitus, AACE recommends an LDL-C goal of less than 100 mg/dL. Lipid goals for all patients should be personalized by levels of risk and suggest that there is no threshold below which LDL-C lowering ceases to be effective, stating that reducing lipids to levels even below recommended targets may be beneficial for certain patients (e.g., those with metabolic syndrome).

AACE recommends aggressive therapy for patients undergoing coronary artery bypass graft, patients with acute coronary syndrome, and certain healthy and functional older patients at high risk who may be appropriate candidates for aggressive therapy.

European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) Guidelines for the Management of Dyslipidaemias

http://www.escardio.org/static_file/Escardio/Guidelines/publications/DYSLIPguidelines-dyslipidemias-FT.pdf

For pharmacologic treatment of hypercholesterolemia, ESC/EAS recommends that physicians prescribe statins up to the highest recommended dose, or to the highest dose tolerated by the patient. In patients who do not reach LDL-C targets with statin therapy alone, a combination of a statin and a bile acid sequestrant, nicotinic acid, or cholesterol absorption inhibitor may be considered. If a patient is statin intolerant, bile acid sequestrants or nicotinic acid should be considered. A cholesterol absorption inhibitor, either alone or combined with a bile acid sequestrant or nicotinic acid, may also be considered.

For patients with HeFH, a high dose statin is recommended. If needed, a combination of statin and cholesterol absorption inhibitor and/or bile acid sequestrant and is recommended. Treatment should be aimed at reaching LDL-C goals of $\leq$100 mg/dL in high risk subjects. A goal of $\leq$70 mg/dL is recommended for high risk subjects with CVD. If targets cannot be reached, maximal reduction of LDL-C using appropriate drug combinations is recommended.

National Lipid Association Recommendations for Patient-Centered Management of Dyslipidemia (September 2014)

http://www.lipidjournal.com/article/S1933-2874(14)00274-8/pdf

The National Lipid Association recommends that for patients in whom lipid-lowering drug therapy is indicated, statin treatment is the primary modality for reducing ASCVD risk. The recommendations emphasize that non-HDL-C is a better primary target for modification than LDL-C, and is considered to be a co-target with LDL-C.

These recommendations note that patients experiencing statin intolerance may improve if switched to a different statin. Alternative strategies include limiting the daily dosage and modified regimens such as every other day or once weekly dosing with statins. In some patients, it may be possible to switch to an alternative concomitant therapy to enhance statin tolerance. For patients who cannot tolerate a statin with the previously discussed strategies, a non-statin drug alone or in combination with another cholesterol lowering agent may be considered.

Non-statin drug classes for lipid management include cholesterol absorption inhibitors (ezetimibe), bile acid sequestrants, fibric acids, long-chain omega-3 fatty acid concentrates, and nicotinic acid. The recommendation references two additional classes of medications available with more limited indications for the treatment of patients with homozygous familial hypercholesterolemia (FH): an antisense oligonucleotide that targets the messenger RNA for apo B, and a microsomal triglyceride transfer protein inhibitor.

Patients with severe hypercholesterolemia phenotype (LDL-C >190 mg/dL) are at increased lifetime risk for ASCVD, particularly premature ASCVD, and may not be able to achieve goal cholesterol levels even with combination drug therapy. When this is the case, an alternative goal should be to lower LCL-C levels by at least 50%. The recommendation references PCSK9 inhibitors (under investigation at the time of publication) as having the potential to make attainment of goal cholesterol levels practical for a greater fraction of patients with severe hypercholesterolemia.

The LDL-C goals for therapy for patients at risk for CAD are LDL-C of <100 mg/dL and LDL-C of <70 mg/dL for all very high risk patients.

Lipid modification: cardiovascular risk assessment and the modification of blood lipids for the primary and secondary prevention of cardiovascular disease. National Institute for Health Care and Excellence (NICE) (July 2014)

http://www.nice.org.uk/guidance/cg181/chapter/1-recommendations#identifying-and-assessing-cardiovascular-disease-cvd-risk-2

Considerations for statin use should follow a formal assessment of cardiovascular risk, except in patients with type 1 diabetes, familial hypercholesterolemia, pre-existing CVD, or eGFR rates less than 60/ml/min/1.73m^2. These groups have high cardiovascular risk and do not require assessment.

For primary prevention, patients should first be offered support for lifestyle modification. If lifestyle interventions are ineffective or unsuited for the patient, statins should be offered to patients with a 10% or greater 10-year risk of developing CVD based on the QRISK2 assessment tool. Dosing should begin with 20mg of atorvastatin. Patients with type 1 diabetes should be offered 20 mg of atorvastatin if they are 40 years or older, have had diabetes for at least 10 years, have established nephropathy, or have other CVD risk factors. Patients age 85 or older should be considered for statin therapy for prevention of myocardial infarction.

For secondary prevention, patients should receive 80 mg of atorvastatin. In the case of potential drug interactions or high risk of adverse reactions, or based on patient preference, a lower dose may be used. If a person is unable to tolerate a high-intensity statin, treat with the maximally tolerated dose. If patients report adverse effects, physicians should try reducing the dose, stopping and restarting the statin to see if symptoms are related to use, or change the statin to a lower intensity group.

The European Atherosclerosis Society consensus statement on treating familial hypercholesterolemia (August 2013)

http://eurheartj.oxfordjournals.org/content/early/2013/08/15/eurheartj.eht273.full

In August of 2013 the European Atherosclerosis Society released a consensus statement, providing guidance for screening and treatment of familial hypercholesterolemia, in order to prevent coronary heart disease (CHD). The statement recommends initiation of cholesterol-lowering drugs immediately at diagnosis in adults along with lifestyle management. The statement ranks specific priorities for pharmacotherapy beginning with maximal potent statin dose, followed by ezetimibe, then bile acid-binding resins, and finally lipoprotein apheresis in homozygotes and in treatment-resistant heterozygotes with CHD. The consensus statement recommends treating to specific LDL-C targets. For adults LDL-C targets are LDL-C of <100 mg/dL and LDL-C of <70 for adults with known CHD or diabetes. The statement advises a clinical assessment of efficacy and safety 4–6 weeks after initiating treatment.

A3. Detailed Coverage Policies

Medicaid

Rosuvastatin (Crestor®)

Of the six New England states, three cover rosuvastatin (Crestor®) without restriction, but quantity limits may apply. The remaining three states require prior authorization or step therapy. Massachusetts requires that patients have tried atorvastatin at a dose of at least 80 mg per day (or a similar statin with equivalent potency) and have not had adequate reduction in LDL-C, or have a contraindication to atorvastatin. Rhode Island requires prior authorization and requires that patients first try atorvastatin. New Hampshire lists Crestor as a non-preferred agent, which typically signals non-coverage.

Ezetimibe/simvastatin (Vytorin®)

With the exception of Maine, every state in New England limits coverage of ezetimibe/simvastatin (Vytorin®). Coverage in Massachusetts is limited to those for whom a prior regimen of atorvastatin at a dose of at least 80 mg/day (or a similar statin with equivalent potency) has failed to achieve adequate reduction in LDL-C , or who havea contraindication to atorvastatin. Vermont utilizes prior authorization and requires a prior regimen of atorvastatin or Crestor. Rhode Island also requires prior authorization. New Hampshire lists Vytorin as a non-preferred agent, and Connecticut does not list Vytorin on its formulary.

Ezetimibe (Zetia®)

A majority of New England states utilize prior authorization criteria for ezetimibe (Zetia®). In Maine, Massachusetts, and Vermont, prior authorization policies require a prior regimen of a statin with inadequate response or the presence of a contraindication to statins. Rhode Island also utilizes prior authorization, though the requirements are not publicly available. New Hampshire requires prior regimen of at least 2 high-potency statins or combination products. Connecticut does not list Zetia® on its formulary.

Regional Private Payers

Rosuvastatin (Crestor®)

Major regional private payers in New England generally cover Crestor as a tier 2 or tier 3 drug. Blue Cross Blue Shield of Massachusetts (BCBSMA), Neighborhood Health Plan of Rhode Island (NHPRI), and ConnectiCare all require step therapy, while BCBSMA and ConnectiCare also

impose quantity limits. Tufts Health Plan (THP) requires prior authorization. Blue Cross Blue Shield of Vermont (BCBSVT) covers Crestor without restriction.

Ezetimibe/simvastatin (Vytorin®)

Most regional plans cover Vytorin as a tier 3 drug, with the exception of THP which covers it as tier 2. NHPRI and ConnectiCare require step therapy, as does Harvard Pilgrim Health Care (HPHC) for higher dose formulations. THP requires prior authorization. BCBSMA and ConnectiCare also use quantity limits. BCBSMA lists Vytorin as a non-covered medication, but physicians may request coverage if no other alternative is suitable for treatment of a patient's condition. Step therapy and quantity limits apply.

Ezetimibe (Zetia®)

Regional plans cover Zetia as a tier 2 or tier 3 medication. BCBSMA and HPHC require step therapy, and NHPRI requires prior authorization. ConnectiCare imposes quantity limits.

National Private Payers/Pharmacy Benefit Managers

Rosuvastatin (Crestor®)

On a national level, private payers generally list Crestor as a tier 2 drug and apply quantity limits. Cigna also applies prior authorization and step therapy for the 5mg and 10mg formulations, and offers a deductible exemption under its preventative drug benefit.

Ezetimibe/simvastatin (Vytorin®)

Most national private payers apply similar criteria to Vytorin, listing it as a tier 2, 3, or 4 drug, depending on the plan. Aetna and Cigna require step therapy. Aetna also applies quantity limits, as do Humana and United Healthcare. Cigna requires prior authorization.

Ezetimibe (Zetia®)

Zetia is generally covered as a tier 2 drug, except in the case of United Healthcare, which covers it as a tier 3 or tier 4 drug. Aetna, Cigna, Humana, and United Healthcare apply quantity limits. Cigna offers a deductible exemption through its preventative drug benefit.

A4. Previous Systematic Reviews and Technology Assessments

We did not identify any prior technology assessments addressing PCSK9 inhibitor therapy. There are two published systematic reviews and meta-analyses that were cited as part of the evidence review. Both reviews identified the same 25 studies included in this New England CEPAC assessment. They are briefly summarized below.

Navarese EP, Kolodziejczak M, Schulze V, et al. Effects of Proprotein Convertase Subtilisin/Kexin Type 9 Antibodies in Adults With Hypercholesterolemia: A Systematic Review and Meta-analysis. *Ann Intern Med.* 2015. PMID: 25915661.

The investigators performed a high quality systematic review that included phase 2 or 3 randomized trials of PCSK9 antibodies, but excluded the OSLER study (combined OSLER 1 and OSLER 2) from their analyses because all of the patients in the OSLER study were included in the 24 earlier studies (n=10,159). The investigators combined the results for both alirocumab and evolocumab. They found that treatment with PCSK9 inhibitors markedly lowered LDL-C levels and reduced all-cause mortality that they describe as "an important preliminary signal of survival benefit compared with no anti PCSK9 treatment." They concluded that PCSK9 antibodies seem safe and effect for adults with dyslipidemia. They note that their conclusions are limited by the rare clinical outcome data and the fact that study level data rather than patient level data were used for their analyses.

Zhang XL, Zhu QQ, Zhu L, et al. Safety and efficacy of anti-PCSK9 antibodies: a meta-analysis of 25 randomized, controlled trials. *BMC Med.* 2015;13:123. PMID: 26099511.

The authors combined results from the 25 trials of 12,200 patients, including patients from the OSLER 1 study twice. They focused much more heavily on evolocumab than alirocumab. They found that evolocumab every two or four weeks reduced LDL-C by 55% versus placebo and 36% versus ezetimibe. Alirocumab 50-150 mg every two weeks reduced LDL-C by 53% versus placebo and 30% versus ezetimibe. Overall they found no significant differences in rates of common adverse events with placebo or ezetimibe controls. Alirocumab, but not evolocumab was associated with a reduced risk of death (p=0.04). Evolocumab was associated with a reduced rate of abnormal liver function (p=0.03). They concluded that both drugs were safe and well tolerated with favorable changes in all lipid parameter. They end stating that they "await the results of ongoing trials evaluating their effects on CVD events."

A5. Ongoing Studies

Title/Trial Sponsor	Study Design	Comparators	Patient Population	Primary Outcomes	Estimated Completion Date
Alirocumab					
ODYSSEY OUTCOMES Sanofi / Regeneron NCT01663402	RCT N = 18,000 5-6 year FU	Alirocumab Placebo	• Post-acute coronary syndrome • Age 40 years • ACS in past 52 weeks • LDL-C ≥ 70 mg/dL	Combination of CHD death, MI, stroke, unstable angina.	Dec 2017
Evolocumab					
FOURIER AMGEN NCT01764633	RCT N = 22,500 5 year FU	Evolocumab Placebo	• History of CVD event at high risk for recurrence • Age 40-85 years • LDL-C ≥ 70 mg/dL or non-HDL ≥ 100 mg/dL	Combination of CHD death, MI, stroke, unstable angina, coronary re-vascularization	Feb 2018

A6. Comparative Clinical Effectiveness Appendix

A6 Table 1: Overview of studies

Reference	Study	Phase	N	FU, weeks	Treatment	Control	Population	Statin Therapy	Age, years	Sex, %F	Prior CVD, %	DM, %
Alirocumab												
Heterozygous (HeFH) or mixed familial hyperlipidemia (FH)												
Stein 2012	-	2	77	12	Alirocumab 150 mg q 2 weeks	Placebo	HeFH	Intensive	53	39	42	4
-	ODYSSEY FH I	3	486	78	Alirocumab 75-150 mg q 2 weeks	Placebo	HeFH	Intensive	52	55	46	12
-	ODYSSEY FH II	3	249	78	Alirocumab 75-150 mg q 2 weeks	Placebo	HeFH	Intensive	53	47	35	4
-	ODYSSEY HIGH FH	3	107	52-78	Alirocumab 150 mg q 2 weeks	Placebo	HeFH	Intensive	52	47	50	14
Robinson 2015	ODYSSEY Long Term	3	2341	78	Alirocumab 150 mg q 2 weeks	Placebo	HeFH / HC	Intensive	61	38	69	35
McKenney 2012	-	2	183	12	Alirocumab 150 mg q 2 weeks	Placebo	FH	Intensive	57	53	6	12
Roth 2012	-	2	92	8	Alirocumab 150 mg q 2 weeks	Placebo	FH	Intensive	57	60	3	15
Hypercholesterolemia (HC)												
-	ODYSSEY ALTERNATIVE	3	251	24	Alirocumab 75-150 mg q 2 weeks	Ezetimibe 10 mg	HC	None	63	45	47	24
Kereiakas 2015	ODYSSEY COMBO I	3	316	52	Alirocumab 75-150 mg q 2 weeks	Placebo	HC	Intensive	63	34	78	43
Cannon 2015	ODYSSEY COMBO II	3	720	104	Alirocumab 75-150 mg q 2 weeks	Ezetimibe 10 mg	HC	Intensive	61	74	81	31
Roth 2014	ODYSSEY MONO	3	103	24	Alirocumab 75 mg q 2 weeks	Ezetimibe 10 mg	HC	None	60	47	NR	4
Bays 2015	ODYSSEY OPTIONS I	3	205	24	Alirocumab 75-150 mg q 2 weeks	Ezetimibe 10 mg	HC	Mixed	66	36	NR	NR
-	ODYSSEY OPTIONS II	3	204	24	Alirocumab 75-150 mg q 2 weeks	Ezetimibe 10 mg	HC	Mixed	60	43	NR	NR
			5334									
Evolocumab												
Homozygous familial hyperlipidemia (HoFH)												
Raal 2015	TESLA Part B	3	49	12	Evolocumab 420 mg q 4 weeks	Placebo	HoFH	Intensive	31	49	43	NR
Heterozygous (HeFH) or mixed familial hyperlipidemia (FH)												
Raal 2012	RUTHERFORD	2	167	12	Evolocumab 420 mg q 4 weeks	Placebo	HeFH	Intensive	50	47	21	NR
Raal 2015	RUTHERFORD 2	3	329	12	Evolocumab 140 mg q 2 weeks and Evolocumab 420 mg q 4 weeks	Placebo	HeFH	Intensive	51	42	62	31
Koren 2014	MENDEL 2	3	614	12	Evolocumab 140 mg q 2 weeks and Evolocumab 420 mg q 4 weeks	Placebo and ezetimibe 10 mg	FH	None	54	69	0	0.1
Hypercholesterolemia (HC)												
Sullivan 2012	GAUSS	2	157	12	Evolocumab 420 mg q 4 weeks	Ezetimibe 10 mg	HC, SI	Nonintensive	62	64	13	NR
Stroes 2014	GAUSS 2	3	307	12	Evolocumab 140 mg q 2 weeks and Evolocumab 420 mg q 4 weeks	Ezetimibe 10 mg	HC, SI	Nonintensive	62	46	NR	20
Giuliano 2012	LAPLACE TIMI 57	2	629	12	Evolocumab 140 mg q 2 weeks and Evolocumab 420 mg q 4 weeks	Placebo	HC	Intensive	62	51	30	16
Koren 2012	MENDEL	2	406	12	Evolocumab 140 mg q 2 weeks and Evolocumab 420 mg q 4 weeks	Placebo and ezetimibe 10 mg	HC	None	51	66	0	0.2
Hirayama 2014	YUKAWA	2	307	12	Evolocumab 140 mg q 2 weeks and Evolocumab 420 mg q 4 weeks	Placebo	HC	Intensive	62	37	25	38
Robinson 2014	LAPLACE 2	3	1896	12	Evolocumab 140 mg q 2 weeks and Evolocumab 420 mg q 4 weeks	Placebo and ezetimibe 10 mg	HC	Mixed	60	46	23	16
Blom 2014	DESCARTES	3	901	52	Evolocumab 420 mg q 4 weeks	Placebo	HC	Mixed	57	52	15	12
Long-term FU of ph ase 2 and 3 studies - all patients already described above												
Sabatine 2014	OSLER	–	4465	52	Evolocumab 140 mg q 2 weeks and Evolocumab 420 mg q 4 weeks	Standard therapy	Mixed	Mixed	58	51	20	13

A6 Table 2: Quality of the studies

Reference	Study	Adequate randomization	Allocation concealment	Patient blinding	Staff blinding	Outcome adjudication blinding	Completeness of follow-up	Intention to treat analysis	Incomplete data addressed	Selective outcome reporting	Industry funding	Free from other bias
Alirocumab												
Heterozygous (HeFH) or mixed familial hyperlipidemia (FH)												
Stein 2012	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
-	ODYSSEY FH I	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
-	ODYSSEY FH II	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
-	ODYSSEY HIGH FH	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Robinson 2015	ODYSSEY Long Term	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
McKenney 2012	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Roth 2012	-	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Hypercholesterolemia (HC)												
-	ODYSSEY ALTERNATIVE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Kereiakas 2015	ODYSSEY COMBO I	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Cannon 2015	ODYSSEY COMBO II	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Roth 2014	ODYSSEY MONO	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Bays 2015	ODYSSEY OPTIONS I	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
-	ODYSSEY OPTIONS II	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Evolocumab												
Homozygous familial hyperlipidemia (HoFH)												
Raal 2015	TESLA Part B	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Heterozygous (HeFH) or mixed familial hyperlipidemia (FH)												
Raal 2012	RUTHERFORD	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Raal 2015	RUTHERFORD 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Koren 2014	MENDEL 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Hypercholesterolemia (HC)												
Sullivan 2012	GAUSS	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Stroes 2014	GAUSS 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Giuliano 2012	LAPLACE TIMI 57	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Koren 2012	MENDEL	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Hirayama 2014	YUKAWA	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Robinson 2014	LAPLACE 2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Blom 2014	DESCARTES			Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	Yes
Long-term FU of phase 2 and 3 studies all patients already described above												
Sabatine 2014	OSLER 1 and 2	Yes	Yes	No	No	No	Yes	Yes	Yes	No	Yes	Yes

Table 3: LDL Outcomes

Reference	Study	Intervention	Baseline LDL	Final LDL	LDL < 70 mg/dL, %	% reduction in LDL vs placebo Q2W	% reduction in LDL vs placebo Q4W	% reduction in LDL vs ezetimibe Q2W	% reduction in LDL vs ezetimibe Q4W
Alirocumab									
Heterozygous (HeFH) or mixed familial hyperlipidemia (FH)									
Stein 2012	-	Alirocumab	147	50	81	57.2	23.5		
		Placebo	151	136	0				
-	ODYSSEY FH I	Alirocumab	140	70	77	57.9			
		Placebo	139	145	7				
-	ODYSSEY FH II	Alirocumab	140	70	77	51.4			
		Placebo	139	145	7				
-	ODYSSEY HIGH FH	Alirocumab	196	113	32	39.1			
		Placebo	201	188	3				
Robinson 2015	ODYSSEY Long Term	Alirocumab	123	48	79	61.9			
		Placebo	122	119	8				
McKenney 2012	-	Alirocumab	124	34	100	53.5	40.4		
		Placebo	130	127	3				
Roth 2012	-	Alirocumab	127	54	90	48.9			
		Placebo	121	104	17				
Hypercholesterolemia (HC)									
-	ODYSSEY ALTERNATIVE	Alirocumab	191	92	42			30.4	
		Ezetimibe	194	157	4				
Kereiakas 2015	ODYSSEY COMBO I	Alirocumab	100	52	5	45.9			
		Placebo	106	102	9				
Cannon 2015	ODYSSEY COMBO II	Alirocumab	109	52	77			29.8	
		Ezetimibe	105	82	46				
Roth 2014	ODYSSEY MONO	Alirocumab	141	87	NR			31.6	
		Ezetimibe	138	121	NR				
Bays 2015	ODYSSEY OPTIONS I	Alirocumab	110	52	78			27.2	
		Ezetimibe	100	78	52				
-	ODYSSEY OPTIONS II	Alirocumab	113	43	68			30.5	
		Ezetimibe	110	69	49				
Evolocumab									
Homozygous familial hyperlipidemia (HoFH)									
Raal 2015	TESLA Part B	Evolocumab	356	282	NR		30.9		
		Placebo	336	356	NR				
Heterozygous (HeFH) or mixed familial hyperlipidemia (FH)									
Raal 2012	RUTHERFORD	Evolocumab	151	70	65		56.4		
		Placebo	162	162	0				
Raal 2015	RUTHERFORD 2	Evolocumab	158	68	66	59.2	61.3		
		Placebo	151	153	2				
Koren 2014	MENDEL 2	Evolocumab	143	62	69	49.6	52.8	35.8	34
		Ezetimibe	144	117	1.4				
		Placebo	142	141	0.7				
Hypercholesterolemia (HC)									
Sullivan 2012	GAUSS	Evolocumab	204	99	NR		47.3		35.9
		Ezetimibe	183	154	0				
Stroes 2014	GAUSS 2	Evolocumab	192	90	44			38.1	37.6
		Ezetimibe	195	162	1				
Giuliano 2012	LAPLACE TIMI 57	Evolocumab	120	63	83	66.1	50.3		
		Placebo	124	122	1				
Koren 2012	MENDEL	Evolocumab	139	72	NR	47.2	52.5	36.7	34.1
		Ezetimibe	143	122	NR				
		Placebo	145	147	NR				
Hirayama 2014	YUKAWA	Evolocumab	139	41	86	68.6	63.9		
		Placebo	143	139	0				
Robinson 2014	LAPLACE 2	Evolocumab	110	44	89	70.9	61.9	43.4	40
		Ezetimibe	109	89	37				
		Evolocumab	108	112	12				
Blom 2014	DESCARTES	Evolocumab	104	51	82				
		Placebo	104	108	6.4				
Long-term FU of phase 2 and 3 studies of all patients already described above									
Sabatine 2014	OSLER	Evolocumab	2976	120	73.6		58.4		0.9
		Placebo	1489	121	3.8				1.3

A6 Table 4: Clinical outcomes – Major adverse cardiac outcomes (MACE)

Reference	Study	Intervention	N	Death	CVD death	MI	Stroke	Angina	MACE
Alirocumab									
Heterozygous (HeFH) or mixed familial hyperlipidemia (FH)									
Stein 2012	-	Alirocumab	16	0	0	0	0	0	0
		Placebo	15	0	0	0	0	0	0
-	ODYSSEY FH II and III	Alirocumab	490	4	2	2	1	1	5
		Placebo	245	0	0	0	0	0	0
-	ODYSSEY FH II	Alirocumab	167	0	0	0	0	0	0
		Placebo	82	0	0	1	0	0	1
-	ODYSSEY HIGH FH	Alirocumab	72	0	0	4	0	0	4
		Placebo	35	0	0	0	0	0	0
Robinson 2015	ODYSSEY Long Term	Alirocumab	1553	11	6	13	10	0	27
		Placebo	788	8	6	17	3	1	25
McKenney 2012	-	Alirocumab	31	0	0	0	0	0	0
		Placebo	31	0	0	0	0	0	0
Roth 2012	-	Alirocumab	30	0	0	0	0	0	0
		Placebo	31	0	0	0	0	0	0
Hypercholesterolemia (HC)									
-	ODYSSEY ALTERNATIVE	Alirocumab	126	0	0	1	0	0	1
		Ezetimibe	125	0	0	0	0	0	0
Kereiakas 2015	ODYSSEY COMBO I	Alirocumab	209	3	2	2	2	0	5
		Placebo	107	2	1	1	0	0	2
Cannon 2015	ODYSSEY COMBO II	Alirocumab	479	2	2	12	1	1	16
		Ezetimibe	241	4	2	3	1	0	5
Roth 2014	ODYSSEY MONO	Alirocumab	52	0	0	0	0	0	0
		Ezetimibe	51	0	0	0	0	0	0
Bays 2015	ODYSSEY OPTIONS I	Alirocumab	104	0	0	0	0	0	0
		Ezetimibe	102	0	0	0	0	0	0
-	ODYSSEY OPTIONS II	Alirocumab	103	0	0	0	0	0	0
		Ezetimibe	101	1	0	1	0	0	1
Evolocumab									
Homozygous familial hyperlipidemia (HoFH)									
Raal 2015	TESLA Part B	Evolocumab	33	0	0	0	0	0	0
		Placebo	16	0	0	0	0	0	0
Heterozygous (HeFH) or mixed familial hyperlipidemia (FH)									
Raal 2012	RUTHERFORD	Evolocumab	56	0	0	0		0	0
		Placebo	56	0	0	0		0	0
Raal 2015	RUTHERFORD 2	Evolocumab	221	0	0	0		0	0
		Placebo	110	0	0	0		0	0
Koren 2014	MENDEL 2	Evolocumab	306	0	0	0		0	0
		Ezetimibe	308	0	0	0		0	0
		Placebo							
Hypercholesterolemia (HC)									
Sullivan 2012	GAUSS	Evolocumab	32	0	0	0		0	0
		Ezetimibe	33	0	0	0		0	0
Stroes 2014	GAUSS 2	Evolocumab	205	0	0	0		0	0
		Ezetimibe	102	0	0	0		0	0
Giuliano 2012	LAPLACE TIMI 57	Evolocumab	158	1	1	0		0	1
		Placebo	157	0	0	0		0	0
Koren 2012	MENDEL	Evolocumab	90	0	0	0		0	0
		Ezetimibe	135	0	0	0		0	0
		Placebo							
Hirayama 2014	YUKAWA	Evolocumab	105	0	0	0		0	0
		Placebo	102	0	0	0		0	0
Robinson 2014	LAPLACE 2	Evolocumab	1117	0	0	0		0	0
		Ezetimibe	779	1	1	0		0	1
Blom 2014	DESCARTES	Evolocumab	599	2	2	1		1	3
		Placebo	302	0	0	0		0	0
Long-term FU of phase 2 and 3 studies – all patients already described above									
Sabatine 2014	OSLER	Evolocumab	2976	4	4	9	3	3	28
		Placebo	1489	6	3	5	2	3	30

Table 5: Adverse outcomes

Reference	Study	Intervention	N	SAE	Discontinue due to AE	CK elevation	ALT elevation	Stroke	Myalgia	Neuro-cognitive	Hyper-sensitivity	Injection reaction
Alirocumab												
Heterozygous (HeFH) or mixed familial hyperlipidemia (FH)												
Stein 2012	-	Alirocumab	16	0	0	0	0	0				7
		Placebo	15	1	0	0	0	0				2
-	ODYSSEY FH I and II	Alirocumab	490	49		17		1				
		Placebo	245	22		15		0				
-	ODYSSEY FH II	Alirocumab	167									
		Placebo	82									
-	ODYSSEY HIGH FH	Alirocumab	72	8	3	2	3			1		6
		Placebo	35	4	1	0	1			1		1
Robinson 2015	ODYSSEY Long Term	Alirocumab	1553	290	111	56	28	9	84	18		91
		Placebo	788	154	46	38	16	2	23	4		33
McKenney 2012	-	Alirocumab	31	0	1	0	0		1			3
		Placebo	31	1	0	1	0		1			0
Roth 2012	-	Alirocumab	30	1	1	0	0					1
		Placebo	31	0	4	1	0					0
Hypercholesterolemia (HC)												
-	ODYSSEY ALTERNATIVE	Alirocumab	126	12	23	3	0		31	3		6
		Ezetimibe	125	10	31	2	0		29	2		6
Kereiakas 2015	ODYSSEY COMBO I	Alirocumab	209	26	13	4		2	7	0	5	11
		Placebo	107	14	8	5		0	4	1	2	3
Cannon 2015	ODYSSEY COMBO II	Alirocumab	479	90	36	13	8	1	21	4		12
		Ezetimibe	241	43	13	6	1	1	12	3		2
Roth 2014	ODYSSEY MONO	Alirocumab	52	1	5	0	0		2			1
		Ezetimibe	51	1	4	1	0		2			2
Bays 2015	ODYSSEY OPTIONS I	Alirocumab	104	4	7	3	0				2	3
		Ezetimibe	102	7	4	1	0				5	3
-	ODYSSEY OPTIONS II	Alirocumab	103	6	5	0	1					4
		Ezetimibe	101	8	8	3	0					0
Evolocumab												
Homozygous familial hyperlipidemia (HoFH)												
Raal 2015	TESLA Part B	Evolocumab	33	0	0	1	2		1	0		0
		Placebo	16	0	0	1	1		0	0		1
Heterozygous (HeFH) or mixed familial hyperlipidemia (FH)												
Raal 2012	RUTHERFORD	Evolocumab	56	2	1	2	1					2
		Placebo	56	0	1	0	0					1
Raal 2015	RUTHERFORD 2	Evolocumab	221	7	0	0	0					
		Placebo	110	5	0	2	0					
Koren 2014	MENDEL 2	Evolocumab	306	4	7	2	3		3	0		16
		Ezetimibe	308	2	11	2	6		6	0		15
		Placebo										
Hypercholesterolemia (HC)												
Sullivan 2012	GAUSS	Evolocumab	23	0	1	0	0		6			
		Ezetimibe	33	0	2	1	0		1			
Stroes 2014	GAUSS 2	Evolocumab	205	6	17	0	0		16	0		6
		Ezetimibe	102	4	13	2	0		18	0		8
Giuliano 2012	LAPLACE TIMI 57	Evolocumab	158	6	2	2	0	0	1		0	1
		Placebo	157	4	0	0	1	0	2		0	3
Koren 2012	MENDEL	Evolocumab	90	1	0	0	0	1	2		0	0
		Ezetimibe	135	0	2	1	0	0	1		0	0
		Placebo										
Hirayama 2014	YUKAWA	Evolocumab	105	3	3	0	0					3
		Placebo	102	0	0	1	1					1
Robinson 2014	LAPLACE 2	Evolocumab	1117	23	21	1	4			1		15
		Ezetimibe	779	15	16	2	9			3		10
Blom 2014	DESCARTES	Evolocumab	599	33	13	7	5		24			34
		Placebo	302	13	3	1	3		9			15
Long-term FU of phase 2 and 3 studies all patients already described above												
Sabatine 2014	OSLER	Evolocumab	2976	222								
		Placebo	1489	111								

A7. Comparative Value Appendix

Input Parameters and Model Calibration

The present version of the CVD Policy Model includes data from prior versions as well as many updates and upgrades.[63-65] The 2010 U.S. Census provides the baseline population [129] and number of 35 year-olds projected to enter the model population from 2010-2060.[130,131] CHD and stroke deaths in 2010 were extracted from U.S. Vital Statistics.[132] Deaths were categorized according to the International Classification of Diseases (ICD) 10 codes:[133] I20-I25 and two-thirds of I49, I50, and I51 were used to estimate coronary heart disease deaths,[134] I60-I69 were used to estimate stroke deaths, and all other deaths were considered non-CVD deaths.

The incidence of coronary heart disease and stroke were based on competing risk Cox proportional hazards analysis of the Framingham Heart Study [135] and the Framingham Offspring Study [136] cohorts from 1988-2007, with further adjustment for risk factor differences between the Framingham cohorts and the contemporary U.S. population represented by the U.S. National Health and Nutrition Examination Survey (NHANES). Incident coronary heart disease events were allocated to angina pectoris, hospitalized myocardial infarction, or cardiac arrest. Prevalence, joint distributions and means of U.S. risk factor values were estimated from pooled, survey design-weighted U.S. National Health and Nutrition Examination Survey (NHANES), 2007-10.[137] Annual transition rates between risk factor levels were calculated to preserve age-range trends. Risk function betas were estimated separately for the risk of incident coronary heart disease events, incident strokes, and non-CVD deaths, using examinations 1-8 of the Framingham Offspring cohort.[136] The Framingham coefficients have been found to be useful for predicting CVD risk relationships across many populations.[138-141] Risk factors were assumed to affect the incidence of myocardial infarction, arrest, and angina in proportion to the overall incidence of coronary heart disease, except tobacco smokers were assumed to have a higher relative risk for infarction and arrest ([142]; personal communication, Sean Coady, National Heart, Lung, and Blood Institute, February, 2006) and a proportionately lower coefficient for angina. Environmental tobacco exposure was assumed to carry a relative risk of 1.26 for myocardial infarction and cardiac arrest compared with non-exposed non-smokers [143] but not to influence angina.

Baseline CVD Policy Model inputs for the year 2010 were within 1% of all targets obtained from U.S. national data sources (**Appendix 7 Table 1**).

Appendix 7 Table 1. Comparisons of selected CVD Policy Model simulation outputs for 2010 (model base year) with national targets for 2010.

Age and sex category	Total myocardial infarctions Target sources: NHDS		Total strokes Target source: NHDS		CHD deaths Target source: national vital statistics		Stroke deaths Target source: national vital statistics		All-cause deaths Target source: national vital statistics	
	Target	Model	Target	Model	Target	Model	Target	Model	Target	Model
Males										
35-44	13,979	13,839	16,535	16,553	4,783	4,862	1,027	1,031	43,345	43,335
45-54	56,129	55,811	43,493	43,710	19,489	19,594	3,298	3,301	111,981	111,933
55-64	77,992	77,395	67,863	68,497	38,032	38,065	6,159	6,133	190,845	190,629
65-74	75,804	75,689	79,450	79,239	45,700	46,096	9,350	9,265	231,327	231,231
75-84	62,982	63,063	76,205	76,436	64,610	65,097	16,215	16,240	312,778	312,873
85-94	37,568	37,483	38,943	39,247	64,071	63,958	15,318	14,742	264,705	263,235
Females										
35-44	6,259	6,144	6,390	6,387	1,710	1,822	873	875	26,538	26,619
45-54	17,071	17,035	36,952	37,083	6,858	6,969	2,609	2,764	71,145	71,352
55-64	40,246	40,403	42,966	43,222	15,122	15,265	4,622	4,605	122,502	122,546
65-74	43,843	43,898	69,473	69,659	24,964	25,137	8,504	8,308	178,530	178,342
75-84	60,097	60,043	93,040	93,434	53,247	53,600	21,492	21,541	313,803	313,894
85-94	57,661	57,403	77,481	77,883	99,680	98,988	35,416	36,233	448,864	447,244
Deviation from target	-0.26%		0.39%		0.27%		0.12%		-0.14%	

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; NHDS, National Hospital Discharge Survey.

The number of hospitalized myocardial infarctions was obtained from discharges coded as ICD-9 code 410 in the 2010 National Hospital Discharge Survey (NHDS) [144] adjusted for likely miscoding,[145] such as patients who were discharged alive after two days or fewer without a percutaneous coronary intervention, and transfer patients. Case-fatality rates and rates of myocardial infarction in subgroups were estimated from national data[144] and a variety of complementary sources.[146-148] Pre-hospital arrest deaths were estimated from the U.S. Vital Statistics[132] and out-of-hospital cardiac arrests surviving to hospital discharge were estimated from national data. [144] Survival after a coronary heart disease event was estimated using California data on the ratio of in-hospital survival to 30 day survival [149] and data from Medicare and Seattle, Washington.[150,151] Rates of coronary revascularizations were estimated from the National Hospital Discharge Survey,[144] with mortalities estimated from aggregated historical data.

Stroke incidence was assumed to independent of the risk of new onset coronary heart disease in the same year. The number of hospitalized strokes was also obtained from the 2010 NHDS. Positive predictive values of specific ICD-9 stroke hospital diagnosis codes (inclusive of ICD 9 codes

430-438) were derived by pooling several studies of stroke incidence that compared hospital diagnoses with a gold standard (e.g., stroke ascertained by Atherosclerosis in Communities Study, the Rochester Epidemiology Study or similar criteria).[152] The positive predictive values were applied to age- and sex-specific NHDS cases in order to estimate total stroke event rates (inclusive of first-ever and recurrent stroke events). Applying 30-day case fatality rates based on the Atherosclerosis in Communities Study [153,154] yielded annual mortality rate estimates within the range of stroke rates reported by the U.S. Centers for Disease Control (CDC Wonder) for 2010. Incidence calibration assumed that 77% of all strokes are incident (first ever),[155] but it was assumed that the proportion first ever/total diminished with age (i.e., >90% of all strokes are first strokes in 35-44 year olds and 50% are first strokes in 85-94 year olds). The resulting incidence of hospitalized stroke approximated age and sex specific stroke incidence rates observed in U.S. stroke cohort and surveillance studies. The annual probabilities of stroke after myocardial infarction [156] and the probability of coronary heart disease in stroke patients was based on natural history studies.[124,157-161]

The background prevalence of CVD by age, sex, and CVD disease state (stroke, coronary heart disease, or both stroke and coronary heart disease) in 2010 was estimated from the National Health Interview Survey data from 2009-2011,[162] assuming that the imperfect positive predictive value of survey data is offset by its imperfect sensitivity.[163-165] Age-specific prevalences for individual CVD disease states were fitted with polynomial or spline functions of age to obtain smooth, monotonically increasing prevalences. The background prevalence of prior coronary revascularization was estimated from revascularizations before 2010 and estimated survival after revascularization, while model projections were used to infer the distribution of revascularization by CVD state.

The LDL-C lowering effect assumptions were validated in a simulation of West of Scotland Coronary Prevention Study [71,110]. Simulations of the US population aged 45-64, imposing the pre- and post-intervention LDL-C and HDL cholesterol levels recorded in the West of Scotland Study 9 [110] produced estimates of key clinical outcomes, i.e., cumulative CHD mortality or first MI, and ratio of events in participants treated with statins or placebo, within one percentage point of the numbers observed in the trial (**Appendix 7 Table 2**).

Appendix 7 Table 2. Validation of the CVD Policy Model Against Data from the West of Scotland Coronary Prevention Study. Comparing the cumulative percentage of persons with a first CHD event (MI or CHD death) in WOSCOPS with estimates from the CVD Policy Model.

	WOSCOPS*			CVD Policy Model		
Year	Placebo	Intervention	Ratio	Placebo	Intervention	Ratio
1	1.7%	1.2%	0.73	1.6%	1.1%	0.67
2	3.2%	2.2%	0.68	3.3%	2.2%	0.67
3	4.9%	3.3%	0.68	5.1%	3.4%	0.67
4	6.5%	4.3%	0.67	7.0%	4.6%	0.66
5	9.2%	6.4%	0.70	8.8%	5.9%	0.67

Abbreviations: CHD, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; WOSCOPS, West of Scotland Study.[110]

* With Kaplan-Meier survival adjustment for censored data.

Appendix 7 Table 3. Baseline characteristics of treatment populations

Characteristic	Subgroup		
	Familial Hypercholesterolemia	History of CVD, statin intolerant	History of CVD, on statin, LDL>=70
n (model base case)	605,000	1,460,000	7,271,000
Mean age (years)	50.7	55.9	61.3
Female (%)	49.4%	51.0%	37.5%
Mean LDL-C (mg/dL)	220.3	124.3	106.5
Mean HDL-C (mg/dL)	53.8	53.5	50.4
Mean BMI (kg/m^2)	29.2	30.9	30.6
Mean SBP (mmHg)	126.3	126.8	127.2
Hypertension (%)	26.6%	25.9%	24.6%
Diabetes mellitus (%)	12.6%	25.3%	32.7%
MACE event rates (per 100 patient-years, estimated over the first five years of the model)	1.2	3.0	3.1

Abbreviations: BMI, Body Mass Index; HDL-C, high-density lipoprotein cholesterol; LDL-C, Low-density lipoprotein cholesterol; MACE, Major Adverse Clinical Events (nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death; SBP, systolic blood pressure.

Appendix 7 Table 4. Select Input Parameters

Parameter	Base case	Range for Sensitivity Analysis	Source
Effect size			
LDL-C Reduction (%)			
PCSK-9 inhibitor without background statin therapy	53.65	47.78 – 59.51	Clinical Effectiveness Review[1]
Addition of PCSK-9 inhibitor to statin (mixed low- and high-intensity statin therapy)	65.24	60.02 – 70.46	Clinical Effectiveness Review
Addition of PCSK-9 inhibitor to statin (high-intensity statin therapy)	57.93	54.91 – 60.95	Clinical Effectiveness Review
Ezetimibe without background statin therapy	18.56	-	Clinical Effectiveness Review
Addition of ezetimibe to statin (mixed low- and high-intensity statin therapy)	23.60	-	Clinical Effectiveness Review
Addition of ezetimibe to statin (high-intensity statin therapy)	23.60	-	Clinical Effectiveness Review
Risk Reduction in nonfatal myocardial infarction or cardiovascular mortality (per 1 mmol/L reduction in LDL-C)			
Statin	0.76	-	[112]
Ezetimibe	0.76	-	[112]
PCSK-9 inhibitor	0.76	-	
Risk Reduction in nonfatal stroke (per 1 mmol/L reduction in LDL-C)			
Statin	0.85	-	[112]
Ezetimibe	0.85	-	[112]
PCSK-9 inhibitor	0.85	-	
Costs			
Annual Drug Costs			
High-intensity statin (atorvastatin)	$810	-	Wholesale acquisition cost averaged across all formulations
Ezetimibe	$2,878	-	Wholesale acquisition cost
PCSK-9 inhibitor	$14,350	$7,175 – 28,700	Wholesale acquisition cost averaged across alirocumab and evolocumab
Costs of CHD care			
Acute fatal MI hospitalization*	$53,565	-	Office of Statewide Health Planning and Development. California Public Patient Discharge Data (OSHPD), 2008.

Acute non-fatal MI hospitalization*	$38,766	-	OSHPD, 2008
Acute non-fatal MI +CABG*	$99,092	-	OSHPD, 2008
Acute MI post-hospitalization year 1 costs*	$12,338	-	OSHPD, 2008
CHD costs, subsequent years	$2,520	-	Medical Expenditure Panel Surveys
Costs of CHF care			
CHF hospitalization	$19,512	-	OSHPD, 2008
Costs of stroke			
Hospitalized fatal stroke	$26,699	-	OSHPD, 2008
Hospitalized non-fatal stroke	$19,732	-	OSHPD, 2008
Remaining year 1 post-stroke cost	$34,712	-	OSHPD, 2008
Stroke costs, subsequent years	$5,305	-	Medical Expenditure Panel Surveys
Utilities			
Quality Adjusted Life Years			
No history of cardiovascular disease	1	-	Assumed
History of angina	0.9064	-	Global Burden of Disease, 2010
History of revascularization	0.9800	-	Global Burden of Disease, 2010
History of myocardial infarction (MI)	0.9648	-	Global Burden of Disease, 2010
History of MI and revascularization	0.9818	-	Global Burden of Disease, 2010
History of stroke	0.8835	-	Global Burden of Disease, 2010
History of MI and stroke	0.8524	-	Global Burden of Disease, 2010
Short term disutilities			
Angina	0.0040	-	Global Burden of Disease, 2010
Revascularization	0.0100	-	Global Burden of Disease, 2010
Acute MI	0.0078	-	Global Burden of Disease, 2010
Acute MI and revascularization	0.0200	-	Global Burden of Disease, 2010
Acute stroke	0.0113	-	Global Burden of Disease, 2010

Abbreviations: CABG, coronary artery bypass grafting; CHD, coronary heart disease; CHF, congestive heart failure; CV, cardiovascular; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

Additional Results:

Appendix 7 Table 5. Additional Clinical and Economic Outcomes Among Patients with FH.*

	Number at risk (baseline cohort)	Number of events averted			Total Cost† (million $)	Non-CV-Related Costs† (million $)	Added Life-years
		CV death	nonfatal MI	nonfatal stroke			
Statin	*comparator*						
Statin + Ezetimibe§,‖	605,000	47,700	41,500	26,800	$33,727	$4,296	528,600
Statin + PCSK9 inhibitor¶,‖	605,000	132,200	111,100	80,900	$193,212	$11,738	1,438,200

Abbreviations: CV, cardiovascular; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In the base case, all patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (10% of the population) received incremental therapy with ezetimibe or a PCSK9 inhibitor. The analytic horizon was lifetime (defined as until the patients reach 95 years of age). Primary results of this analysis were presented in Table 14.

† All costs are reported in 2015 U.S. dollars. Future costs are discounted 3% a year.

§ Patients who are statin intolerant only receive ezetimibe.

¶ Patients who are statin intolerant only receive a PCSK9 inhibitor.

|| Both statin+ezetimibe and statin+PCSK9 inhibitor arms are compared with the statin (control) arm.

Appendix 7 Table 6. Scenario Analysis: Assuming "Full Treatment" of FH patients with statins as tolerated prior to incremental treatment with ezetimibe or a PCSK9 inhibitor.*

	Number at risk (baseline cohort)	Number of events averted			Added CV Cost† (million $)	Added Non-CV-Related Costs† (million $)	Added Life-years
		CV death	nonfatal MI	nonfatal stroke			
Statin	*comparator*						
Statin + Ezetimibe§,‖	748,000	57,600	49,000	33,800	$39,508	$5,338	652,600
Statin + PCSK9 inhibitor¶,‖	748,000	136,200	113,400	85,800	$227,278	$12,018	1,469,500

Abbreviations: CV, cardiovascular; FH, familial hypercholesterolemia; ICER, incremental cost-effectiveness ratio; MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In the base case, all patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (10% of the population) received incremental therapy with ezetimibe or a PCSK9 inhibitor (748,000 patients in 2015). The analytic horizon was lifetime (defined as until the patients reach 95 years of age). Primary results of this analysis were presented in Table 15. Future costs are discounted 3% a year.

§ Patients who are statin intolerant only receive ezetimibe.

¶ Patients who are statin intolerant only receive a PCSK9 inhibitor.

|| Both statin+ezetimibe and statin+PCSK9 inhibitor arms are compared with the statin-only arm.

Appendix 7 Table 7. Additional Clinical and Economic Outcomes Among Statin-Intolerant Patients with a Prior History of CVD.*

	Number at risk (baseline cohort)	Number of events averted			Added CV Cost† (million $)	Added Non-CV-Related Costs† (million $)	Added Life-years
		CV death	nonfatal MI	nonfatal stroke			
Statin	*comparator*						
Statin + Ezetimibe§,‖	1,460,000	220,500	139,800	85,800	$122,599	$18,020	2,146,300
Statin + PCSK9 inhibitor¶,‖	1,460,000	619,900	389,400	245,100	$648,823	$50,428	5,999,100

Abbreviations: CV, cardiovascular; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT_5, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In the base case, we assumed that 10% of the population was statin-intolerant. Patients who had a prior history of cardiovascular disease and LDL-C >70mg/dL received incremental treatment with ezetimibe or a PCSK9 inhibitor. The analytic horizon was lifetime (defined as until the patients reach 95 years of age). Primary results of this analysis were presented in Table 16.

† All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.

§ Both ezetimibe and PSCK9 inhibitor arms are compared with the control (no additional lipid-lowering therapy) arm.

Appendix 7 Table 8. Additional Clinical and Economic Outcomes Among Patients with a Prior History of CVD and LDL-C ≥ 70mg/dL on Statin Therapy.*

	Number at risk (baseline cohort)	Number of events averted			Added CV Cost† (million $)	Added Non-CV-Related Costs† (million $)	Added Life-years
		CV death	nonfatal MI	nonfatal stroke			
Statin	*comparator*						
Statin + Ezetimibe§,‖	7,271,000	1,097,800	704,400	451,600	$587,635	$89,913	10,948,200
Statin + PCSK9 inhibitor¶,‖	7,271,000	2,733,300	1,698,900	1,189,600	$3,195,990	$219,813	26,723,800

Abbreviations: CV, cardiovascular; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT_5, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In the base case, patients who had a prior history of cardiovascular disease and LDL-C >70mg/dL on statin therapy received incremental treatment with ezetimibe or a PCSK9 inhibitor. The analytic horizon was lifetime (defined as until the patients reach 95 years of age). Primary results of this analysis were presented in Table 17.

† All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.

§ Both statin+ezetimibe and statin+PSCK9 inhibitor arms are compared with the statin-only arm.

Appendix 7 Table 9. Additional Clinical and Economic Outcomes Among Patients Initiating Therapy with Ezetimibe or PCSK9 After Incident (First-Ever) MI.*

	Number at risk (baseline cohort)	Number of events averted			Added Cost† (million $)	Added Non-CV-Related Costs† (million $)	Added Life-years
		CV death	nonfatal MI	nonfatal stroke			
Statin§	*comparator*						
Statin + Ezetimibe§,||	169,000	7,800	6,800	2,200	$4,769	$1,036	120,200
Statin + PCSK9 inhibitor¶,||	169,000	20,400	16,800	6,000	$27,059	$2,597	299,600

Abbreviations: CV, cardiovascular; LDL, low-density lipoprotein; MACE, major adverse cardiovascular event (nonfatal MI, nonfatal stroke, and cardiovascular death); NNT_5, number-needed-to-treat; PCSK9, proprotein convertase subtilisin/kexin type 9; QALY, quality-adjusted life year.

* In this scenario analysis, all patients who had an incident (first-ever) MI in 2015, were receiving statin therapy if tolerated received incremental treatment with ezetimibe or a PCSK9 inhibitor for life. In 2015, 169,000 patients met the inclusion criteria for this analysis. Ten percent of the population was assumed to be statin-intolerant. The analytic horizon was lifetime (defined as until the patients reach 95 years of age). Primary results of this analysis were presented in Table 18.

† All costs are reported in 2015 U.S. dollars. Future costs and QALYs are discounted 3% a year.

§ Patients deemed to be statin-intolerant (base-case prevalence = 10%) received only ezetimibe.

¶ Patients deemed to be statin-intolerant (base-case prevalence = 10%) received only a PCSK9 inhibitor.

|| Both statin+ezetimibe and statin+PSCK9 inhibitor arms are compared with the statin-only arm.

Appendix 7 Table 10. Clinical Events Among Patients with FH Initiating PCSK9 Inhibitors.

	Analytic Horizon = 1 Year Events averted*				Analytic Horizon = 5 Year Events averted*			
	Total MACE	CVD deaths	Nonfatal MIs	Nonfatal Strokes	Total MACE	CVD deaths	Nonfatal MIs	Nonfatal Strokes
Compared with statins (as treated)†	4,000	1,100	1,700	1,200	22,800	6,400	9,500	6,900
Compared with statins (full treatment)§	4,100	1,100	1,700	1,300	23,400	6,500	9,700	7,200

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolemia; MACE, major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke); MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9.

* To reflect the precision of the model, all clinical events are rounded to the 100s.

† In the base case, all patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (10% of the population) received incremental treatment with a PCSK9 inhibitor (n=605,000 in 2015). Primary results presented in Table 14.

§ In a scenario analysis, all statin-tolerant FH patients who were not already receiving statins were first treated with high-intensity statins, after which the entire FH subpopulation (n = 748,000 patients in 2015) was incrementally treated with a PCSK9 inhibitor. Primary results presented in tables 14 and 15.

Appendix 7 Table 11. Clinical Events Among Statin-Intolerant Patients with a History of CVD Initiating PCSK9 Inhibitors.

	Analytic Horizon = 1 Year Events averted*				Analytic Horizon = 5 Year Events averted*			
	Total MACE	CVD deaths	Nonfatal MIs	Nonfatal Strokes	Total MACE	CVD deaths	Nonfatal MIs	Nonfatal Strokes
Compared with no additional lipid-lowering therapy†	13,400	4,900	5,200	3,300	79,700	30,200	29,800	19,700

Abbreviations: CVD, cardiovascular disease; MACE, major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke); MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9.

* To reflect the precision of the model, all clinical events are rounded to the 100s.

† In the base case, we assumed that 10% of the population was statin- intolerant (n=1,460,000 in 2015). Patients who had a prior history of cardiovascular disease received incremental treatment with a PCSK9 inhibitor. Primary results presented in Table 16.

Appendix 7 Table 12. Clinical Events Among Patients with a History of CVD on Statin Therapy Initiating PCSK9 Inhibitors.*

	Analytic Horizon = 1 Year Events averted*				Analytic Horizon = 5 Year Events averted*			
	Total MACE	CVD deaths	Nonfatal MIs	Nonfatal Strokes	Total MACE	CVD deaths	Nonfatal MIs	Nonfatal Strokes
History of CVD, LDL-C ≥ 70mg/dL on Statin Therapy (as treated) †	64,200	23,000	24,500	16,700	375,500	140,200	137,900	97,400
First-ever MI in 2015, incremental treatment with a PCSK9 inhibitor^	3,600	500	2,600	600	11,100	3,900	5,700	1,500

Abbreviations: CVD, cardiovascular disease; MACE, major adverse cardiovascular event (cardiovascular death, nonfatal myocardial infarction, nonfatal stroke); MI, myocardial infarction; PCSK9, proprotein convertase subtilisin/kexin type 9.

* To reflect the precision of the model, all clinical events are rounded to the 100s.

† In the base case, patients who had a prior history of cardiovascular disease and LDL-C>70mg/dL on statin therapy received incremental treatment with a PCSK9 inhibitor. Primary results presented in table 17.

^ In a scenario analysis, all patients who had an incident (first-ever) MI in 2015 and were receiving statin therapy if tolerated, received incremental treatment with a PCSK9 inhibitor (n = 169,000). Ten percent of the population was assumed to be statin-intolerant and only received a PCSK9 inhibitor. Primary results presented in Table 18.

Appendix 7 Table 13. Budgetary Impact of PCSK9 Inhibitors Among Patients with FH.

	Analytic Horizon = 1 Year				Analytic Horizon = 5 Years			
	PY of treatment (thousands)	Drug Cost (millions)*	Other CVD Costs (millions)*	Net CVD Costs (millions)*	PY of treatment (thousands)	Drug Cost (millions)*	Other CVD Costs (millions)*	Net CVD Costs (millions)*
Compared with statins (as treated)†	605	$8,676	-$318	$8,358	3,201	$45,937	-$1,875	$44,062
Compared with statins (full treatment)§	748	$10,736	-$324	$10,413	3,881	$55,695	-$1,917	$53,779

Abbreviations: CVD, cardiovascular disease; FH, familial hypercholesterolemia; PCSK9, proprotein convertase subtilisin/kexin type 9; PY, person-years.

* All costs are undiscounted. To reflect precision in the model, person-years of treatment were rounded to the thousands and costs were rounded to the millions.

† In the base case, patients who met the operational definition of FH and were either already receiving statin therapy or deemed statin-intolerant (10% of the population) received incremental therapy with a PCSK9 inhibitor (n = 605,000 in 2015). The comparator was statin therapy (as treated) among patients who were statin-tolerant, and no lipid-lowering therapy among patients who were statin-intolerant (base-case prevalence = 10%). Primary results presented in Table 14.

§ In the scenario analysis, we evaluated the impact of "full treatment" in which all statin-tolerant patients who were not already receiving statins were first treated with high-intensity statins, after which the entire FH subpopulation (n = 748,000 patients in 2015) was incrementally treated with a PCSK9 inhibitor. The comparator was statin therapy (fully treated) among patients who were statin-tolerant, and no lipid-lowering therapy among patients who were statin-intolerant (base-case prevalence = 10%). Primary results presented in Table 15.

Appendix 7 Table 14. Budgetary Impact of PCSK9 Inhibitors Among Statin-Intolerant Patients with a History of CVD.

	Analytic Horizon = 1 Year				Analytic Horizon = 5 Years			
	PY of treatment (thousands)	Drug Cost (millions)*	Other CVD Costs (millions)*	Net CVD Costs (millions)*	PY of treatment (thousands)	Drug Cost (millions)*	Other CVD Costs (millions)*	Net CVD Costs (millions)*
Compared with no additional lipid-lowering therapy†	1,460	$20,952	-$1,250	$19,702	8,018	$115,053	-$6,999	$108,053

Abbreviations: CVD, cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9; PY, person-years.

* All costs are undiscounted. To reflect precision in the model, person-years of treatment were rounded to the thousands and costs were rounded to the millions.

† In the base case, patients who had a history of CVD and were statin-intolerant (base-case =10% of the population) received treatment with a PCSK9 inhibitor (n = 1,460,000 in 2015). Primary results presented in Table 16.

Appendix 7 Table 15. Budgetary Impact Among Patients with a History of CVD.

	Analytic Horizon = 1 Year				Analytic Horizon = 5 Years			
	PY of treatment (thousands)	Drug Cost (millions)*	Other CVD Costs (millions)*	Net CVD Costs (millions)*	PY of treatment (thousands)	Drug Cost (millions)*	Other CVD Costs (millions)*	Net CVD Costs (millions)*
History of CVD, LDL-C ≥ 70mg/dL on Statin Therapy (as treated) †	7,271	$104,369	-$5,994	$98,375	40,025	$574,364	-$33,332	$541,031
First-ever MI in 2015 ^	169	$2,421	-$158	$2,263	817	$11,727	-$878	$10,849

Abbreviations: CVD, cardiovascular disease; PCSK9, proprotein convertase subtilisin/kexin type 9; PY, person-years.

* All costs are undiscounted. To reflect precision in the model, person-years of treatment were rounded to the thousands and costs were rounded to the millions.

† In the base case, only patients with pre-existing CVD and LDL-C ≥ 70mg/dL on statin therapy received incremental therapy with a PCSK9 inhibitor (n = 7,271,000 patients in 2015). The comparator was statin therapy (as treated). Primary results presented in Table 17.

^ In a scenario analysis, all patients who had an incident (first-ever) MI in 2015, were receiving statin therapy as tolerated, received incremental therapy with a PCSK9 inhibitor (n = 169,000 in 2015). The comparator was statin therapy among those who were able to tolerate it and no lipid-lowering therapy among patients who were statin-intolerant. Primary results presented in Table 18.

Appendix 7 Table 16. Calculation of Drug Costs and Cost Offsets over Five-Year Time Horizon.

		Cost Offset by Duration of Drug Exposure	Annual Budget Impact by Duration of Drug Exposure	Total Budget Impact by Duration of Drug Exposure
		Calculations (per Patient)		
FH	One Year	592	13,824	13,824
(n=453,443)	Two Years	618	13,801	27,601
	Three Years	630	13,789	41,366
	Four Years	643	13,777	55,108
	Five Years	656	13,765	68,825
Weighted Avg.		*628*	*13,791*	*41,345*
CVD, Statin-	One Year	1,010	13,496	13,496
Intolerant	Two Years	1,025	13,488	26,977
(n=364,948)	Three Years	1,032	13,484	40,453
	Four Years	1,039	13,480	53,921
	Five Years	1,046	13,476	67,382
Weighted Avg.		*1,031*	*13,485*	*40,446*
CVD, Not at LDL	One Year	967	13,529	13,529
Target	Two Years	977	13,525	27,049
(n=1,817,788)	Three Years	982	13,522	40,567
	Four Years	987	13,520	54,079
	Five Years	991	13,517	67,587
Weighted Avg.		*981*	*13,523*	*40,562*
CVD, High-Risk	One Year	961	13,391	13,391
Subset	Two Years	1,091	13,346	26,692
(n=169,000)	Three Years	1,156	13,324	39,971
	Four Years	1,222	13,301	53,205
	Five Years	1,287	13,279	66,395
Weighted Avg.		*1,143*	*13,328*	*39,931*

Appendix 7 Table 17. Calculation of Potential Budgetary Impact Threshold Price.

Population	(A) Five-Year N	(B) Five-Year Price Benchmark ($904m X 5)	(C) Weighted Cost-Offset per Patient (Table 16)	(D) Total Cost-Offset (A) x (C)	(E) Cost-Offset per Drug* (D) ÷ 2	(F) PBI Threshold Price ((B) + (E)) ÷ (A)
FH	453,443	$4,518,234,926	$628	$284,626,715	$142,313,357	$ 10,278
CVD, Statin-Intolerant	364,948	$4,518,234,926	$1,031	$376,119,135	$188,059,567	$ 12,896
CVD, Not at LDL-C Target	1,817,788	$4,518,234,926	$981	$1,782,796,960	$891,398,480	$ 2,976
TOTAL	2,636,179	$4,518,234,926	$927	$2,443,542,809	$1,221,771,405	$ 2,177

*Total cost offset divided by 2 due to assumption that each PCSK9 inhibitor achieves an equal share of the offset

FH: Familial hypercholesterolemia; CVD: Cardiovascular disease; LDL: low-density lipoprotein; PBI: potential budgetary impact

A8: Meeting Agenda and Participants

Time	Activity
9:30AM – 10:00AM	• Registration
10:00AM – 10:15AM	• Meeting Convened and Opening Remarks: ○ Steven Pearson, MD, MSc, President, Institute for Clinical and Economic Review
10:15AM – 11:30AM	• Presentation of the Evidence: ○ Jeffrey Tice, MD, Associate Professor, UCSF School of Medicine ○ Dhruv S. Kazi, MD, MSc, MS, Assistant Professor, UCSF ○ Kirsten Bibbins-Domingo, MD, PhD, MAS, Professor, UCSF ○ Daniel Ollendorf, PhD, Chief Review Officer, Institute for Clinical and Economic Review
11:30AM – 12:00PM	• Public Comments and Discussion: *Members of the public pre-registered to deliver oral remarks.*
12:00PM – 12:30PM	• Break for Lunch
12:30PM – 2:30PM	• Council Q&A with Clinical Experts • Council Deliberation and Votes: *ICER staff and clinical experts will be available for questions from the Council during deliberation.*
2:30PM – 3:50PM	• Policy Roundtable: *Consideration by Council and Roundtable of best practice recommendations.*
3:50PM – 4:00PM	• Meeting Adjourned

Council Members	Policy Roundtable Participants
Robert H. Aseltine, Jr., PhD (Vice-chair) Professor, Division of Behavioral Sciences and Community Health, University of Connecticut Health Center Deputy Director, Center for Public Health and Health Policy Director, Institute for Public Health Research, University of Connecticut	**Leslie Fish, PharmD** Vice President of Pharmacy, Fallon Health
	Jonathan Karas Patient Representative
Teresa Fama, MD, MS (Chair) Physician, Central Vermont Rheumatology	**Dolores Mitchell** Executive Director, Group Insurance Commission
Claudia B. Gruss, MD, FACP, FACG, CNSC Physician, ProHealth Physicians	**Patrick O'Gara, MD** Senior Physician, Brigham and Women's Hospital Professor of Medicine, Harvard Medical School
Claudio Gualtieri, JD Associate State Director of Advocacy Connecticut AARP	**William Shrank, MD, MSHS** Senior Vice President, Chief Scientific Officer and Chief Medical Officer, Provider Innovation and Analytics, CVS Health
Felix Hernandez, MD, MMM Medical Director, Surgical Services Medical Director, Undergraduate Medical Education Eastern Maine Medical Center	**Thomas Siepka, RPh, MS FACHE** Vice President, System Pharmacy and Outreach, Dartmouth Hitchcock
Toni Kaeding, MS, RN Special Projects, Green Mountain Care Board	**Paul Thompson, MD** Chief of Cardiology, Hartford Hospital Professor of Medicine, University of Connecticut
Stephen Kogut, PhD, MBA, RPh Associate Professor, University of Rhode Island College of Pharmacy	
Eleftherios Mylonakis, MD, PhD Chief of Infectious Diseases, Rhode Island Hospital and the Miriam Hospital	
Julie Rothstein Rosenbaum, MD Associate Professor, Yale School of Medicine	
Jeanne Ryer, MS Director, New Hampshire Citizens Health Initiative	
Keith A. Stahl, MD Physician and Medical Director, Catholic Medical Center	
Jason Wasfy, MD, MPhil Assistant in Medicine (Cardiology) at Mass General Hospital	
Rob Zavoski, MD, MPH (ex-officio) Medical Director, Connecticut Department of Social Services	