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Cost effectiveness of lifelong therapy with PCSK9 inhibitors for lowering cardiovascular events in patients with stable coronary artery disease: Insights from the Ludwigshafen Risk and Cardiovascular Health cohort

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ABSTRACT

Proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) reduce cardiovascular events in coronary artery disease (CAD). Their costs exceed that of established oral lipid-lowering agents. Previous cost-effectiveness assessments have been inconsistent. Markov cohort state transitions models for stable CAD patients were calculated using information from 1530 participants of the Ludwigshafen Risk and Cardiovascular Health Study (LURIC) with known causes of deaths. Non-fatal to fatal event rates, drug prices, direct treatment costs, and utility weights were from public sources. At an assumed relative risk reduction of 32.5% and an annual drug price of 8500 Euros, QALYs gained were 1.23 and 1.20, savings were 2390 and 2410 Euros, and ICERs were 112,530 and 108,660 Euros in women and men, respectively. When the annual cost of this medication was set at 1600 Euros, corresponding ICERs were 21,180 and 20,450 Euros. PCSK9i treatment is cost-effective in stable CAD at a threshold of 150,000 Euro and annual costs of 8500 Euros. As the broad use of PCSK9i therapy in CAD would have a disruptive impact on the healthcare budget, treatment should be focused on very high risk patients (≥3 comorbidities, annual risk of 10%); alternatively, and for lower risk, significant cost reductions would be needed.

1. Introduction

Both European and North American guidelines focus on LDL cholesterol (LDL-C) as the therapeutic target of lipid-lowering [1,2]. In Europe, the treatment targets of LDL-C proposed by the Joint European Society of Cardiology and the European Atherosclerosis Society Guidelines are followed. They recommend LDL-C lowering to < 100 mg/dl (2.6 mmol/l) and < 70 mg/dl (1.8 mmol/L) in persons at high and at very high risk, respectively [2]. Statins and ezetimibe are the major status quo treatment options [1,2]. The inter-individual variability in response to statins is, however, substantial; Ridker et al. reported that only 50% of the JUPITER participants reached reductions in LDL-C of 50% or more with 20 mg daily of rosuvastatin [3]. In patients with very high untreated LDL-C (for instance in familial hypercholesterolemia, FH) LDL-C treatment targets are often not achieved using these medicines [4–6]. In addition, statins may be difficult to use at their highest doses as a result of adverse effects such as muscle symptoms [7].

Fully human monoclonal antibodies against PCSK9, alirocumab and evolocumab, are available for LDL-C lowering and their effectiveness

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has been demonstrated in patients with statin intolerance [8], FH [9], and high and very high cardiovascular risk [10,11]. The safety and cardiovascular efficacy of the PCSK9 antibodies alirocumab [12], bocozizumab [13], and evolocumab [14] have been demonstrated in prospective outcome trials. Bocozizumab, a partially human monoclonal antibody, has been withdrawn due to an immune response involving neutralizing antibodies and loss of efficacy [15].

Across Europe, the annual costs for PCSK9i treatment range up to approximately 8500 Euros. The costs of PCSK9i therapy thus markedly exceeds that of conventional oral lipid-lowering agents, which are currently available in generic form. Consequentially, there is controversy as to whether the budget for these medicines is economically justified across many national health care systems. On the basis of an annual drug price of $14,350 (the approximate purchase costs of evolocumab and alirocumab valid in 2015 in the USA), Kazi and colleagues have calculated that adding a PCSK9i to statin treatment in patients with atherosclerotic vascular disease would result in a Quality Adjusted Life Year (QALY) of $414,000 and would thus not be cost-effective at the threshold of $ 100,000 per QALY [16]. The authors predicted that a reduction in the annual drug cost to $4536 per patient or less would, however, be needed for cost-effectiveness at $100,000 per QALY. Using a separate set of input assumptions for baseline event rates, clinical endpoints, utility weights and LDL-C concentrations, Fonarow and colleagues arrived at an incremental cost-effectiveness ratio (ICER) of $268,637 per QALY gained (or $165,689 at a discounted price of $10,311). These authors concluded that an annual net price of $ 9669 would be required to consider PSCK9i cost-effective at a threshold of $150,000 per QALY.

To date, cost-effectiveness estimates applicable to real-world demographics, risk factors, comorbidities and event rates in Central European countries are lacking. We therefore sought to model the cost effectiveness of PCSK9i treatment on top of standard background statin therapy using the LURIC cohort of patients with stable atherosclerotic vascular disease in Germany.

2. Material and methods

2.1. Study population

We analyzed data drawn from the Ludwigshafen Risk and Cardiovascular Health (LURIC) Study. The study recruited 3316 patients who were referred for coronary angiography to the Ludwigshafen Heart Center in South-West Germany, between July 1997 and January 2000 [17]. Follow-up information on vital status was obtained from local population registries. Death certificates, medical records of local hospitals, and autopsy data were reviewed to classify the causes of death. We here included 1530 participants with stable CAD, consisting of 373 women and 1157 men, with stable CAD with known causes of death.

The study was approved by the Ethics Committee of the Physicians Chamber of Rheinland-Palatinate and performed in accordance with the Declaration of Helsinki. All participants gave written informed consent.

2.2. Risk stratification

We used a modification of the recently published TIMI Risk Score for Secondary Prevention (TRS2P) [18], in which age was replaced by FH. The modified score thus included FH (Dutch Lipid Clinics Network Score > 5), congestive heart failure (New York Heart Association classification III–IV), hypertension, diabetes mellitus, previous myocardial infarction, previous stroke, previous CABG, peripheral vascular disease, chronic kidney disease (glomerular filtration rate < 60 ml/min/1,73 m^2 calculated according to the CKD-EPI formula), and current smoking, all of which were weighted identically with one additional point.

2.3. Model assumptions and analysis

We generated Markov cohort state transition models by exploiting data from 1530 participants in the LURIC study with stable CAD. The states, transitions and assumptions of our model are described with Supplementary Fig. 1. Non-fatal coronary and cerebrovascular events have not been recorded in the LURIC study, we therefore used non-fatal to fatal event ratios of 2.89 (https://www.helmholtz-muenchen.de/herzschlag-info) and 3.31 [19] for coronary or cerebrovascular events, respectively. To model the effects of maximal conventional, oral (non PCSK9i) lipid lowering treatment, we provisionally multiplied the estimated probabilities of vascular events by: 1.0 and 0.85 (corresponding to an assumed relative risk reduction of 15%) for cerebrovascular events and all other cardiovascular events, respectively, in patients who received statins at baseline in the LURIC study; and by 0.85 (assumed relative risk reduction of 15%) and 0.70 (assumed relative risk reduction of 30%) for cerebrovascular events and all other cardiovascular events, respectively, in patients who did not receive statins. We set the discount rate (for definition cf. Supplementary Table 1) at 0.03. Utility weights (cf. Supplementary Table 1) were derived from the literature (see also Legend to Supplementary Fig. 1) [20,21].

The estimation of the direct medical costs of one coronary event in Germany was based on a longitudinal analysis using data from a large German health insurance company [22]. The estimation of direct medical costs of one cerebrovascular event was based on national projections from the population-based stroke registry of The Erlangen Stroke Project [23]. The following assumptions of direct costs were made: fatal coronary event, 7384 Euros; non-fatal coronary event, 13,061 Euros; fatal cerebrovascular event, 19,179 Euros; and non-fatal cerebrovascular event, 46,710 Euros.

The main outcomes were the savings resulting from coronary and cerebrovascular events avoided, Quality Adjusted Life Years (QALYs, cf. Supplementary Table 1) gained per person and the incremental cost-effectiveness ratio (ICER, cf. Supplementary Table 1). We considered a range of relative risk reductions between 10 and 50% achieved through PCSK9i treatment on top of conventional, maximal lipid-lowering treatment.

2.4. Sensitivity analyses

We performed the following sensitivity analyses setting the relative reduction of each endpoint at 32.5%: a) annual PCSK9i treatment costs of 8500 Euros (the approximate official current list price of both PCSK9 inhibitors in Germany), 6000, 4000, and 1600 Euros respectively (cf. Fig. 2); b) age at initiation of treatment below 60, between 60 and 70, and above 70 years of age (cf. Fig. 3); and c) number of concomitant conditions according to the modified TIMI Risk Score for Secondary Prevention (TRS2P) [18] (Fig. 4). All analyses were conducted in both genders separately.

2.5. Eligibility for PCKSi treatment

To estimate the proportion of CAD patients potentially in need of PCSK9i treatment, we modelled the number of patients whose LDL-C level would still exceed the goal of 70 mg/dl (1.8 mmol/l) after exploiting the full potential of conventional oral lipid-lowering (mainly statins and ezetimibe). For this purpose, we calculated the baseline, treatment-naïve LDL-C from the type and dose of the statin used [24] in patients receiving statins at the time of recruitment. We then assumed that maximal lipid-lowering treatment would diminish LDL-C levels by 50% and determined the proportion of patients with an LDL-C above 70 mg/dl (1.8 mmol/l). We equally estimated the proportion of CAD patients in whom the LDL-C level on conventional treatment remained above 100 mg/dl (2.6 mmol/l) and who displayed 3 or more points in the modified TRS2P (Table 2; fields with bold numbers).

3. Results

3.1. Cohort

The mean age of our female and male patients at the time of recruitment was 66 and 63.4 years, respectively. Some 532 (34.8%) participants died during a median follow-up of 9.88 years (range 0.01–11.85 years, interquartile range 7.3–10.74 years, mean 8.59 years, standard deviation 3.21 years). Cardiovascular mortality included the following categories: sudden cardiac death ($n = 150$, 9.8%), fatal myocardial infarction ($n = 55$, 3.59%), death due to congestive heart failure ($n = 87$, 5.69%), death after intervention to treat CAD ($n = 14$, 0.92%), fatal stroke ($n = 30$, 1.96%), and other causes of death due to CAD ($n = 13$, 0.85%). The estimated mean total *overall* annual event rate per person was 0.1042 (10.42%), and 0.0944 (9.44%) for coronary events and 0.00984 (0.984%) for cerebrovascular events estimated by the fatal to non-fatal event rates provided in the Methods section. The annual rates were 0.10178 (10.178%) and 0.00969 (0.969%) for coronary events and cerebrovascular events in men and 0.07292 (7.292%) and 0.01026 (1.026%) in women, respectively.

3.2. Risk stratification

We determined the hazard ratios for cardiovascular mortality according to the number of comorbidities in the modified TRS2P and estimated the annual rates of fatal and non-fatal cardiovascular events from the non-fatal to fatal ratios. If there were no comorbidities, then the risk was not significantly different from the risk of patients of the same age without angiographic CAD; in the presence of risk factors, the risk increased in parallel to their number. The hazard ratios and projected annual event rates increased continuously and in parallel to the modified TRS2P score, with a sharp increase occurring between 2 and 3 points (HRs of 2.01 and 3.92 as compared to patients with no angiographic CAD, cf. Supplementary Table).

3.3. Main outcomes

We generated Markov cohort state transition models for clinically stable patients with CAD by exploiting data from 1530 participants in the LURIC study with stable CAD. Projected on a life-long horizon, ICERs per QALY ranged from 408,720 to 379,230 Euros in women and men, respectively, at a 10% relative risk reduction through incremental PCSK9i treatment, and from 68,390 to 67,090 Euros at 50% relative risk reduction (Table 1, Fig. 1). At a 15% relative risk reduction, ICERs were 267,920 and 247,740 Euros in women and men respectively (Fig. 1). At 40% relative risk reductions by contrast, ICERs were 88,980 and 86,460 Euros in women and men, respectively.

At a potential relative risk reduction of 32.5%, ICER values were 112,530 and 108,660 Euros in women and men, respectively, while QALYs gained were 1.23 and 1.24 in women and men, respectively. The savings achieved through coronary and cerebrovascular events avoided were then 2390 or 2440 Euros per female or male patient, respectively.

3.4. Sensitivity analyses

3.4.1. Drug price

At a relative risk reduction of 32.5%, ICERs decreased from 112,530 and 108,660 Euros in women and men, respectively, to 21,180 and 20,450 Euros if the annual drug price for PCSK9i was set at 1600 Euros. At a 15% relative risk reduction and annual cost of 1600 Euros, ICERs were 50,430 and 46,630 Euros in women and men, respectively (Fig. 2). Remarkably, at 40% relative risk reductions, ICERs fell to 16,750 and 16,280 Euros in men and women, respectively.

3.4.2. Age at the initiation of PCSK9i treatment

At annual treatment costs of 8500 Euros, ICERs were 72,540 and

Table 1
A. Cost effectiveness of incremental treatment of patients with stable CAD with a PCSK9i at relative reductions of the risk of a fatal or non-fatal ASCVD event by 32.5% on a life-long perspective assuming annual drug costs of Euro 8500.

	Women					Men				
	Mean	Standard deviation	25th per-centile	median	75th per-centile	Mean	Standard deviation	25th per-centile	Median	75th per-centile
Total QALYs per person (conventional maximal lipid-lowering treatment)	14.27	0.32	14.13	14.31	14.47	13.67	0.18	13.58	13.68	13.78
Total QALYs per person (incremental treatment with PCSK9 inhibitor)	15.50	0.32	15.34	15.53	15.71	14.91	0.17	14.82	14.91	15.02
additional drug costs per person in 1000 Euro (8500 Euro/year per person)	137.23	1.89	135.91	137.26	138.52	135.92	1.23	135.07	135.83	136.77
Savings through avoided coronary and cerebrovascular events per person in 1000 Euro	2.39	0.75	1.91	2.41	2.89	2.44	0.37	2.19	2.43	2.70
QALYs gained per person	1.23	0.21	1.10	1.20	1.33	1.24	0.12	1.17	1.23	1.30
ICER in 1000 Euro (8500 Euro/year per person)	112.53	16.44	102.32	112.33	122.02	108.66	9.69	103.07	108.31	113.78

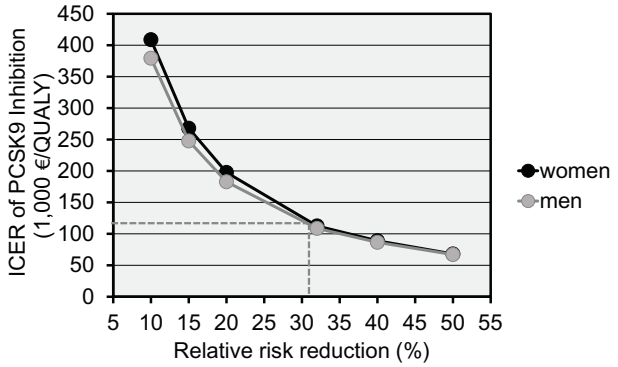

Fig. 1. ICERs for PCSK9i on top of maximum conventional lipid-lowering in stable CAD at different relative reductions in the rate of atherosclerosis related cardiovascular events. Dark blue: women, light blue B: men. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

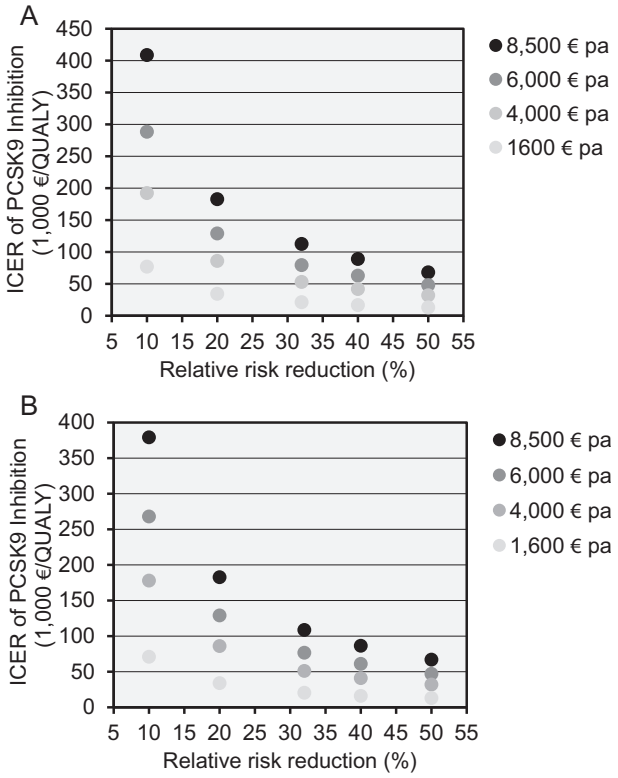

Fig. 2. Sensitivity of ICERs for PCSK9i treatment to annual drug costs in patients with CAD disease at different relative reductions in atherosclerosis related cardiovascular events. Panel A: women, panel B: men.

83,940 Euros in men and women, respectively, when treatment was started at or above 70 years of age, but were 150,240 and 176,600 Euros when treatment was started below 60 years of age. At an annual cost of 1600 Euros, the age at treatment initiation had a smaller effect on ICERs (Fig. 3).

3.4.3. Risk of recurrent events

We also simulated the impact of the number of comorbidities on cost-effectiveness. This analysis (Fig. 4) demonstrates a stronger impact of the number of comorbidities at high annual treatment costs compared to low annual treatment costs. At an annual drug budget of 8500 Euros, ICERs in women and men were 112,530 and 108,660 Euros, respectively, on average in all persons with stable CAD. At the same

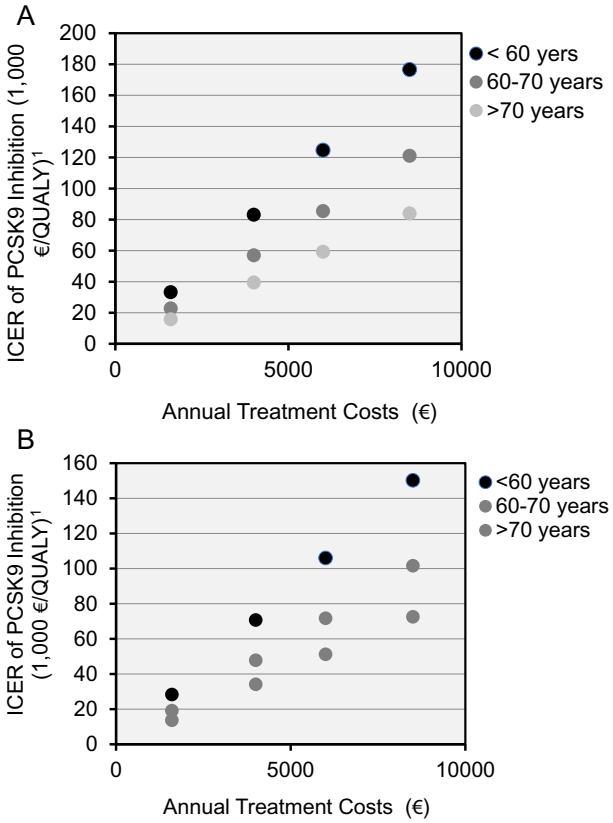

Fig. 3. Sensitivity of ICERs for PCSK9i treatment to age at initiation of treatment in patients with stable CAD at different treatment costs. Panel A: women, panel B: men.

drug price, ICERs in women and men were 9490 (minus 13.4%) and 90,950 (minus 16.3%) Euros, respectively, if the TRS2P score was 3 or larger. At a drug price of Euro 1600, ICERs in women and men were 18,350 and 17,120 Euro, respectively.

3.5. Eligibility for PCK9i treatment

After accounting for the effect of the medication in patients receiving statins at baseline, we estimated that the mean untreated LDL-C level was 143.4 mg/dl (3.69 mmol/l) (SD 49.2 mg/dl (1.26 mmol/l)) in our cohort. When we assumed that all patients were given maximum oral lipid-lowering therapy to reduce their LDL-C by 50%, then approximately 47% of the LURIC cohort would have remained above the target of 70 mg/dl (1.8 mmol/l).

We also sought to determine the proportion of CAD patients in whom the LDL-C level on conventional treatment remained above 100 mg/dl (2.6 mmol/l) and who displayed 3 or more points in the modified TRS2P score; 5.7% of the cohort fell into this category (Table 2, bold fields).

4. Discussion

4.1. Cost-effectiveness of PCSK9i for preventing atherosclerosis-related cardiovascular events

To our knowledge, we present the first analysis of the cost effectiveness of PCSK9i treatment based on real world data from a Central European country, Germany. Our key finding is that PCSK9i would be cost-effective at the commonly accepted ICER of 150,000 Euros per QALY if one assumes a relative reduction of the risks of fatal and non-fatal cardiovascular events in the range of one third over a life-time

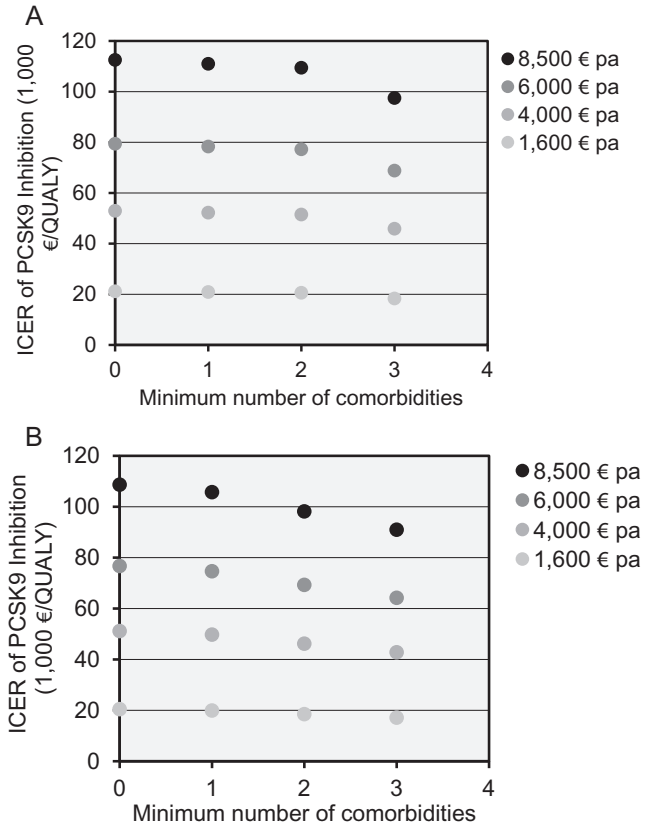

Fig. 4. Sensitivity of ICERs for PCSK9i treatment according to the minimum TRS2P score points in patients with stable CAD at different annual treatment costs. Panel A: women, panel B: men.

Table 2
Distribution of LDL-C (in percent) in 1,471[a] clinically stable patients of the LURIC study with a defined modified TIMI Risk Score for Secondary Prevention (TRS2P).[b]

LDL-C (mg/dl)	< 70	70–100	100–130	> 130
LDL-C (mmol/l)	< 1.81	1.81–2.59	2.59–3.37	> 3.37
TRS2P: 0	2.18	1.56	0.27	0.00
TRS2P: 1	9.93	9.31	1.63	0.07
TRS2P: 2	16.93	10.4	2.65	0.95
TRS2P: 3	13.39	9.11	**2.11**	**0.68**
TRS2P: 4	7.21	3.54	**1.70**	**0.48**
TRS2P: ≥ 5	3.4	1.77	**0.54**	**0.20**

Bold fields indicate patients in whom the LDL-C level on conventional treatment would remain above 100 mg/dl (2.6 mmol/l) and who display 3 or more points in the modified TRS2P. We suggest that these patients would be eligible for PCSK9i treatment.

[a] 1,471 instead of 1530 because in 59 persons not all variables to generate the TRP2P score were available.

[b] Familial hypercholesterolemia (Dutch Lipid Clinics Network Score > 5), congestive heart failure (New York Heart Association classification III–IV), hypertension, diabetes mellitus, previous myocardial infarction, previous stroke, previous CABG, peripheral vascular disease, chronic kidney disease, and current smoking. Entries are percentages of the total cohort of 1471 patients with stable CAD. In patients taking statins upon recruitment, treatment naïve LDL-C was estimated by taking into account type and dosage of the statin used [24]. The treatment naïve LDL-C values were then divided by 2 to simulate the effect of a maximal conventional lipid-lowering regimen.

perspective.

A crucial driver of cost-effectiveness analysis is the risk reduction brought about by the therapeutic intervention. According to the Cholesterol Treatment Trialists Collaboration (CTTC) meta-analysis, every 1.0 mmol/l (40 mg/dl) reduction in LDL-C produces a consistent 22% relative reduction in atherosclerosis-related cardiovascular events starting by the second year of exposure [25]. A 1.5 mmol/l (60 mg/dl) decrease in LDL-C from PCSK9i treatment would therefore translate into a 32.5% relative risk reduction, at which ICERs were 112,530 and 108,660 Euros in women and men respectively.

Is such an expectation realistic? The two available outcome studies with PCSK9i, FOURIER and ODYSSEY OUTCOMES [12,14] indicate a smaller risk reduction, but they were relatively short in duration and hence they might not have revealed the full long-term potential of these medicines to confer clinical benefit. We therefore believe that assuming a relative risk reduction of one third is compatible with the available and projected data. In the FOURIER study, the absolute difference in LDL-C levels between the placebo and the evolocumab group was 62 mg/dl (1.6 mmol/l), which would have predicted a relative event reduction of > 32% according to the CTTC data [259639]. Evolocumab actually reduced the rate of the primary endpoint by 15% (HR 0.85, 95% confidence interval 0.79–0.92) over a short period (2.2 years). The annual event rate in this trial was higher than expected, resulting in the occurrence of the events required for termination within a median observation period of 2.2 instead of 4 years. Even in intervention trials involving statins, a small relative risk reduction of 9% per each mmol/l reduction in LDL-C was seen within the first year of observation, which was typically followed by a 22% reduction in the second year of follow-up. The results of the FOURIER trial hence align with the findings that would be expected by extrapolation over the treatment period from clinical trials with statins.

The efficacy and long-term safety of alirocumab was evaluated in the ODYSSEY Outcomes study [12]. In this intervention trial, the difference in on treatment LDL-C level between the alirocumab and the placebo arms was 53 mg/dl (1.4 mmol/l) at four months and 37 mg/dl (1.0 mmol/l) at 48 months after randomization, an absolute decrement which was less than that in the FOURIER study. The difference in absolute decrement in LDL-C may have been compensated by a slightly longer median observation time (2.8 years compared to 2.2 years), so that the decrease in the primary endpoint by 15% over the study period (HR: 0.85, 95% CI: 0.78–0.93, $P = .0003$) perfectly matches the principle finding in the FOURIER study.

In consequence to the uncertainty of the long-term benefit, we examined ICERs across a range of potential relative risk reductions from 10 to 50% on a life-long horizon in our main analysis. ICERs ranged from 379,230 to 408,720 Euros in men and women, respectively, at a 10% relative risk reduction, and from 68,390 to 67,090 Euros respectively at a 50% relative risk reduction. As ICERs between 100,000 and 150,000 Euros are tolerated by payers in most developed health care systems, a relative reduction in the risk of cardiovascular events by approximately one third would be needed for PCSK9i treatment to become cost-effective at a drug price of 8500 Euros.

We also wish to note that this analysis included less women ($n = 373$) than men ($n = 1157$). While the point cost-effectiveness estimates for men and women were essentially similar, the estimates for their standard deviations were larger in women than in men. This reflects the sharper estimate made possible by the greater number of males.

Another important component in cost-effectiveness models is the absolute risk at baseline. For instance, Kazi et al. [16] used an annual rate of myocardial infarction, stroke and cardiovascular death of 3.7%, whereas Fonarow et al. [26] used 6.4% for myocardial infarction, stroke or cardiovascular death, and 9.7% after inclusion of revascularization. The mean total annual event rate per person for any myocardial infarction, stroke and cardiovascular death in our cohort was elevated at 10.42%, a factor which may have strongly contributed to the lower ICERs found herein in comparison to the findings of Kazi et al. [16] and of Fonarow et al. [26]. It should also be emphasized that on the one hand, we allowed for recurrent events in our models, which

substantially contribute to ASCVD burden [27] and that on the other, we relied on real-world observational rates which, importantly, may be twofold greater than those observed in clinical trials [28]. As such our event rates are well within the range assumed in other studies of the cost-effectiveness of PCSK9i treatment based on real-world disease burden [29,30], and importantly, in the range of recent registry experience [27.]

4.2. Sensitivity analyses

While budgetary savings due to avoidance of non-fatal and fatal events were negligible, cost-effectiveness was strongly affected by treatment costs. At a relative risk reduction of 32.5%, ICERs of 21,180 and 20,450 Euros in women and men respectively were identified when the annual drug price was set at 1600 Euro, which is in the range of ICERs historically attributed to branded statins [31].

Under the - probably too conservative - assumption of a 15% relative risk reduction as observed over the short-term in the FOURIER [14] and ODYSSEY Outcomes trials [12] and annual drug costs of 1600 Euros, ICERs were 50,430 and 46,630 Euros in women and men respectively (Fig. 2). Also, the PCSK9i therapy as recently shown [12] can decrease all-cause mortality over the long term in very high-risk patients which additionally improve the cost/benefit ratio for these agents. However, any future pricing for evolocumab or alirocumab needs to take account of the higher production costs of biologicals as compared to chemical medicines (for comparison: the annual drug costs for branded atorvastatin 40 mg/day in Germany in 2004 was 652 Euros). Thus, for instance at approximate annual treatment costs of 6000 Euros ICERs would fall below 100,000 Euro under the assumption of risk reduction of one third (Fig. 2).

To estimate the impact of overall cardiovascular risk at baseline on cost-effectiveness, we made use of an established risk stratification algorithm, the TIMI Risk Score for Secondary Prevention (TRS2P) [18], which we modified to include FH (Dutch Lipid Clinics Network Score $>$ 5) in place of age. FH has recently been recognized as a high-risk feature for the stratifying patients with CVD in the 2018 North American Guideline for the Management of Blood Cholesterol [1]. The rationale for omitting age was to avoid shifting treatment preferences towards the elderly. While this score can theoretically attain a maximum of ten points, we limited cost-effectiveness analyses to those patients presenting with a minimum of 0 to 3 points, as the prevalence rate of patients with 4 or more points was low; as a consequence, our statistical models became unstable. As expected, ICERs decreased in parallel to the modified TRS2P score (Fig. 4), but the effect of comorbidities on cost-effectiveness was obviously lower than that of modification in treatment costs. While the modified TRS2P score had a discernible impact on ICERs at high treatment costs, it was comparatively low at low cost.

Finally, ICERs were lower as age advanced at the beginning of the treatment, an effect due to the fact that absolute cardiovascular risk increases in parallel to age and that a higher risk at baseline decreases the number needed to treat to prevent one event and accordingly improves cost-effectiveness. This finding however does not justify the exclusion or limited access of younger CAD patients from PCSK9i treatment, in particular as it appears that the relative benefit of cholesterol lowering in the elderly is less than that in the young [32].

4.3. Eligibility for PCSK9i treatment and budget impact

Assuming an average treatment -naïve LDL-C concentration of 143 mg/dl (3.69 mmol/l), and assuming that conventional lipid-lowering would diminish LDL-C by 50%, we estimated that 47% of stable CAD patients would not reach the target of 70 mg/dl (1.8 mmol/l) by using maximum conventional lipid-lowering. The prevalence rate of CAD in Germany is approximately six million persons [33,34]; 2.82 million patients not reaching the LDL-C target would thus have an indication for PCSK9i, generating a total budget impact of 19 billion Euros at annual treatment costs of 8500 Euros. Taking into consideration this budgetary effect, it is evident that access to PCSK9i should be focused on patients with cardiovascular disease at an extremely high risk of recurrent events and an LDL-C markedly above the target value of 70 mg/dl (1.8 mmol/l). The recently presented TIMI risk score for Secondary Prevention (TRS2P) may offer an easy-to-use instrument to stratify patients with prevalent CAD according to their global risk [18]. This score has been validated empirically in the FOURIER trial [35]. In the placebo group of the FOURIER study, the three years incidence rate for the key secondary endpoint (cardiovascular death, non-fatal myocardial infarction or stroke) sharply increased between a score of 4 and 5 points or more [35]. As age should not be a criterion to drive the prescription of PCSK9i [36], we modified the TRS2P score by replacing age with the diagnosis of FH (which has been acknowledged as a high-risk condition recently [1]). The hazard ratios for cardiovascular mortality and the calculated annual rates of fatal and non-fatal cardiovascular events increased continuously and in parallel with the modified TRS2P score, with a sharp increase occurring at a score of 2 and 3 points (Supplementary Table 1). We then sought to determine the proportion of CAD patients in whom the LDL-C level on conventional treatment would remain above 100 mg/dl (2.6 mmol/l) (assuming a reduction of LDL-C by 50% which might be optimistic), and who display 3 or more points in the modified TRS2P score. Approximately 5.7% or 340,000 of German CAD patients would meet these criteria and would be eligible for PCSK9i treatment (Table 2, bold fields).

It might also be tempting to examine the cost-effectiveness of PCSK9 inhibition in the subpopulation for which we propose treatment (at least three comorbidities and LDL-C above 100 mg/dl (2.6 mmol/l) on conventional oral lipid-lowering). This subpopulation includes 5.7% (84 individuals) of the study sample and may therefore be too small to generate any reliable estimate. We also believe that cost-effectiveness estimates provided with Fig. 4 for all patients with more than three comorbidities (regardless of LDL cholesterol) already reflect the cost-effectiveness in the “eligible” subgroup: The event rate in the 84 patients in the “eligible” subgroup (bold fields of Table 2) was 26 (31%) and is very similar to the event rate of 201 (35.5%) in those 565 patients with TRS2P greater 3 and “treated” LDL-C below 100 mg/dl ($p > .05$ on chi square testing). The event rate (and correspondingly the cost-effectiveness) within this very high-risk population may therefore not be driven by LDL-C any more. In line with this, the TRS2P does not include LDL cholesterol as risk marker.

An ESC and EAS Task force [36] has proposed the use of PCSK9i in patients with CAD who either have an LDL-C of 140 mg/dl (3,6 mmol/l) or more in the absence, or 100 mg/dl (2,6 mmol/l) or more in the presence of additional markers for high risk (such as familial hypercholesterolemia, diabetes mellitus, or extensive or progressive ASCVD). When we applied the ESC/EAS criteria to the LURIC database, we estimated that approximately 5% (or 300,000) of German patients with CAD would have an indication for PCSK9 inhibition. Thus, our considerations are consistent with those of the ESC/ EAS Task force [36]; equally, the Task Force risk stratification criteria may be used and implemented. An advantage of the TRS2P score may, however, be that it has been empirically validated in two clinical trials [18,35], while this is not the case for the ESC / EAS criteria. Yet, underreporting of comorbidities may encumber the correct use of the TRS2P score. The treatment of 300,000 German CAD patients with PCSK9i would generate a budgetary impact of approximately 2.55 billion Euros at current drug prices. Health politicians and payers will have to decide in which patients and at what cost the prescription of PCSK9i is warranted. Therein, a “highest-risk-highest benefit” strategy [37] will clearly have to be pursued at current drug prices. In addition, the manufacturers of PCSK9i biologics should seriously consider the possibility of offering price cuts to facilitate both access and uptake of this highly innovative, beneficial and safe treatment strategy by the medical community.

Our study has limitations. As the two cardiovascular outcome trials

involving PCSK9i were of short duration, some uncertainty remains with respect to the reduction of cardiovascular event risk achieved by long-term treatment. Participants in the LURIC study were recruited between 1997 and 2001; since that time, secondary prevention has changed markedly, such that we may have overestimated risk at baseline. However, there is evidently no alternative approach to collect real world data on the long-term prognosis of CAD patients as waiting. Further, we did not account for a potential impact of life style interventions which hold a substantial potential but might be hard to achieve.

Another indication for PCSK9i treatment is severe FH in which an especially high risk of ASCVD is evident due to lifelong exposure to LDL-C (7% or more per year); such risk has not however been addressed in the current analysis. Finally, our findings apply to a Caucasian population recruited in Central Europe and may not be transferrable to other ethnicities or geographical regions.

5. Conclusion

PCSK9i treatment appears to be cost-effective individually at ICER thresholds with costs in the range of 100,000 to 150,000 Euros per QALY; nonetheless, the absolute budget impact of widespread utilization of these drugs would be prohibitive. As long as drug costs are maintained at current levels, we consider it prudent to focus the use of PCSK9i on CAD patients with concomitant risk factors at very high risk. Based on event rates in this LURIC cohort, patients at very high risk are exemplified by men exhibiting an annual risk of 10% or more for coronary and/or cerebrovascular events, and women at 8% annual risk or greater for such events; such individuals typically display three or more comorbidities according to our modified TRS2P score including FH. Under these circumstances, PCSK9i treatment should be initiated only after use of other lipid-lowering agents (at least statins and ezetimibe) at their maximally tolerated dose have failed to reduce LDL-C to goal.

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