Proposition for Individualized Value-based PCSK9-inhibitor Prices:

A Statement for Health Care Authorities

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Introduction

Demand and supply, rationing of effective medicines, issues about prices and technology assessment models have to be addressed in a new way. New developments, increasing burden due to non-communicable diseases in an aging population, increasing health care costs are all phenomena that increase the risk of unjustified rationing in health care.

Cost for research and development (R&D) have to be in balance with expected sales and incomes (S&I). If such a situation is out of balance, e.g. by establishing toxic prices for a certain medication, legal issues about fraud must be considered. Financial toxicity has reached the discussion of pharmacy regulators [1] and may lead to a situation, where appropriate use of such medication must be rationed (regulatory limitation). Pharmaceutical enterprises are free to price their products in many markets including the US[1] and Europe. And retail prizes go up and up[2]. Aims to restrict free prizing to 0.5 Mia € per annum have been negotiated by the German political authorities and pharmaceutical companies[3]. However, pharmaceutical companies are key players in national economies and health care systems. This reinforces their power up to a situation, where the balance between the financial possibilities of national economies and pharmaceutical financial greed is lost.

The World Health Organization says: "Governments need to develop strategies and put appropriate legislation and sanctions into place to reduce corruption and criminal activity"[4]. The problem is: how can toxic pricing be defined and be made amenable to criminal complaints? Toxic pricing can be detected in two ways, when we consider the financial input and output of a pharmaceutical company. At the input level we count for costs due to R&D, marketing and regulatory frameworks. At the output level we can observe - over time - world wide realized revenues or we can estimate expected revenues per period of time. With both methods, estimates on input and output can be made and the likelihood of discrepancies between them can be established.

Within the legal framework in Switzerland, pharmaceutical companies face legal issues when prices reach levels of profiteering (Article 157 Swiss Criminal Law[5]), while on the other hand, medications granted by Swissmedic cannot legally be rationed by the Federal Office of Public Health [2].

Within this area of conflict therefore, both pharmaceutical companies and national health care authorities both produce a situation, which is not acceptable for those who need effective medical inventions.

Current pricing of PCSK9-inhibitors is 18.37 CHF per day and eventually reimbursed by health insurers, if a patient is in secondary prevention and has an LDL cholesterol above 3.5 mmol/l despite optical medical treatment. Occasionally, in patients having undergone a recent second cardiovascular event, also a PCSK9-inhibitor therapy in patients with an LDL above 2.5 mmol/l may be reimbursed at current prices.

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[1] https://hbr.org/2015/09/its-time-to-rein-in-exorbitant-pharmaceutical-prices
[2] https://www.aarp.org/content/dam/aarp/ppi/2014-11/rx-price-watch-report-AARP-ppi-health.pdf
[3] https://www.bundesgesundheitsministerium.de/fileadmin/Dateien/3_Downloads/P/Pharmadialog/Pharmadialog_Abschlussbericht.pdf
[4] https://www.aarp.org/content/dam/aarp/ppi/2014-11/rx-price-watch-report-AARP-ppi-health.pdf
[5] https://www.admin.ch/opc/de/classified-compilation/19370083/index.html#a157

This approach is therefore mainly LDL driven. However, the value of a therapy is mainly driven by a patient's risk and this risk should therefore be included for calculation of value-based prices. Based upon the published results of FOURIER and ODYSSEY, variables that are relevant for the calculation of treatment effects have become available (Table 1).

Table 1: Variables defining value of PCSK9-inhibitors

	Evolocumab	Alirocumab
Relative risk reduction RRR in % per 1 mmol/l LDL reduction	10.6	15.5
On treatment LDL reduction in % with	58	44
A patient's LDL level		
Risk in secondary prevention	Literature [3]	
Direct + indirect costs of a cardiovascular event over 10 years	251'000	
Choice of CHF/QALY that are acceptable	150'000	150'000
Bonus for R+D in %	25	25
Primary and secondary risk calculator	https://docfind.ch/AspirinStatinCompass.xlsx	

Clinical examples

Alice Meyer is a 65 year old female in secondary prevention with a treated blood pressure of 120 mm Hg, with diabetes Type II, previous aortocoronary bypass operation, previous myocardial infarction without heart failure, renal impairment (GFR 41 ml/min), non-smoker, Cholesterol 5.2 mmol/l, HDL 1.1 mmol/l, LDL 2.2 mmol/l with some statin intolerance and with use of Ezetimibe 10 mg/d. Here 10-year risk is calculated to be 50.4% in 10 years to experience another cardiovascular event. According to Table 1, value-based Price PEP/day is on average price of 6.18 CHF/day. For the same patient but with an LDL of 3.6 mmol/l, average price would be CHF 10.34/day in this case.

Peter Mueller is a 55 year old non-smoking, statin-intolerant man in primary prevention presenting with extensive carotid atherosclerosis (total plaque area 120 mm^2, arterial age 73 years), confirmed by presence of coronary calcifications (Agatston Score 169, arterial age 76 years), treated blood pressure of 125 mm Hg, Cholesterol 6.6 mol, HDL 1.1 mol, LDL 3.4 mmol/l with Ezetimibe 10 mg/d (baseline LDL in the last years below 5.0 mmol/), non-diabetic. Using chronological age, this patient is at intermediate risk, but because of advanced atherosclerosis, the target of preventive therapy we calculate his risk using an arterial age of 73 years, which puts this patient into the high risk category (FRAMINGHAM calibrated with 0.7 for Switzerland 29%, SCORE low risk populations 7.6%, SCORE SMB 42% (SMB=Swiss Medical Board assumption). For further negociation, an average price could be calculated, CHF 8.08 CHF/day in this case.

The calculations are available in the internet (www.docfind.ch/PEPPricing.xlsx)

Discussion

We describe a novel risk- and value-based price model using two different ways of cost-efficiency calculations (see Appendix). First, risk calculations should be performed and audited by independent medical staff based upon a patient's clinical chart in order to exclude price frauds at any level and requests and patient variables are recorded nationally by the Federal Office of Public Health. We developed such a risk calculator for primary and secondary prevention that is available in the Internet (https://docfind.ch/AspirinStatinCompass.xlsx). The prices calculated are comparable to a more sophisticated analysis provided by PICORI [4].

Based on the risk calculations in primary or secondary prevention, the MD transmits a request for reimbursement to the health insurer and requests the delivery of the drug from the pharmaceutical company or a pharmacy. The price payed could be the average of the two models. After one year, quarterly measured on-drug LDL levels are used to correct for the initial price.

This approach relieves the threat of legal persecution for those involved in defining prices or rationing and is likely to guarantee expected sales and incomes to the pharmaceutical companies producing PCSK9-inhibitors.

Further, as calculated in the Appendix, we expect several thousand avoided cardiovascular events in Switzerland, if a more aggressive lipid lowering therapy could be installed (Appendix, Table 5).

Conclusion

We would like to conclude with words by Prof. Th. Szucs paper about the enigma of value [5]: "Introducing payers and health economists into the process could surely make health care more affordable in the future, given the important budget impacts ahead. Moreover, authorities need to keep in mind what our systems are based on: solidarity and equity. In order to guarantee a sustainable system, future pharmaceuticals are to be made accessible to patients who are in true need by finding ''the right price.' ".

We are confident that our work assists to improve the transparency about the value of LDL lowering lipid therapy and may lead to novel price models that are truly value-based.

Appendix:

Background Paper regarding further scientific information

Introduction

Morbidity and mortality due to atherosclerosis is highly prevalent worldwide [6,7] and could be prevented by up to 90%, if all risk factors were treated [8]. One major and independent risk factor is cholesterol [9] and lowering LDL cholesterol with statins reduces the risk of cardiovascular events by a relative risk of 21% per 1 mmol/l LDL reduction achieved [10,11]. Moreover, atherosclerosis detected by imaging is a marker of all-cause mortality [12,13] and may personalize preventive therapies [14–16]. In the Cardiovascular Disease Policy Model, a simulation model of US adults aged 35 to 94 years, adding PCSK9 inhibitors to statins in primary prevention of subjects affected by heterozygous familial hypercholesterolemia (FH) was estimated to prevent 316'300 major adverse cardiac events (MACE) and to prevent 4.3 million MACE [17]. The total amount of LDL- and apolipoprotein B accumulation during lifetime is correlated to an exponential increase in cardiovascular morbidity and mortality [18].

There is therefore an important public health potential for PCSK-9 inhibitors to further decrease the cardiovascular disease burden in both primary and secondary prevention, but cost-issues might mitigate the benefit that could be derived from such therapies [19].

Evolocumab (Repatha, Amgen), a PCSK9-inhibitor, was found in Fourier study to reduce cardiovascular events by a relative risk of 10.6% per 1.0 mmol/l LDL reduction for the primary endpoint. Median LDL was 2.38 mmol/l at baseline and reduced to 0.83 mmol/l. The observed relative risk reduction of 10.6% was lower than could be expected from aggregated statin studies (CTT metaanalysis: RRR 21%) [10,20,21]. Recently, data have been published on the ODYSSEY OUTCOME study [22]. In this trial involving 18'924 patients with acute coronary syndromes within the past 12 months, patients were treated with either alirocumab, a PCSK9-inhibitor or placebo on top of standard lipid lowering therapy. The primary outcome of time to first coronary heart disease death, nonfatal myocardial infarction, ischemic stroke, or hospitalization for unstable angina compared with those given placebos was reduced by 15% from 11.1% to 9.5%, an absolute risk reduction of 1.6% and a number-needed-to-treat of 63 after a median observation time of 2.8 years. The average baseline LDL was 2.26 mmol/l and reduced by an average of 0.98 mmol/l with intention-to-treat alirocumab, therefore, per 1.0 mmol/l LDL reduction, the relative risk reduction of the primary outcome was 15.5%, which is comparable to the Fourier study. This lower RRR is important for value-based calculations and the reasons for it remain to be evaluated. From Mendelian studies it appears that PCSK-9 Inhibitors may have weaker effects on very-low-density lipoprotein lipids compared with statins [23].

The burden of atherosclerosis increases with age, as we have shown in a cross-sectional observation for a Swiss and a German group of healthy subjects [15]. If indicated by cardiovascular risk estimates – especially when

documented by the presence of atherosclerosis assessed by carotid plaque imaging – any attempt should be made to lower LDL cholesterol [24,25]. While statins are now available as a generic at relatively low costs (CHF 0.35 - 0-68 per day), PCSK9-inhibitors are new-comers in the market and sold in Switzerland at costs of CHF 18.37/day (CHF 6'705/year). Such costs have been termed toxic, because they can hardly be afforded even in rich industrialized countries [26–28]. By consequence, it is recommended to save costs to health care systems by rationing PCSK9-inhibitors in those not at highest risk. Indeed, Swiss health care authorities decided in 2017 not to reimburse Evolocumab in patients with a baseline LDL < 3.6 mmol/l.

Quality of life measurements integrated into QALY have been criticized for subjectivity and ethical considerations [29], calculations of value-based prices are difficult [5] and the results of such *fixed pricing* are dependent on the average risk levels and the chosen cutoff of CHF or USD per QALY gained [30,31]. As an alternative, estimates of direct and indirect costs per cardiovascular event can be related to costs of a lipid lowering drug and the individually expected achieved LDL reduction. When individual preventive costs are equal to avoided costs, then we define this to be value-based in our *individual pricing* model.

In this study we first calculate value-based *fixed pricing* using a QALY model proposed by the Swiss Medical Board SMB [32] at the CHF 150'000/QALY gained level; second, we calculate value-based *individual pricing* in primary and secondary prevention using risk estimates and base-line LDL levels (instead of QALY). Third, we estimate the reduction of cardiovascular disease burden in Switzerland by implementing aggressive lipid-lowering with statins and PCSK9-inhibitors in primary care subjects affected by prognostically relevant carotid atherosclerosis and with a baseline LDL level of at least 2.6 mmol/l.

Methods

Calculation of medical effects and costs

Calculation of individual risk in primary prevention: in every subject we used the following risk calculators: 1) Framingham for cardiovascular events [9], 2) pooled cohort equation as proposed by the cholesterol guidelines of ACC/AHA in 2013 [33], 3) SCORE for fatal cardiovascular events multiplied by 5.5 in order to obtain an estimate of the CTT combined outcome (as proposed by the Swiss Medical Board in 2014 [34]). Additionally, we used two posttest risk calculators: 1) arterial instead of chronological age in order to include the atherosclerotic burden into the risk estimate of an individual [35]; 2) the posttest risk using the total carotid plaque area (TPA), sensitivity and specificity and the Bayes formula has been described elsewhere [14].

Estimation and calculation of individual risk in secondary prevention: The risk for a second event in secondary prevention is not well known in Switzerland. Based upon a Swiss survey, the second event risk is 2.5% for an acute coronary syndrome in the first 100 days in patients without familial hypercholesterolemia and this risk flattens down to another 2.5% for the rest of the first year [36]. Assuming a linear increase in risk beyond the first 100 days, then the 10-year risk would be 35% for a second acute coronary syndrome with about another 5% risk for a third event in 10 years. Similarly, according to the Swiss SPUM cohort, at 1 year 2.5% recurrent myocardial infarctions and 1.3% cerebrovascular events occurred, by extrapolation to ten years equaling an event rate of 38% [37]. In the Fourier study, the incidence rate for the primary endpoint was 21% in 3 years in North America or about 70% in 10 years, whilst in Europe the primary endpoint was reached in 13.1% in 3 years or about, by extrapolation, 44% in 10 years.

For individual risk calculation we recommend the risk calculator developed by Dorresteijn [38], which we have adopted from 5 years by linear extrapolation to 10 years and with the assumption, that cardiovascular events occur after 5 years in average and that for every event there will be another event with a risk of 50% over 5 years during the remaining 5 years, which increases the risk calculated by the calculator by 25%.

Calculation of absolute risk reduction over 10 years: Per 1 mmol/l LDL reduction we calculated for Evolocumab a relative risk reduction (RRR) of 11% for the combined CTT outcome. *Example:* as found in the Fourier study, PCSK9-inhibitors reduced LDL by 58% [21]. LDL was therefore reduced from baseline 2.38 mmol/l by 1.6 mmol/l with a RRR of 11% per 1.0 mmol/l, which results in a total RRR of 18% (1.6 x 11%) for the Fourier study group. Per 1 mmol/l LDL reduction we calculated for Alirocumab a relative risk reduction (RRR) of 14% for the primary outcome per 1.0 mmol/l LDL reduction. *Example:* as found in the ODYSSEY

OUTCOMES study, PCSK9-inhibitors reduced LDL by 53% [22]. LDL was therefore reduced from baseline 2.38 mmol/l by 1.1 mmol/l with a RRR of 14% per 1.0 mmol/l, which results in a total RRR of 15 % (1.1 x 14%) for the ODYSSEY OUTCOMES study.

Calculation of direct and indirect medical costs: Direct and indirect costs of fatal and non-fatal myocardial infarction and stroke were assumed to be 251'622 per event, irrespective of additional cost over time after the event. Based on the final Swiss report on NCD costs 2014 [39] for the year 2011 (www.docfind.ch/CVDCosts2011.xlsx):

- Acute myocardial infarction cost estimates Swiss Francs 4'798'000'000
- Stroke cost estimates Swiss francs 3'168'000'000
- Swiss death registers found 7'703 deaths due to ischemic heart disease in the year 2011.

Assuming that for every death there are 3 non-fatal myocardial infarctions (based on Framingham Data), we estimate the number of fatal and non-fatal myocardial infarctions to be 38'515 (Switzerland, 2011). Assuming a ratio of myocardial infarction and stroke of 3.5, which is comparable to the ratio derived from Framingham risk charts (4.5 in male and 2.6 in female, average 3.5), then 11'805 strokes are estimated to have occurred in 2011. The sum of first myocardial infarctions and strokes is therefore 50'320. For subsequent events we estimate additional rate of 34% for myocardial infarction and of 24% for stroke over a period of 5 years [40]. Direct and indirect costs for myocardial infarction are divided by 37'578 patients with events, resulting in 147'995 Swiss Francs per myocardial infarction or 345'125 per stroke. Accounting for the case-mix estimate, the average costs per patient are 251'622 Swiss Francs. In view of the fact that avoidable cost was calculated over a time of 10 years, these costs per patient may even underestimate true costs, since we did not include an additional cardiovascular event that may have occurred in years 6 to 10. In order to achieve a conservative estimation of costs, we used avoidable direct and indirect medical costs of 200'000 Swiss francs per event (coronary revascularization included). Our cost estimate is comparable to the key inputs in the economic model of Fonarow et al [30] and is a conservative estimate of direct and indirect costs associated with cardiovascular diseases in Switzerland.

Ideal costs were calculated as follows: based on the expected absolute risk reduction obtained by the individually expected magnitude of treatment on LDL reduction, an individual's NNT was calculated for a 10-year period. The price of the drug was customized in such a way that treatment costs equal CHF 200'000 (which is the expected direct and indirect cost of a prevented cardiovascular event).

Further, we calculated the potential for cost-savings over 10 years in Swiss subjects aged 40 years or more by making the following assumptions: primary care subjects from our database had to have a posttest risk for CVD of at least 20% and an LDL of at least 2.5 mmol/l. Posttest risk was calculated using either arterial age (aa) [35]

or the Bayes theorem (pt) [14] derived from the amount of carotid plaque and SCORE, PCE and FRAM as the pretest estimate. We did not recalibrate the pretest estimate for Switzerland [41]. We used the average LDL and average risk and the RRR for statins and the two PCSK-9 inhibitors (21% and 16% respectively), assuming that the RRR is around 16% for PCSK-9 inhibitors after the first year of treatment [21]. Further we assumed that statins reduce LDL by 50% and corrected this down to 35% in order to account for statin intolerance in the whole of our population. For PCSK-9 inhibitors we assumed a 56% LDL reduction of a period of 10 years. Finally, we assumed that the proportion of the treatment group selected by the posttest risk algorithm corresponds to the proportion of subjects in the general populations that might present high risk and LDL > 2.5 mmol/l and assuming that out of 8.4 Mio inhabitants (in 2016) in Switzerland, 4.48 Mio inhabitants are aged 40 years or more (Swiss federal bureau of statistics). We estimated direct costs to be 100'000 SFr per event and indirect costs to be 100'000 Sfr. per event, summing up to 200'000 Sfr. per event.

Calculation of cost/QALY using a Swiss Model

According to the Swiss Medical Board, cost-efficiency for cardiovascular events can be calculated based upon an effect model developed for statins [32]. In brief, the SMB model for calculating cost/QALY is as follows. For one fatal cardiovascular event (myocardial infarction, stroke, coronary revascularisation), 4.5 nonfatal events occur. The cost is CHF 8500 per fatal event and CHF 25 000 per nonfatal event in the first year and CHF 8000 in subsequent years. Loss of QALY is 1.0 for fatal and 0.2 for nonfatal events. The annual preventive medical cost per individual is CHF 365.00 for statins and CHF 170 for medical monitoring (Total CHF 470). All cardiovascular events occur uniformly after 50% of the total observation time of five years. Loss of QALY at 2.5 years was therefore $2 \times 2.5 \times 1 = 5.0$ QALY for fatal events and $9 \times 2.5 \times 0.2 = 4.5$ QALY for nonfatal events, and thus $5.0 + 4.5 = 9.5$ QALY in 1000 persons or 0.0095 QALY per person. When this effect model is applied to a 10-year period, then 4 fatal events and 18 non-fatal events can be prevented; therefore, $4 \times 5 \times 1 = 20$ QALY for fatal and $18 \times 5 \times 0.2 = 18$ QALY for nonfatal events, or a total of 38 QALY losses, can be prevented in 1000 persons, which is 0.038 QALY per person. Therefore, the effect model is 4 times higher in 10 years when compared with 5 years. For this paper, we evaluated annual costs for the PCSK9 inhibitor Evolocumab in order to obtain a threshold of CHF 150'000/QALY gain at various 10-year risk levels, for which we found the formula *annual costs* = [risk x 0.1852-0.4655] x 365.

Subject selection

Primary care subjects were assessed at the practice based level as described elsewhere [15,35,42]. In the Swiss (CH) Imaging Center in Olten, subjects were referred by their primary care physician (57%) or self-referred to the vascular risk foundation (43%; www.varifo.ch). In the German (DE) Center in Koblenz, all subjects were referred

within a workplace medicine setting [43]. Subjects had to be free of cardiovascular symptoms or diseases. The medical history was assessed, laboratory values, blood pressure determined locally and entered into a data spread-sheet (Excel, Microsoft, Richmond, USA).

Description of atherosclerosis imaging

Burden of longitudinal carotid plaque surface was imaged with a high-resolution ultrasound linear transducer probe (7.5–12.0 MHz), which identified plaques with intimal thickening ≥1.0mm. The longitudinal area of all plaques was summed up to the total plaque area (TPA) in mm^2. All TPA measurements were made by M.R. in Olten and by A.A. in Koblenz. Intraobserver reproducibility by author M.R. for both carotid arteries in 57 patients showed a correlation coefficient of r^2 0.964 (left carotid artery: r^2 0.944, both arteries r^2 0.986). For the cutoffs of TPA 0–9mm^2, 10–49mm^2, 50–99mm^2 and ≥100mm^2 Kappa value was good with 0.80 (95% CI: 0.69–0.90). Intraobserver reproducibility was tested for both carotid arteries in 56 patients by for author A.A with a correlation coefficient of r^2 = 0.976 (left carotid artery: r^2 0.949, both arteries r^2 0.953). For the cutoffs of TPA 0–9mm^2, 10–49mm^2, 50–99mm^2 and ≥100mm^2 Kappa value was very good with 0.97 (95% CI: 0.92–1.00).

Results

We assessed 2'202 healthy Swiss and 2'942 healthy German subjects as described elsewhere [15]. From this original group, we selected subjects (41% women) with a selected age between 30 and 75 years (average 53±8), leaving a group of 4'389 subjects. The details of the clinical characteristics are outlined in Table 1. Depending on the risk calculator used, the group was placed into a low (Swiss adopted PROCAM, pooled cohort equation) to intermediate risk (FRAMINGHAM, SCORE). On average, the integration of the posttest risk based on carotid plaque resulted into a shift from intermediate to borderline high risk. Average systolic blood pressure was slightly elevated (127 mm Hg) and average LDL cholesterol was 3.8 mmol/l.

The calculation of ideal PEP prices is possible with the formula [(a x RISK + b) x LDL - 0.3288], where (a) was 0.0529, 0.0575, 0.0253, 0.0337, 0.0384 for Atorvastatin, Rosuvastatin, Ezetimibe, Evolocumab and Alirocumab respectively, and where (b) was -0.00003, 0, 0, -0.00003 and -0.00007, respectively.

For the typical study patient from Fourier and Odyssey, baseline LDL was 2.38 mmol/l and the cardiovascular risk extrapolated to 10 years was 51% in Fourier and 38% in Odyssey. Table 2 shows, that using a fixed price model, current costs/d are overpriced between 68% and 83%.

Table 3 displays the result of *individual pricing* using the PEP model for statins, Ezetimibe, Evolocumab and Alirocumab. Based on a patient's baseline LDL and the expected 10-year risk, the range of acceptable value-based prices show a large variability.

The number of subjects with posttest risk of 20% or more (based on carotid plaque imaging) and with a baseline LDL > 2.5 mmol/l ranged between 14% (arterial age pooled cohort equation) and 38% (Bayes posttest Framingham CVD equation, Table 4).

Table 5 shows the calculated potential for cost-saving of LDL lowering on preventable cardiovascular events in Switzerland is around 7'371 (20%) regarding preventable CVD events out of about 37'578 total events with cost-savings of 1.47 Billion of Swiss francs per year (737 Mio Sfr saved direct or indirect costs, respectively).

Discussion

To the best of our knowledge, this is the first study that tried to estimate the potential benefit of PCSK9-inhibitors in primary care and to furnish a value-based price of PCSK9-inhibitors across various levels of cardiovascular risk and LDL levels in primary and secondary prevention.

In this study we calculated *fixed pricing* of the typical Fourier and Odyssey patient using a Swiss QALY and our PEP model and found that PCSK-9 inhibitors are overpriced between 68% and 83%. As calculated by Arrieta using a life-time Markov model for Fourier patients at the threshold of 100'000/QALY gained ($ 5'459), overpricing was found to be 62% [31].

In order to eliminate the poor reproducibility and subjectivity inherent to QALY calculations [29,44], we propose a different model that we term *individual pricing*, where QALY is replaced by preventive and evidence-based effects of the relative risk reduction inherent to LDL lowering drugs [21]. Therefore, we calculated personalized value-based prices for a wide range of clinical scenarios with 10-year cardiovascular risk ranging between 10% and 100% and baseline LDL ranging between 2.0 mmol/l and 5.0 mmol/l. As can see from Table 3, the range of value based daily prices is very large for PCSK-9 inhibitors ranging between CHF 0.30 to CHF 16.52. For the QALY model, prices could be about 50% higher, which gives an estimate of the ranges for value-based pricing using the two models.

Following a strategy in primary prevention, where we would lower LDL in every subject with a cardiovascular risk of 20% or more in 10 years and a baseline LDL of > 2.5 mmol/l, we found an average LDL of 4.15 mmol/l in such subjects from Switzerland and Germany that subsequently, according to published effects on LDL lowering of these drugs [22,45] could be lowered to 1.5 mmol/l using the combination of statins and PCSK9-inhibitors. The therapeutic effects are expected – by averaging two risk models using FRAM and PCE with inclusion of risk prediction with carotid plaque imaging – to prevent 7'600 cardiovascular events or 20% of all cardiovascular events annually in Switzerland with cost-savings of about 1.53 Billion Swiss Francs in a population at risk of 4.5 Mio subjects with an expected high risk of 20% in 14% to 38% of this population.

In secondary prevention, we estimated the risk of subsequent cardiovascular events to be around 40% in 10 years in Switzerland, which matches the extrapolated 10-year event rate in the FOURIER study (in Europe the primary endpoint was reached in 13.1% in 3 years or about, by extrapolation, 44% in 10 years). In the typical Fourier patient with a baseline LDL of 2.38 mmol/l, a treated risk of 40% using Evolocumab would lead to an ideal daily price of CHF 4.60/QALY (Alirocumab CHF 5.56/QALY) and in the PEP model value-based prices would be CHF 2.88/day and CHF 3.32/day respectively.

Both in primary and secondary prevention, using a risk estimation and a patient's LDL level allows for stratified calculations of value-based costs using *individual pricing* (Table 3). However, the exact risk for subsequent events in primary care is difficult to estimated. For the practical estimation of an individual's risk for subsequent cardiovascular events in Europe we recommend to use the calculator proposed by Dorrestejin et al [38]. This allows for the same way to calculate LDL-based personalized individual prices as for primary prevention. Dorrestejin used the data from the Treating to New Targets trial and age, sex, smoking, diabetes mellitus, total cholesterol, high-density lipoprotein cholesterol, systolic blood pressure, history of myocardial infarction, coronary artery bypass grafting, congestive heart failure or abdominal aortic aneurysm, glomerular filtration rate, and treatment status (ie, atorvastatin 80 mg or 10 mg). The calculator is available online (www.docfind.ch/AspirinStatinCompass.xlsx)

In July 2017, the Swiss Federal Office of Health has limited Evolocumab to those in secondary prevention with a baseline LDL of at least 3.5 mmol/l. As outlined in Table 3, even at a baseline risk of 50% and LDL of 5.0 mmol/l, ideal costs cannot be higher than about CHF 10.00/d. Therefore, when patients are treated in secondary prevention with PCSK-9 inhibitors in Switzerland, prices are not value-based using *personalized pricing*.

However, rationing of effective drugs because of toxic prices is not a responsible choice. The burden of cardiovascular disease is a leading cost driver and once effective drugs such as PCSK9-inhibitors are available, they should be available for all high-risk subjects. Governments should buy these drugs in order to create a situation, were a new price model includes a sales guarantee for 10 years, and prices should be adjusted posteriori based on sales figures.

Based upon our assumptions, the potential for prevention with LDL reduction is high with cost-savings of 1.5 Billion Swiss Francs per year if only high-risk patients with an LDL of > 2.5 mmol/l at baseline in primary care were treated with a combination of statins and PCSK9-inhibitors. The limitation to treat only patients in secondary prevention or patients with familial hypercholesterolemia is not a clinical but an economic decision of health care authorities, who are confronted with toxic prices of PCSK9-inhibitors.

Value-based *fixed price* costs in primary and secondary prevention using QALY models are 68% to 82% overpriced. Poor reproducibility of QALY models and inherent problems to the subjectively determined amount of QALY, however, limit their use and scientific rationale. *Personalized price* value-based models can replace QALY by the calculation of an evidence-based effect of LDL lowering. Individually determined costs have the potential to reduce the rationing of PCSK9-inhibitors in primary and secondary care. The use of PCSK-9 inhibitors should be broadened in order to achieve lower lipid levels and risk in many of our patients. Our calculations may help to model value-based prices that can be integrated into new price models, where a sales guarantee for a certain

period is included, and prices could be adjusted posteriori based on sales figures. This might prevent that pharmaceutical companies establish starting prices that are toxic for health care systems.

Compliance with Ethical Standards:

Conflict of Interest: The authors declare that they have no conflict of interest.

Ethical approval: For this type of study formal consent is not required.

Informed consent: According to Swiss and German regulations, no formal consent is required when information is collected from routine medical records. Subjects screened within the vascular risk foundation gave written informed consent and these activities where approved by the ethical committee of the canton of Solothurn.

Funding / potential competing interests:

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Literature

1. Eichler H-G, Hurts H, Broich K, Rasi G. Drug Regulation and Pricing — Can Regulators Influence Affordability? N Engl J Med. 2016;374:1807–9.
2. Kieser U. Gutachten zur Rationierung. 2015; Available from: www.docfind.ch/GutachtenKieserRationierung032015.pdf
3. Dorresteijn JAN, Visseren FLJ, Ridker PM, Wassink AMJ, Paynter NP, Steyerberg EW, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. BMJ. 2011 Jan;343:d5888.
4. Kazi DS, Coxson PG, Penko J, Bibbins-Domingo K. Alirocumab for Treatment of High Cholesterol: Effectiveness and Value. Inst Clin Econ Rev [Internet]. 2019;1–12. Available from: https://icer-review.org/wp-content/uploads/2019/02/ICER_Alirocumab_Final_NEU_021519.pdf
5. Szucs TD, Weiss M, Klaus G. The enigma of value: in search of affordable and accessible health care. Eur J Heal Econ. 2016;18:667–70.
6. Mancia G, De Backer G, Dominiczak A, Cifkova R, Fagard R, Germano G, et al. 2007 Guidelines for the management of arterial hypertension: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2007 Jun;28:1462–536.
7. WHO. Global status report on noncommunicable diseases 2014. World Health. 2014.
8. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, et al. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case control study. Lancet. 2004;364:937–52.
9. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. American Heart Association, Inc.; 2008 Feb 12;117(6):743–53.
10. Mihaylova B, Emberson J, Blackwell L, Keech A, Simes J, Barnes EH, et al. The effects of lowering LDL cholesterol with statin therapy in people low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012;380:581–90.
11. Nanchen D, Pletcher MJ, Cornuz J, Marques-Vidal P-M, Paccaud F, Waeber G, et al. Public health impact of statin prescribing strategies based on JUPITER. Prev Med (Baltim). 2011;52:159–63.
12. Cao JJ, Arnold AM, Manolio TA, Polak JF, Psaty BM, Hirsch CH, et al. Association of carotid artery intima-media thickness, plaques, and C-reactive protein with future cardiovascular disease and all-cause mortality - The cardiovascular health study. Circulation. 2007;116(1):32–8.
13. Störk S, Feelders RA, van den Beld AW, Steyerberg EW, Savelkoul HFJJ, Lamberts SWJJ, et al. Prediction of Mortality Risk in the Elderly. Am J Med. 2006;119:519–25.
14. Romanens M, Ackermann F, Spence JD, Darioli R, Rodondi N, Corti R, et al. Improvement of cardiovascular risk prediction: time to review current knowledge, debates, and fundamentals on how to assess test characteristics. Eur J Cardiovasc Prev Rehab. 2010;17(1):18–23.
15. Romanens M, Mortensen MB, Sudano I, Szucs T, Adams A. Extensive carotid atherosclerosis and the diagnostic accuracy of coronary risk calculators. Prev Med Reports. The Authors; 2017;6:182–6.
16. Budoff MJ, Young R, Burke G, Carr JJ, Detrano RC, Folsom AR, et al. Ten-year association of coronary artery calcium with atherosclerotic cardiovascular disease (ASCVD) events: the multi-ethnic study of

atherosclerosis (MESA). Eur Hear J. 2018;39:2401–8.

17. Kazi DS, Moran AE, Coxson PG, Penko J, Ollendorf DA, Pearson SD, et al. Cost-Effectiveness of PCSK9 inhibitor therapy in patients with heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease. JAMA - J Am Med Assoc. 2016;316(7):743–53.
18. Ference BA, Graham I, Tokgozoglu L, Catapano AL. Impact of Lipids on Cardiovascular Health. JACC. 2018;72(23):2980–95.
19. Hlatky MA, Kazi DS. PCSK9 Inhibitors: Economics and Policy. J Am Coll Cardiol [Internet]. Elsevier; 2017;70(21):2677–87. Available from: https://doi.org/10.1016/j.jacc.2017.10.001
20. Cholesterol Treatment Trialists' Ctt Collaborators. CTT Appendix Online 2012. Append online [Internet]. Available from: https://researchonline.lshtm.ac.uk/1649027/1/mmc1.pdf.
21. Sabatine MS, Giugliano RP, Keech AC, Honarpour N, Wiviott SD, Murphy SA, et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med. 2017;376:1–10.
22. Steg P, Schwartz G, Szarek M. Alirocumab in patients after acute coronary syndrome. The ODYSSEY OUTCOMES Study. In: American College of Cardiology (ACC) 2018 Annual Scientific Session [Internet]. 2018. Available from: https://seekingalpha.com/article/4155622-sanofi-sny-updates-results-odyssey-outcomes-trial-slideshow
23. Sliz E, Kettunen J, Holmes M, Williams C, Boachie C, Wang Q, et al. Metabolomic Consequences of Genetic Inhibition of PCSK9 Compared With Statin Treatment. Circulation. 2018;138(22):2499–2512.
24. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013;34:2159–219.
25. Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. Eur Heart J. 2016;37(29):2315–81.
26. Craddy P, Foxon G. Are the PCSK9 Inhibitors, Repatha and Praluent, the new Sovaldi ? [Internet]. Vol. 9, REMAP Consulting Perspectives. 2015. p. 9–10. Available from: www.remapconsulting.com/wp-content/uploads/Are-the-PCSK9-Inhibitors-Repatha-and-Praluent-the-new-Sovaldi-1_0.pdf.
27. LLP C. UK Competition AuthorityTakes Action Against Suspected Excessive Pricing of Pharmaceuticals. COOLEY [Internet]. 2015;(August). Available from: https://www.cooley.com/news/insight/2015/uk-competition-authority-takes-action-against-suspected-excessive-pricing-of-pharmaceuticals
28. Abbott FM. Excessive Pharmaceutical Prices and Competition Law : doctrinal development to protect public health. UC Irvine Law Rev [Internet]. 2016;6(3):1–33. Available from: https://papers.ssrn.com/sol3/papers.cfm?abstract_id=2719095
29. Beresniak A, Medina-Lara A, Auray JP, De Wever A, Praet J-C, Tarricone R, et al. Validation of the Underlying Assumptions of the Quality-Adjusted Life-Years Outcome: Results from the ECHOUTCOME European Project. Pharmacoeconomics. 2015;33(1):61–9.
30. Fonarow GC, Keech AC, Pedersen TR, Giugliano RP, Sever PS, Lindgren P, et al. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. JAMA Cardiol. 2017;2:1069–78.
31. Arrieta A, Hong JC, Khera R, Virani SS, Krumholz HM, Nasir K. Updated Cost-effectiveness Assessments of PCSK9 Inhibitors From the Perspectives of the Health System and Private Payers. JAMA

Cardiol. 2017;33139:1369–74.

32. Romanens M, Sudano I, Szucs T, Adams A. Medical costs per QALY of statins based on Swiss Medical Board assumptions. Cardiovasc Med. 2017;17(4):96–100.
33. Stone NJ, Robinson JG, Lichtenstein AH, Bairey Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: A report of the American college of cardiology/American heart association task force on practice guidelines. J Am Coll Cardiol. 2014;63:2889–934.
34. Felder S, Jüni P, Meier CA, et al. SMB Statin Recommendation [Internet]. 2014. Available from: https://www.swissmedicalboard.ch/fileadmin/public/news/2013/bericht_smb_statine_primaerpraevention_lang_2013.pdf
35. Romanens M, Ackermann F, Sudano I, Szucs T, Spence JD. Arterial age as a substitute for chronological age in the AGLA risk function could improve coronary risk prediction. Swiss Med Wkly. 2014;144:w13967.
36. Nanchen D, Gencer B, Muller O, Auer R, Aghlmandi S, Heg D, et al. Prognosis of Patients with Familial Hypercholesterolemia after Acute Coronary Syndromes. Circulation. 2016;134:698–709.
37. Gencer B, Koskinas KC, Räber L, Karagiannis A, Nanchen D, Auer R, et al. Eligibility for PCSK9 inhibitors according to American College of Cardiology (ACC) and European Society of Cardiology/European Atherosclerosis Society (ESC/EAS) guidelines after acute coronary syndromes. J Am Heart Assoc. 2017;(11):e1-10.
38. Dorresteijn JAN, Matthijs Boekholdt S, Van Der Graaf Y, Kastelein JJP, Larosa JC, Pedersen TR, et al. High-dose statin therapy in patients with stable coronary artery disease: Treating the right patients based on individualized prediction of treatment effect. Circulation. 2013;127:2485–93.
39. Wieser S, Tomonaga Y, Riguzzi M, Fischer B, Telser H, Pletscher M, et al. Die Kosten der nicht übertragbaren Krankheiten in der Schweiz [Internet]. 2014. Available from: https://www.zora.uzh.ch/id/eprint/103453/
40. Yeo KK, Zheng H, Chow KY, Ahmad A, Chan BPL, Chang HM, et al. Comparative analysis of recurrent events after presentation with an index myocardial infarction or ischaemic stroke. Eur Hear J - Qual Care Clin Outcomes. 2016;3.
41. Pennells L, Kaptoge S, Wood A, Sweeting M, Zhao X, White I, et al. Equalization of four cardiovascular risk algorithms after systematic recalibration: individual-participantmeta-analysis of 86 prospective studies. Eur Hear J [Internet]. 2018; Available from: https://spiral.imperial.ac.uk:8443/bitstream/10044/1/65233/6/ehy653.pdf
42. Romanens M, Ackermann F, Schwenkglenks M, Szucs T, Spence JD. Posterior probabilities in sequential testing improve cardiovascular risk prediction using carotid total plaque area. Kardiovaskuläre Medizin. 2011;14:53–7.
43. Adams A, Bojara W. Vorhersage einer stenosierenden KHK durch Bestimmung von Plaque-Fläche und -Dicke vs. IMT an der A. carotis. Herz. 2015;40(5):817–22.
44. Rappange DR, Brouwer WBFF, van Exel J. A long life in good health: subjective expectations regarding length and future health-related quality of life. Eur J Heal Econ. 2016;17:577–89.
45. Hamilton P. Evolocumab and clinical outcomes in patients with cardiovascular disease. Ann Clin Biochem. 2017;54(4):511.

Tables

Table 1: Clinical data, carotid atherosclerosis and coronary risk in 4'389 primary care subjects

Country	**CH**	**DE**	**ALL**
Patients (N)	2111	2278	4389
Women N (%)	986 (47%)	792 (35%)	1778 (41%)
Chronological Age (SD)	56 ± 8	50 ± 6	53 ± 8
Arterial Age (SD)	49 ± 20	43 ± 22	46 ± 21
Systolic blood pressure (mm Hg (SD)	129 ± 15	125 ± 16	127 ± 16
Family history for CVD N, %	391 (19%)	531 (23%)	922 (21%)
Smoker N, %	443 (21%)	533 (23%)	976 (22%)
Cholesterol mmol/l (SD)	5.9 ± 1.2	6.1 ± 1.1	6.0 ± 1.2
HDL mmol/l (SD)	1.5 ± 0.4	1.5 ± 0.4	1.5 ± 0.4
LDL mmol/l (SD)	3.7 ± 1	3.9 ± 0.9	3.8 ± 1
TG mmol/l (SD)	1.5 ± 0.9	1.7 ± 1.2	1.6 ± 1.1
TPA mm^2 , average (SD)	51 ± 48	45 ± 52	48 ± 50
FRAM % (SD)	13 ± 9	11 ± 9	12 ± 9
FRAMAA % (SD)	16 ± 13	15 ± 15	16 ± 14
FRAMPT % (SD)	22 ± 16	18 ± 16	20 ± 16
SCORE SMB % (SD)	12 ± 12	7 ± 8	10 ± 10
SCOREAA % (SD)	20 ± 21	17 ± 24	18 ± 23
SCOREPT % (SD)	25 ± 25	15 ± 20	20 ± 23
PCE % (SD)	7 ± 6	5 ± 5	6 ± 5
PCEAA % (SD)	10 ± 9	9 ± 10	10 ± 9
PCEPT % (SD)	14 ± 12	10 ± 11	12 ± 12
AGLA % (SD)	4 ± 5	4 ± 5	4 ± 5

Legend: (TPA=total plaque area of carotid artery plaques; CVD= cardiovascular disease, FRAM=Framingham risk; FRAMAA= Framingham risk with arterial age; FRAMPT= FRAM with posttest risk based on the Bayes theorem of TPA sensitivity and specificity; SCORE SMB= SCORE risk with the extension of the Swiss Medical Board, SCOREAA= same risk calculated with arterial age; SCOREPT= see FRAMPT, PCE=pooled cohort equations; PCEAA= PCE risk with arterial age; PCEPT= see FRAMPT; AGLA= PROCAM based coronary risk calculator with a factor of 0.7 for Switzerland).

Table 2: Cost/QALY in a typical study patient with baseline LDL of 2.38 mmol/l and a risk of 51% in Fourier and of 40% in Odyssey. Comparison at the actual daily price (CHF 18.37) and the 150'000/QALY threshold

	Evolocumab	**Alirocumab**
Cost/QALY current price	501'603	581'953
150'000/QALY threshold	CHF 5.49/d	CHF 4.73/d
Overpricing	68%	74%
PEP price/day	CHF 3.76	CHF 3.22
Overpricing	80%	82%

Table 3: Value based daily medication cost for various risk and LDL thresholds regarding high dose statins, Ezetimibe, Evolocumab and Alirocumab using the personalized price (PEP) model.

RISK	LDL mmol/l	Atorva 40	Rosuva 20	Ezetimibe 10	Evolocumab	Alirocumab
10	**5.0**	2.32	2.55	0.94	1.36	1.59
	4.0	1.79	1.97	0.68	1.02	1.21
	3.0	1.26	1.40	0.43	0.68	0.82
	2.0	0.73	0.82	0.18	0.34	0.44
20	**5.0**	4.96	5.42	2.20	3.04	3.51
	4.0	3.91	4.27	1.70	2.37	2.74
	3.0	2.85	3.12	1.19	1.69	1.97
	2.0	1.79	1.97	0.68	1.02	1.21
30	**5.0**	7.61	8.30	3.47	4.72	5.42
	4.0	6.02	6.58	2.71	3.71	4.27
	3.0	4.44	4.85	1.95	2.70	3.12
	2.0	2.85	3.12	1.19	1.69	1.97
40	**5.0**	10.26	11.18	4.73	6.41	7.34
	4.0	8.14	8.88	3.72	5.06	5.81
	3.0	6.02	6.58	2.71	3.71	4.27
	2.0	3.91	4.27	1.70	2.37	2.74
50	**5.0**	12.90	14.05	6.00	8.09	9.26
	4.0	10.26	11.18	4.73	6.41	7.34
	3.0	7.61	8.30	3.47	4.72	5.42
	2.0	4.96	5.42	2.20	3.04	3.51
60	**5.0**	15.55	16.93	7.27	9.78	11.18
	4.0	12.37	13.48	5.75	7.76	8.88
	3.0	9.20	10.03	4.23	5.74	6.58
	2.0	6.02	6.58	2.71	3.71	4.27
70	**5.0**	18.20	19.81	8.53	11.46	13.10
	4.0	14.49	15.78	6.76	9.10	10.41
	3.0	10.79	11.75	4.99	6.75	7.73
	2.0	7.08	7.73	3.22	4.39	5.04
80	**5.0**	20.84	22.68	9.80	13.15	15.01
	4.0	16.61	18.08	7.77	10.45	11.95
	3.0	12.37	13.48	5.75	7.76	8.88
	2.0	8.14	8.88	3.72	5.06	5.81
90	**5.0**	23.49	25.56	11.06	14.83	16.93
	4.0	18.73	20.38	8.78	11.80	13.48
	3.0	13.96	15.21	6.51	8.77	10.03
	2.0	9.20	10.03	4.23	5.74	6.58
100	**5.0**	26.14	28.44	12.33	16.52	18.85
	4.0	20.84	22.68	9.80	13.15	15.01
	3.0	15.55	16.93	7.27	9.78	11.18
	2.0	10.26	11.18	4.73	6.41	7.34

Table 4: distribution and percentages of subjects with high CVD risk (20% or more) based on posttest-calculations derived from carotid atherosclerotic burden

	CA	**AA**	**PT**
FRAM	649 15%	1 063 24%	**1 667** **38%**
SCORE	512 12%	1 215 28%	1 385 32%
PCE	111 3%	**631** **14%**	821 19%

Table 5: expected benefits from population-wide lipid lowering with statins and PCSK-9 inhibitors in those with high CVD risk (20% or more) based on posttest-calculations derived from carotid atherosclerotic burden and their observed LDL at baseline (4.14 mmol/l)

	10 year	**Per year**
Baseline LDL mmol/l	4.15	
Risk PCE AA	28	
Risk FRAM PT	36	
LDL reduction with statins 50% (-15% intolerance)	35	
RRR with statins % per 1.0 mmol/l LDL	21	
RRR with PCSK9-I % per 1.0 mmol/l LDL (after 1st year)	16	
Achieved LDL reduction in mmol/l with statins	1.5	
RRR with statins %	30.5	
Risk Reduction for PCE risk with statin	8.5	
Risk Reduction for FRAM risk with statin	11.0	
LDL reduction with PCSK9-Inh. %	56	
Achieved LDL reduction in % with statin + PCSK9-inh.	91	
Achieved LDL reduction in mmol/l *	1.5	
RRR with PCSK9-Inh %	24.2	
Risk Reduction for PCE with PCSK9-Inhibitors	6.8	
Risk Reduction for FRAM with PCSK9-Inhibitors	8.7	
ARR PCE for statins plus PCSK9-Inhibitors	15.3	
ARR FRAM for statins plus PCSK9-Inhibitors	19.6	
NNT PCE for statins plus PCSK9-Inhibitors	6.5	
NNT FRAM for statins plus PCSK9-Inhibitors	5.1	
Population at risk	4477589	
PCE proportion	643736	
FRAM proportion	1700647	
PCE expected 10-year CVD events	180005	18001
FRAM expected 10-years CVD events	610733	61073
PCE prevented events in 10 years	27519	2752
FRAM prevented events in 10 years	119910	11991
Average expected CVD events	395369	39537
Average expected prevented CVD events	73714	7371
Cost per event in 10 years	200000	
Prevented costs (in Mio)	14743	1474
Prevented treatment costs (in Mio)	7371	737

* with statin and PCSK9-Inhibitors LDL is reduced from 4.15 mmol/l to 1.5 mmol/l over 10 years.