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FULL RESEARCH PAPER

The need for PCSK9 inhibitors and associated treatment costs according to the 2019 ESC dyslipidaemia guidelines vs. the risk-based allocation algorithm of the 2017 ESC consensus statement: a simulation study in a contemporary CAD cohort

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Background The recently updated European Society of Cardiology (ESC) dyslipidaemia guidelines recommend a lower low-density lipoprotein cholesterol (LDL-C) goal of <55 mg/dL for patients with atherosclerotic cardiovascular disease (ASCVD), with a concomitant Class IA upgrade for proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9i) for patients not reaching their LDL-C goal under conventional lipid-lowering therapy.

Aims We aim to quantify the need for PCSK9i and the related costs to achieve the revised LDL-C goal in ASCVD patients compared to former ESC recommendations, in particular the risk-based 2017 ESC consensus update.

Methods and results We included patients with ASCVD from an observational cohort study ongoing since 2015. A Monte Carlo simulation incorporating a treatment algorithm adding sequentially a statin, ezetimibe, and a PCSK9i was applied with consideration of partial and total statin intolerance. The need for PCSK9i was calculated for three different ESC recommendations (2019 guidelines, 2016 guidelines, 2017 consensus update). Preventable events and treatment costs due to PCSK9i were calculated for a range of annual event rates from 2% to 8% and annual treatment costs of ca. 6050 €. We included 1780 patients (mean age 69.5 years). Median LDL-C at baseline was 85.0 mg/dL, with 61% of patients taking lipid-lowering medication. The need for PCSK9i was simulated to be 42.0% (ESC 2019), 31.9% (ESC 2016), and 5.0% (ESC 2017). The LDL-C goals were achieved in 97.9%, 99.1%, and 60.9% of patients, respectively. Annual treatment cost for PCSK9i per 1 000 000 ASCVD patients would be 2.54 billion € (ESC 2019) compared to 0.30 billion € (ESC 2017). Costs per prevented event due to PCSK9i initiation differed widely, e.g. 887 000 € for an event rate of 3% and a treatment goal of <55 mg/dL compared to 205 000 € for an event rate of 7% and risk-based use of PCSK9i.

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Conclusion The revised LDL-C treatment goals increase the projected need for PCSK9i with a substantial increase in associated treatment cost. An allocation strategy based on residual LDL-C and clinical or angiographic risk factors leads to a more tailored target population for PCSK9i with a reasonable benefit/cost ratio.

Keywords Atherosclerotic cardiovascular disease • LDL-C • PCSK9 inhibitors • Target population

Introduction

The accumulation of low-density lipoprotein cholesterol (LDL-C) in the vascular wall initiates and maintains the atherosclerotic cascade.[1] In particular for patients with prevalent atherosclerotic cardiovascular disease (ASCVD), the reduction of LDL-C is associated with an improved outcome and a decrease of further ASCVD events.[2] Recently developed monoclonal antibodies against proprotein convertase subtilisin/kexin type 9 (PCSK9) lead to a potent reduction of LDL-C in addition to standard lipid-lowering medication (LLM) with statins and ezetimibe. The use of PCSK9 inhibitors (PCSK9i) has been demonstrated to be safe and to be associated with a further reduction of major cardiovascular events.[3,4] In order to account for this evidence, the European Society of Cardiology (ESC) published new guidelines on the management of dyslipidaemias in August 2019.[5] In these, the LDL-C treatment goal for patients with documented ASCVD was lowered from <70[6] to <55 mg/dL combined with a ≥50% reduction compared to pre-treatment LDL-C levels (Class IA recommendation). Concomitantly, the use of PCSK9i in patients not achieving their LDL-C goal under combination therapy with a high-intensity statin and ezetimibe was upgraded from a Class IIB to a Class IA recommendation. As a result of the new guidelines, more patients will be eligible for treatment with PCSK9i. Due to the high treatment costs currently associated with PCSK9i and the lack of cost-effectiveness analyses of the new guidelines, the health economic impact of the current recommendations remains unclear. Previous work by Cannon *et al.*[7] estimated that 14% of patients with ASCVD would be eligible for PCSK9 inhibition after maximized oral LLM when considering an LDL-C goal of <70 mg/dL. More recently, Allahyari *et al.*[8] simulated a need of 51% for PCSK9i when applying an LDL-C goal of <55 mg/dL combined with a ≥50% reduction from baseline to a nationwide registry of post-myocardial infarction patients. However, due to the underlying registry-based design, these studies lacked detailed patient characteristics required for the comparison of these rates with an individualized risk-based allocation algorithm as recommended by the ESC consensus statement 2017, which still reflects current clinical practice. Therefore, we set out (i) to calculate the proportion of patients eligible for PCSK9i considering the LDL-C goal of <55 vs. <70 mg/dL in a precisely characterized contemporary coronary artery disease (CAD) cohort, (ii) to evaluate an allocation strategy taking into account angiographic and clinical risk factors based on the previously applicable ESC consensus statement concerning the use of PCSK9i,[9] and (iii) to apply our findings to treatment cost considerations.

Methods

The INTERCATH study is an observational cohort study ongoing since January 2015 including patients undergoing coronary angiography at the University Heart and Vascular Center Hamburg. The study protocol of the INTERCATH study was approved by the Ethics Committee of Hamburg, Germany (PV4303). Each patient gave written informed consent. Design and rationale have been described in detail previously.[10–12]

Inclusion and exclusion criteria

Patients <18 years of age or incapable to give written informed consent or patients without sufficient knowledge of the German language were not considered for inclusion. Furthermore, all patients with cardiogenic shock, life-threatening arrhythmias, or other circumstances of haemodynamic instability were not screened for inclusion in the INTERCATH cohort. For the present analysis, all patients with chronic ASCVD [angiographically documented CAD, history of peripheral artery disease (PAD), or history of stroke] were included. We excluded patients without cholesterol-measurements, patients without specified lipid-lowering therapy, patients presenting with acute myocardial infarction, and patients with dialysis-dependent chronic kidney disease (Supplementary material online, *Figure S1*).

Assessment of lipid-lowering medication

Lipid-lowering medication, specifying drug and dosage, was assessed by questionnaire and written medical reports. In cases where LLM had been altered within 7 days before study inclusion, the last medication before alteration was used. High-intensity statin therapy was defined as Rosuvastatin ≥20 mg per day or Atorvastatin ≥40 mg per day. All other statin therapy was classed as moderate intensity.

Assessment of comorbidities and cardiovascular risk factors

Comorbidities were assessed by a questionnaire at enrolment as well as written medical reports. Patients taking antihypertensive medication or with arterial hypertension documented as a diagnosis in a written medical report were classified to have arterial hypertension. Patients were defined to have diabetes mellitus in the case of intake of oral blood glucose-lowering therapy, regular substitution of insulin, HbA1c levels >6.5%, or documented diabetes in a written medical report.

Assessment of atherosclerotic cardiovascular disease risk severity

Patients with at least one of the following clinical/angiographic criteria were classed as having ASCVD with an additional index of risk severity based on the ESC consensus statement 2017:[9] diabetes mellitus + smoking, diabetes mellitus + systolic blood pressure at inclusion ≥160 mmHg, diabetes mellitus + chronic kidney disease (estimated glomerular filtrations rate < 60 mL/min/1.73 m^2), CAD + history of PAD, three-vessel CAD, left main disease (lesion-specific Gensini score ≥10), involvement of the proximal left anterior descending coronary artery (lesion-specific Gensini score ≥5), and rapidly progressing CAD (repeated acute coronary syndromes or unplanned coronary interventions within 5 years of the index event).

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Laboratory methods

All blood samples were drawn from a peripheral vein before coronary angiography. Blood counts, renal function parameters, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and HbA1c at baseline were determined directly after sampling by standardized routine laboratory methods. Low-density lipoprotein cholesterol was calculated using the Friedewald formula. In $n = 72$ patients where the Friedewald formula could not be applied due to hypertriglyceridaemia, LDL-C was defined as non-HDL-C minus 30 mg/dL.

Simulation treatment algorithm

We used an established Monte Carlo simulation model to simulate an intensification of LLM according to recommendations by the 2019 ESC guidelines.[5,7,8] In a first step, we calculated the baseline LDL-C of patients pre-treated with LLM using the LDL-C reduction of the specific LLM, which was sampled from β probability density functions derived from clinical trials (Supplementary material online, *Table S1*). For treatment-naive patients, the LDL-C at inclusion was set as the baseline LDL-C. Next, a treatment algorithm as detailed in *Figure 1* was applied, sequentially uptitrating to the highest tolerated statin dose (maximum Atorvastatin 80 mg per day), followed by addition of ezetimibe (10 mg per day) and evolocumab (140 mg biweekly or 420 mg monthly) in case of a missed treatment goal. Three main scenarios were considered: (i) LDL-C treatment goal <55 mg/dL and a ≥50% reduction from baseline LDL-C (ESC guidelines 2019), (ii) LDL-C treatment goal <70 mg/dL and a ≥50% reduction from baseline LDL-C (ESC guidelines 2016), and (iii) use of PCSK9i restricted to (a) patients with a residual LDL-C >140 mg/dL and (b) patients with residual LDL-C >100 mg/dL with clinical or angiographic risk factors (based on the ESC consensus update 2017) as detailed in the section on Assessment of atherosclerotic cardiovascular disease risk severity. Additional calculations were performed for each scenario without the requirement of a ≥50% LDL-C reduction. The achieved LDL-C concentration under a given treatment was calculated using a probabilistically chosen treatment effect sampled from β probability density functions for each drug and dose (Supplementary material online, *Table S1*). The treatment algorithm was run 1000 times on the baseline cohort of 1780 ASCVD patients, yielding a simulation cohort of 1 780 000 patients. Due to the individual treatment effects for each step of treatment intensification being chosen anew for every run, each patient in the simulation cohort traced a unique path through the algorithm.

Statin intolerance

We defined partial statin intolerance as the inability to tolerate a high-intensity statin and full statin intolerance as the inability to tolerate any statin at any dose. We set a fixed rate of 10% partial intolerance and 2% full intolerance for the whole study population, in line with data from previous meta-analyses and studies.[13–15] Patients with partial statin intolerance were randomly selected from the subgroup of patients on a moderate-intensity statin or no statin therapy at inclusion. Patients with full statin intolerance were randomly selected from the subgroup of patients with no statin therapy at inclusion, whilst patients on monotherapy with ezetimibe were directly classed as fully statin intolerant. Statin intolerance was allocated anew for each run of the Monte Carlo simulation according to these principles. Partially statin intolerant patients were uptitrated to Atorvastatin 20 mg per day, followed by ezetimibe and a PSCK9i, whilst fully statin intolerant patients received ezetimibe directly followed by a PCSK9i.

Treatment cost calculations

Based on the residual LDL-C levels pre-PCSK9i, assuming an average LDL-C reduction of 59% by PCSK9i[3] and taking into account the established rate of a 22% relative risk reduction (RRR) for cardiovascular events per 38.7 mg/dL (1 mmol/L) LDL-C reduction,[2] we calculated RRRs for the PCSK9i target populations in the three scenarios. We then calculated potential absolute risk reductions and preventable cardiovascular events for a range of annual event rates from 2% to 8%. Assuming annual treatment costs for PCSK9i of 6049 € per patient,[16] we determined the cost per prevented event per year as well as overall annual treatment cost per 1 000 000 ASCVD patients.

Statistical analyses

Continuous variables are shown as mean ± standard deviation or as median (25th percentile, 75th percentile), whereas binary variables are shown as absolute numbers and percentages. For each run of the Monte Carlo simulation, the proportion of patients achieving their treatment goal as well as the distribution of LLMs was recorded. We report means and 95% confidence intervals for the final medications based on the 1000 runs. All statistical tests were computed using R version 3.5.2 (20 December 2018).

Results

Baseline characteristics

The baseline characteristics of the study cohort are shown in *Table 1*. Of a total of 1780 patients, 25.1% ($n = 446$) were female. The mean age of the study cohort was 69.5 ± 10.7 years. Prior to coronary angiography, an ASCVD was known in 1242 (71.8%) patients. Median LDL-C was 85.0 mg/dL with an interquartile range of 65.0 – 114.0 mg/dL. 15.1% and 31.5% of patients had an LDL-C <55 and <70 mg/dL, respectively. 61.3% of patients were taking LLM (48.4% monotherapy with a moderate-intensity statin, 7.9% monotherapy with a high-intensity statin, 4.1% combination therapy of any statin with ezetimibe, 0.9% ezetimibe only). Considering the subgroup of patients with known ASCVD prior to coronary angiography, 18.0% and 37.7% had an LDL-C <55 and <70 mg/dL, respectively, whilst 75.1% were taking LLM. *Figure 2A* and Supplementary material online, *Figure S2* show the LDL-C distributions and LLM at study inclusion for the entire study population and the subgroup with history of ASCVD, respectively. The further cardiovascular risk factors were distributed as follows: arterial hypertension 92.6%, current smoking 27.2%, and diabetes mellitus 31.1%.

Simulation of intensification of lipid-lowering medication

Figure 2B demonstrates the simulated LDL-C distributions and LLMs for scenarios 1–3. In scenario 1, 97.9% of patients reached their LDL-C treatment goal of <55 mg/dL and a ≥50% reduction from baseline, the required medications being: 30.3% statin monotherapy, 27.6% combination therapy of any statin with ezetimibe, and 42.0% any therapy containing a PCSK9i.

In scenario 2, more patients obtained their treatment goal of <70 mg/dL and a ≥50% reduction from baseline on a statin monotherapy (38.7%), with 29.3% requiring a combination therapy of any statin with ezetimibe, whilst only 31.9% required the use of a PCSK9i. Under these medications, 99.1% of patients reached their LDL-C treatment goal.

In scenario 3, 57.9% and 68.1% of patients reached the LDL-C treatment goals of <50 mg/dL and a ≥50% reduction and <70 mg/dL

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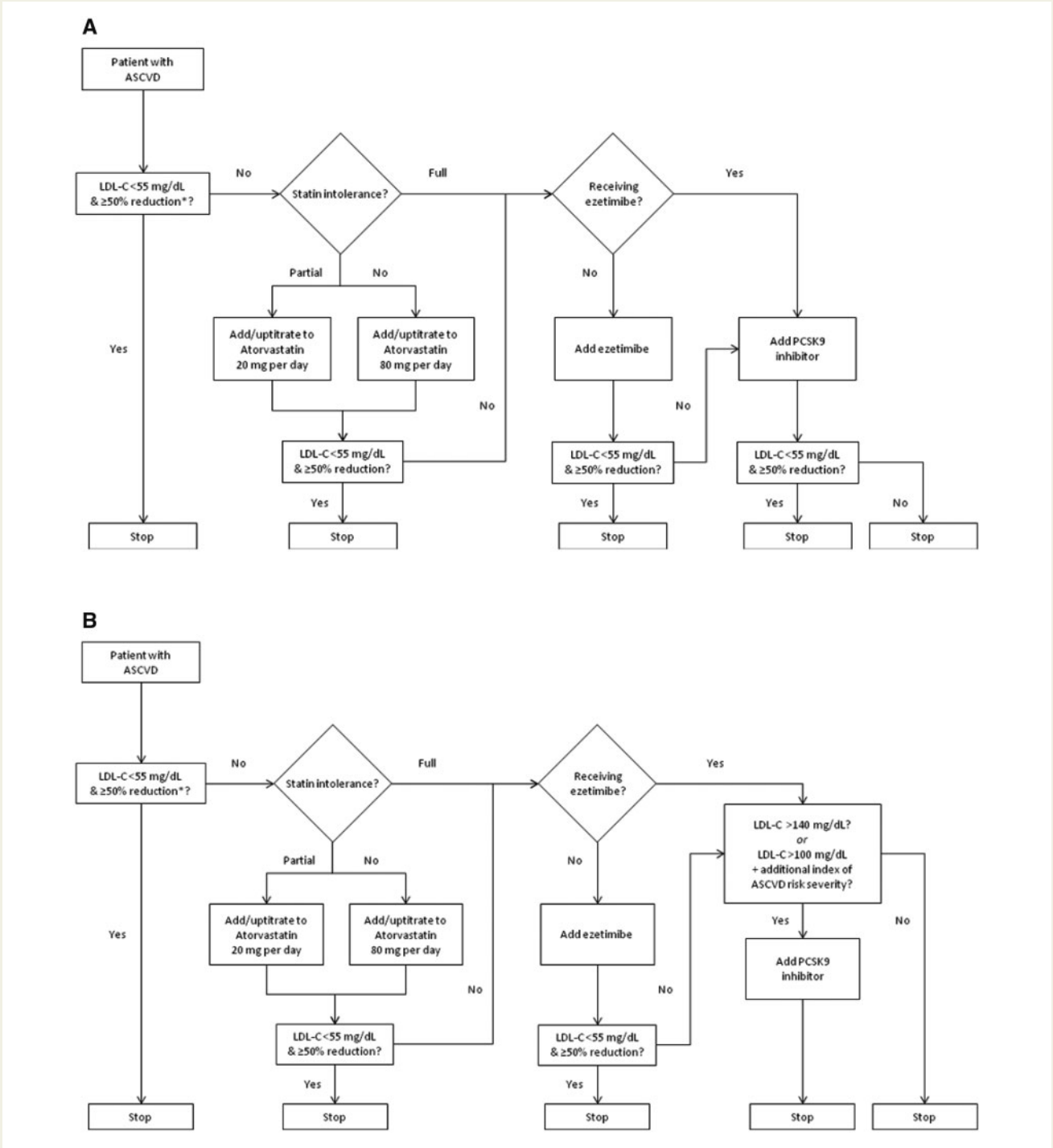

Figure 1 Algorithms for treatment intensification of lipid-lowering medication. (*A*) Exemplary algorithm for scenario 1 (low-density lipoprotein cholesterol treatment goal <50 mg/dL and ≥50% reduction from baseline). Algorithm for scenario 2 (low-density lipoprotein cholesterol treatment goal <70 mg/dL and ≥50% reduction from baseline) analogous. (*B*) Algorithm for scenario 3 (risk and residual LDL-C-based use of PCSK9 inhibitors). For definition of indices of ASCVD severity and statin intolerance, see sections Assessment of atherosclerotic cardiovascular disease risk severity and Statin intolerance. *In patients pre-treated with lipid-lowering medication, the low-density lipoprotein cholesterol reduction from baseline was evaluated using the low-density lipoprotein cholesterol reducing efficacy of the specific medication. ASCVD, atherosclerotic cardiovascular disease; LDL-C, low-density lipoprotein cholesterol; PCSK9, proprotein convertase subtilisin/kexin type 9.

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Table 1 Baseline characteristics of the study cohort

Patient characteristics	All (*N* = 1780)
Age (years)	69.5 ± 10.7
Female gender (%)	446 (25.1)
ASCVD	
History of ASCVD (%)	1242 (71.8)
History of CAD (%)	1104 (64.5)
History of PCI (%)	703 (65.3)
History of MI (%)	467 (26.9)
History of CABG (%)	235 (13.4)
History of PAD (%)	206 (11.9)
History of stroke (%)	216 (12.4)
Current CAD (%)	1734 (97.4)
Gensini score	13.5 (4.3–37.0)
Lipid-lowering medication	
Intake of cholesterol-lowering drugs (%)	1091 (61.3)
Statin monotherapy (%)	1002 (56.3)
Statin combined with ezetimibe (%)	73 (4.1)
Ezetimibe monotherapy (%)	16 (0.9)
High-intensity statin (%)	163 (9.2)
Moderate-intensity statin (%)	912 (51.2)
Ezetimibe (%)	89 (5.0)
Lipid status	
Total cholesterol (mg/dL)	159.0 (135.0–193.0)
Non-HDL cholesterol (mg/dL)	111.00 (87.4–143.6)
LDL cholesterol (mg/dL)	85.0 (65.0–114.0)
HDL cholesterol (mg/dL)	45.0 (37.0–56.0)
Cardiovascular risk factors	
Diabetes (%)	549 (31.1)
Arterial hypertension (%)	1646 (92.6)
Ex-smoking (%)	286 (16.7)
Current smoking (%)	466 (27.2)
Body mass index (kg/m^2)	26.8 (24.1–30.5)
Laboratory parameters	
Haemoglobin (g/dL)	13.1 (11.8–14.2)
Serum creatinine (mg/dL)	1.00 (0.84–1.23)
HbA1c (%)	5.7 (5.4–6.3)

Categorical variables presented as number (percentage) of patients. Continuous variables presented as mean ± standard deviation or as median (25th percentile, 75th percentile). Differences to total *N* are due to missing values; the calculation of proportions does not include missing values in the denominator.
ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; CAD, coronary artery disease; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein; MI, myocardial infarction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

and a ≥50% reduction, respectively, without the use of a PCSK9i. Of the remaining patients, only 5.0% were classed as eligible for PCSK9 inhibition (see Supplementary material online, *Table S2* for classification details). The overall rate of treatment goal attainment after addition of PCSK9i rose marginally to 60.9% and 72.1%, respectively.

Supplementary material online, *Figure S3* demonstrates the results for the simulation without the requirement of a ≥50% reduction of LDL-C from baseline levels. Supplementary material online, *Table S3* details the 95% confidence intervals for the proportion of ASCVD patients by lipid-lowering therapy for the different scenarios.

Treatment cost considerations

The median residual LDL-C values of patients receiving PCSK9i before their initiation were 67.7 mg/dL (scenario 1), 73.9 mg/dL (scenario 2), and 125.8 mg/dL (scenario 3). Assuming a 59% average LDL-C reduction by PCSK9i,[3] the LDL-C would be reduced by 39.9, 43.6, and 74.2 mg/dL due to PCSK9i (see *Table 2*). Assuming a 22% average RRR for a cardiovascular event per year per 1 mmol/L (38.7 mg/dL) LDL-C reduction[2] yields RRRs of 22.7%, 24.8%, and 42.2% for scenarios 1–3.

Table 2 additionally shows the annual treatment cost given the current annual treatment cost per patient of 6049 € for evolocumab in Germany. Per 1 000 000 ASCVD patients the resulting annual treatment cost would be 2.54, 1.93, and 0.30 billion € for scenarios 1–3.

Table 3 shows the cost per prevented cardiovascular event per annum (p.a.) for the different scenarios and a range of annual cardiovascular event rates. For example, scenario 1 and an assumed event rate of 3% yielded a cost per prevented event of 887 000 € p.a., whilst the risk- and LDL-C-based allocation algorithm of scenario 3 and an assumed event rate of 7% results in a more favourable 205 000 € p.a.

Discussion

The main findings of the present study are (i) the current ESC guidelines on the management of dyslipidaemias substantially increase the projected need for PCSK9i compared with former recommendations and (ii) an allocation strategy based on individual risk factors and LDL-C levels reduces the target population for PCSK9i and lowers the cost per prevented cardiovascular event due to the higher absolute risk reduction and conceivable higher cardiovascular event rates in this specified subgroup.

Lipid-lowering medication and low-density lipoprotein cholesterol levels at study inclusion

Our cohort consists of patients with documented ASCVD, the vast majority (97.4%) of which being patients with chronic coronary syndromes. Any patient with a documented ASCVD is classed by the dyslipidaemia guidelines to be in the very high-risk category of cardiovascular risk, to which the newly recommended LDL-C goal of <55 mg/dL applies. Less than one-fifth of the subgroup with known ASCVD prior to coronary angiography achieved this goal at study inclusion, whilst little more than one-third of patients achieved the previously applicable goal of <70 mg/dL. The failure to meet LDL-C treatment goals is a frequent finding of a comparable magnitude in ASCVD cohorts,[17–20] with an even larger discrepancy between observed and recommended LDL-C levels due to the new dyslipidaemia guidelines.[21] Furthermore, only 75% of patients in the subgroup with known ASCVD were taking LLM at study inclusion, highlighting the untapped potential of LLM treatment intensification prior to initiation of PCSK9i.[20]

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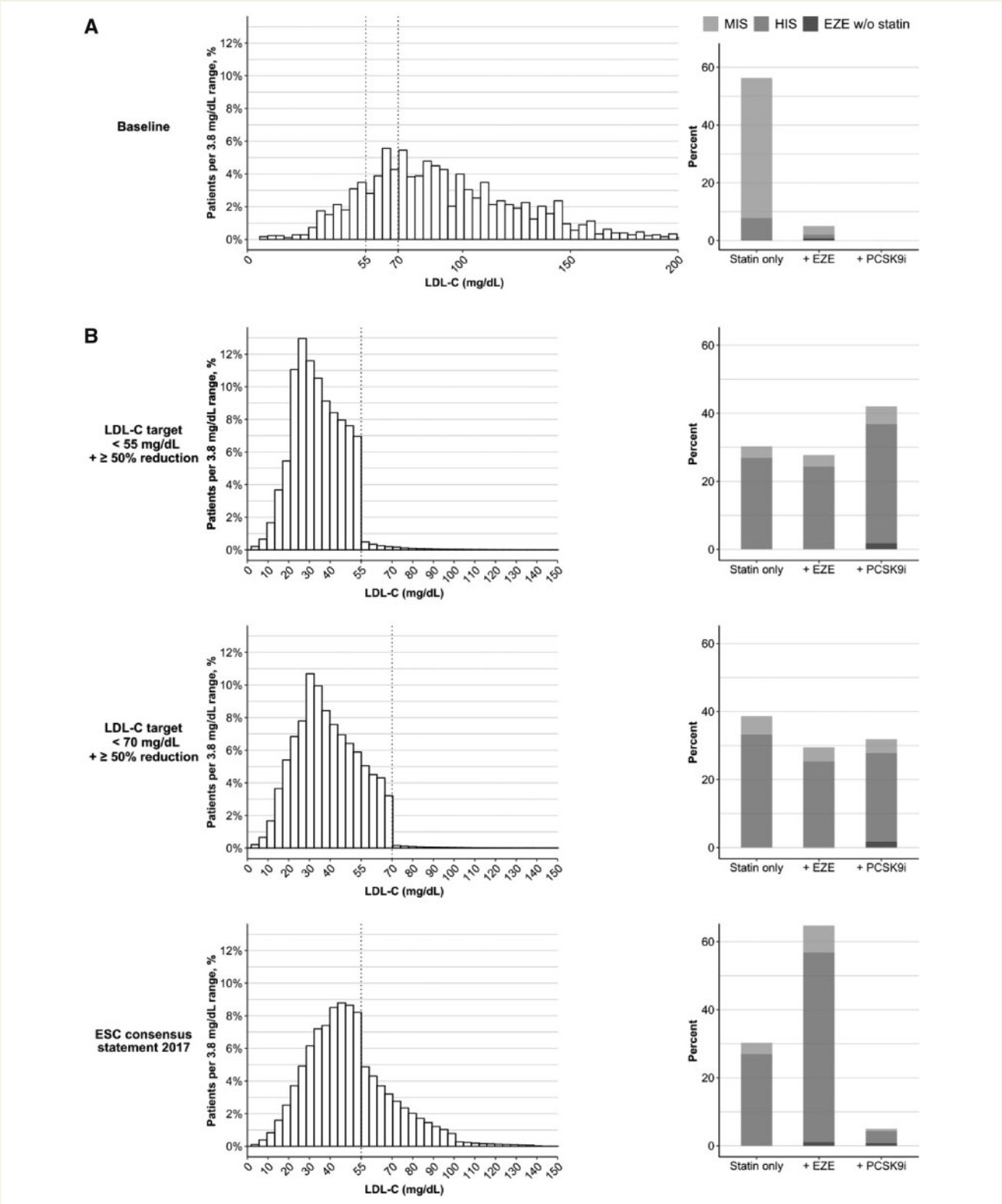

Figure 2 Low-density lipoprotein cholesterol distributions and lipid-lowering medications (*A*) at baseline (*B*) after uptitration of lipid-lowering medication according to scenarios 1–3. Note that 0.96% of patients had baseline low-density lipoprotein cholesterol values >200 mg/dL (data points not shown). For the baseline medication, difference to 100% is due to patients not taking lipid-lowering medication. ESC, European Society of Cardiology; EZE, ezetimibe; HIS, high-intensity statin; LDL-C, low-density lipoprotein cholesterol; LLM, lipid-lowering medication; MIS, moderate-intensity statin; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors.

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Table 2 Achieved relative risk reductions and annual treatment cost for evolocumab per 1 000 000 ASCVD patients

Scenario	Median LDL-C pre-PCSK9i (mg/dL)	Median LDL-C under PCSK9i (mg/dL)	Absolute Δ LDL-C due to PCSK9i (mg/dL)	Achievable RRR (%)	Projected PCSK9i use (%)	N eligible for PCSK9i/1 000 000 ASCVD patients	Treatment cost p.a. (€)/1 000 000 ASCVD patients
Scenario 1 (LDL-C < 55 mg/dL and ≥50% reduction)	67.7	27.8	39.9	22.7	42.0	420 000	2 540 580 000
Scenario 2 (LDL-C < 70 mg/dL and ≥50% reduction)	73.9	30.3	43.6	24.8	31.9	319 000	1 929 631 000
Scenario 3 (risk and LDL-C-based ESC 2017 algorithm)	125.8	51.6	74.2	42.2	5.0	50 000	302 450 000

Assumptions: 59% average LDL-C reduction by evolocumab, 22% average relative risk reduction for a CV event per year per 1 mmol/L (38.7 mg/dL) LDL-C reduction, 6049 € p.a treatment cost for evolocumab.
ASCVD, atherosclerotic cardiovascular disease; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein-cholesterol; p.a., per annum; PCSK9i, proprotein convertase subtilisin/kexin type 9 inhibitors; RRR, relative risk reduction.

Table 3 Prevented cardiovascular events per 1 000 000 ASCVD patients per annum and the corresponding cost per prevented event for the three different scenarios (rows) according to a cardiovascular event rates ranging from 2% to 8% per annum (columns)

Scenario		CV event rate p.a. (%)						
		2	3	4	5	6	7	8
Scenario 1 (LDL-C < 55 mg/dL and ≥50% reduction)	Prevented CV events p.a. per 1 000 000 patients	1909	2863	3818	4772	5727	6681	7635
	Cost/prevented CV event p.a. (€)	1 330 958	887 305	665 479	532 383	443 653	380 274	332 740
Scenario 2 (LDL-C < 70 mg/dL and ≥50% reduction)	Prevented CV events p.a. per 1 000 000 patients	1583	2374	3165	3956	4748	5539	6330
	Cost/prevented CV event p.a. (€)	1 219 295	812 863	609 647	487 718	406 432	348 370	304 824
Scenario 3 (risk and LDL-C-based ESC 2017 algorithm)	Prevented CV events p.a. per 1 000 000 patients	422	633	845	1056	1267	1478	1689
	Cost/prevented CV event p.a. (€)	716 263	477 509	358 131	286 505	238 754	204 647	179 066

Large absolute LDL cholesterol reductions and high cardiovascular event rates yield favourable cost per prevented event ratios for PCSK9 inhibitors.
CV, cardiovascular; ESC, European Society of Cardiology; LDL-C, low-density lipoprotein cholesterol; p.a., per annum; PCSK9, proprotein convertase subtilisin/kexin type 9.

Need for PCSK9 inhibitors

As to be expected, the need for PCSK9i is dependent on the ambition of the LDL-C treatment goal, varying from 42.0% (scenario 1) to 31.9% (scenario 2) to 5.0% (scenario 3). With 42.0% we thus find a slightly lower need for PCSK9i than a simulation of post-myocardial infarction patients in the SWEDEHEART register (50.7% for a treatment goal of <55 mg/dL and a ≥50% reduction from baseline)[8] as well as a further recent simulation of post-acute coronary syndrome patients in a Swiss cohort (51.0% for a treatment goal of <55 mg/dl, albeit using a different methodology).[22] A reason for this difference might be that these were patients with an acute coronary event, with fewer receiving LLM at inclusion (20% and 25%, respectively) and higher baseline LDL-C levels (120 and 126 mg/dL, respectively). Applying a goal of 70 mg/dL without a requirement on ≥50% reduction of the baseline LDL-C, Cannon *et al.*[23] found a need for PCSK9i of 16.6% in a mixed ASCVD cohort from an administrative database from US medical and pharmacy claims when accounting for 10% partial and 2% full statin intolerance. Our main analysis for the treatment goal of 70 mg/dL accounting also for a ≥50% reduction from baseline found a higher rate (31.9%). However, an additional analysis of our cohort without the requirement for a

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relative reduction found a comparable PCSK9i need of 18.3% (see Supplementary material online, *Table S3*).

Treatment cost considerations for the use of PCSK9 inhibitors

Whilst it is encouraging that 58% of patients in our model would achieve the new LDL-C treatment goal of <55 mg/dL with a consequent application of conventional LLM consisting of statins and ezetimibe, a 42% projected use of PCSK9i in ASCVD patients would be barely affordable for any healthcare system. In 2018, the non-private (statutory) German health insurances, covering ~90% of the population, spent 38.7 billion € on pharmaceuticals.[24] Given a population of ca. 83 million (86% of which adults) and a prevalence of CAD of 4.8% averaged over the whole adult population,[25] a use of PCSK9i in 42% of these 3.4 million patients would result in annual treatment cost for PCSK9i of over 8.7 billion €, equivalent to almost a quarter of all current pharmaceutical expenditure. Cost would be even higher when also considering patients with other atherosclerotic manifestations, such as PAD. Clearly, an allocation strategy for PCSK9i taking into account the expected benefit based on pre-PCSK9i LDL-C levels and the individualized risk for subsequent ASCVD events whilst balancing treatment cost is required.

Subgroup analyses from the FOURIER and the ODYSSEY trials provide evidence that patients with greater severity of ASCVD or polyvascular ASCVD and patients with baseline LDL-C level of >100 mg/dL benefit most from PCSK9 inhibition, driven by higher cardiovascular event rates and large absolute LDL-C reductions, respectively.[4,26,27] Both the ESC in 2017 and the AHA/ACC in 2018 published recommendations concerning the use of PCSK9i taking into account the pre-PCSK9i LDL-C levels and the absolute cardiovascular risk as the key determinants of expected clinical benefit,[9,28] although the ESC consensus statement has since been superseded by the new dyslipidaemia guidelines. We demonstrate here that an algorithm based on the ESC 2017 consensus statement considerably reduces the projected use of PCSK9i to ~5% of the highest risk ASCVD patients. Due to higher pre-PCSK9i LDL-C levels in these patients the relative cardiovascular risk reduction through PCSK9i is almost double the value compared to the reduction when any patient with an LDL-C ≥55 mg/dL despite maximized oral LLM is treated with a PCSK9i as recommended by the 2019 ESC Guidelines (42.2% vs. 22.7%, *Table 2*). This translates into lower costs per prevented event for a given event rate for scenario 3 (*Table 3*, read vertically). The difference between costs per prevented event is further accentuated when taking into account differing cardiovascular event rates across subpopulations with ASCVD. An analysis of the IMPROVE-IT trial showed that average annual cardiovascular event rates over a 7-year follow-up period diverge drastically between 1.2% and 9.8% when patients are stratified according to readily available clinical characteristics such as history of PAD, prior coronary artery bypass graft, diabetes mellitus, or smoking.[29] Hence *Table 3* should also be read diagonally, as higher annual cardiovascular event rates in high-risk populations further lower the cost per prevented cardiovascular event.

Although a full cost-effectiveness analysis is beyond the scope of this manuscript, our data support results from the most recent cost-effectiveness analysis of evolocumab in patients with very high-risk ASCVD which found ICERs of <50 000 $/quality-adjusted life-year gained for any baseline cardiovascular event rate of 6.9 or more events per 100 patient-years,[30] a threshold deemed as 'high-value'. From a public health perspective, particular care should be assigned to identifying ASCVD patients at very high cardiovascular risk who are young and still part of the workforce. PSCK9i could play a crucial part in preventing early mortality and long-term morbidity associated with cardiovascular disease in this subgroup, with positive societal and economic effects. In addition to preventing cardiovascular endpoints, PCSK9i were recently found to significantly improve quality of life in a younger cohort, driven by improved psychosocial factors, underlining a further dimension of potential clinical benefit.[31]

The future of tailored lipid-lowering therapy in the setting of secondary prevention for ASCVD patients thus lies in individualized risk stratification according to biomarkers, clinical characteristics, and angiographic risk factors, in order to select the patients with highest expected clinical benefit from cost-intensive lipid reduction.

Strengths and limitations

Strengths of the present study are (i) a very precise characterization of the study population with a complete segment-based scoring of the CAD severity for every patient which allowed us to apply the individualizing risk-based algorithm of the ESC Consensus statement 2017 compared to former registry-based studies in this field, (ii) the use of a very contemporary ASCVD cohort, with particular attention paid to ensuring the accuracy of the LLM recorded, and (iii) our model took into account full and partial statin intolerance to a realistic degree and also considered the variability of LDL-C reductions between different patients in response to LLM.

Some caveats should, however, be considered: (i) our study population is drawn from a single-centre cohort based in a German university clinic, and the study findings might thus not be completely generalizable to other international ASCVD populations or different healthcare settings. Particularly, the older age of the study cohort with a large fraction of retired people might weaken our considerations concerning the cost-effectiveness of PCSK9i. On the other hand, the INTERCATH cohort is an all-comers cohort without multiple inclusion or exclusion criteria ensuring a broad and representative spectrum of CAD patients. Furthermore, evolocumab has similar efficacy regardless of age, meaning our calculation of treatment cost per prevented event is valid over a broad age range.[32] (ii) Our study cohort excluded patients with acute myocardial infarction at baseline and those in life-threatening conditions, who arguably have an intrinsically higher cardiovascular event rate. Use of PCSK9i in these patients might be associated with an improved cost per prevented cardiovascular event due to their high baseline risk. However, the vast majority of ASCVD patients are patients in a chronic setting, to which our findings apply. (iii) Annual cost for PCSK9i treatment differs between countries. However, the ratios between cost per prevented event for the different scenarios remains unchanged regardless of the absolute treatment cost. (iv) No complete data was available for subtypes of strokes, meaning some patients might have entered the study on the basis of a non-ischaemic stroke. However, only 37 patients entered the study due to a stroke being their only ASCVD, of which 21 could be classed as non-haemorrhagic whilst 16 were of unknown type, therefore the risk of a non-warranted inclusion is low. (v) The simulation assumed full adherence to LLM at

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inclusion, which is unrealistic. It is likely that this led to an overestimation of baseline LDL-C values, as LDL-C efficacy was based on data from clinical trials with a high adherence rate. On the other hand, the same LDL-C efficacy data were used in the simulated treatment intensification. On balance, the two effects are likely to cancel each other out. (vi) Scenario 3 is likely to slightly underestimate the need for PCSK9 inhibition due to the lack of exact data on familial hypercholesterolaemia.

Overall, our study complements the existing literature on the need for PCSK9i by considering a contemporary and precisely characterized ASCVD cohort and applying a simulation based on reasonable assumptions. Furthermore, it demonstrates the efficacy of a risk-based algorithm to select patients for the use of PCSK9i.

Conclusion

The revised LDL-C treatment goals and the concomitant upgrade of PCKS9i to a Class IA recommendation in case of a missed treatment goal with conventional LLM substantially increase the projected need for PCSK9i. This results in costs which are hardly affordable for any health care system. An allocation strategy based on residual LDL-C and clinical or angiographic risk factors would lead to a smaller and more tailored target population for PCSK9i with a reasonable benefit/cost ratio.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology* online.

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