Statins, Ezetimibe and PCSK9-Inhibitors in Swiss Primary and Secondary Care: Clinical Cost-Efficiency Ratios

A Vascular Risk Foundation Analysis

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Data Source
Database encompasses over 5'000 primary care subjects with data on file about all independent cardiovascular risk factors and total plaque area from both carotid arteries. The cohort is continously upbdated. For more details refer to: https://sites.google.com/site/arteriscohorts/

Additional Material
www.docfind.ch/QALYVarifo2016.xlsx
www.docfind.ch/NTTSwitchTableHelp.xlsx
www.docfind.ch/NNTVarifo2016.xls

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Future developments
The paper is open for review.

Reprints
Only with reference notification available at www.docfind.ch/varifocostmodel.pdf and message for use to michel.romanens@gmail.com

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24th April 2016: Atorvastatin effect was modified according to the formula y = 7.1948ln(x) + 19.523, where x is Atorvastatin in mg and y is the percent LDL reduction (ref. Karlson, Eur J Prev Cardiol, 2016, DOI: 10.1177/2047487315598710)
28th April 2016: Title has been changed to give more emphasis to the individualized view of cost-efficiency per risk and per LDL level
30th April 2016: Part 2 was added to have a derivation model and a verification model.
06th May 2016: Part 3 and 4 was added

Content

Part 1: Individual Effects and costs based on randomised controlled trials

Abstract

Aim

Cost-efficiency of lipid interventions using Statins, Ezetimibe and PCSK9-Inhibitors are lacking for Switzerland. A QALY based approach, as performed for Statins by the Swiss Medical Board in 2014 may be misleading. We aim to look at individualized cost-efficiencies.

Method

Prior 10 year risk for cardiovascular disease (CVD) is calculated with the Framingham formula and a Markov model for those who switched from primary to secondary prevention over time. For secondary prevention, the Utrecht formula was used. Relative risk reduction per mmol/l LDL was 21%. Daily costs (percent lowering of LDL) were Sfr 0.37 for generic Atorvastatin (46%), SFr 2.30 for Ezetimibe (20%) and SFr 19.91 for PCSK9-Inhibitors (60%). Direct and indirect cost per event was estimated to be SFr 191'494.

Results

The SMB QALY model showed Statins cost/QALY of SFr 210'000 for 5 years and low cardiovascular risk, but only SFr 2'000 for very high risk subjects in 10 years. Using the SMB model for the combination Atorvastatin+PCSK9-Inhibitors, cost/QALY remained above SFr 100'000 even for the highest risk. Cost-efficiency remained low for Atorvastatin+PCSK9-Inhibitors and was comparable to Statins only in high risk subjects up from an LDL of 4.0 mmol/l, if daily costs were SFr 19.91. At a daily cost of SFr 6.90, PCSK9-Inhibitors are cost-efficient also in low risk subjects when combined with Statins up from an LDL level of at least 3.8 mmol/l. The cost-efficiency were lower in higher risk subjects with higher levels of LDL.

Discussion

The SMB cost/QALY model should not be used for resource allocation. Further, there was no fixed ICER threshold that could be used to find a fix price for PCSK9-Inhibitors in all individuals, both for primary and secondary prevention. The restriction of PCSK9-Inhibitors to secondary care cannot be justified. At daily costs of SFr 6.90 for PCSK9-Inhibitors, cost-efficiency would be comparable to usual Statin cost.

Conclusion

A fixed cost/QALY model is misleading and excludes many patients from primary and secondary prevention. This has legal and ethical implications. A federal agency expressed limitation on PCSK9-Inhibitors cannot be based on a uniform ICER threshold. PCSK9-Inhibitors should be used in primary and secondary care at daily cost of SFr 6.90 in order to have a maximum public health effect.

Background

Expanding medical possibilities and cost call for estimates about efficient resource allocation. Traditionally, quality adjusted life years (QALY), incremental cost efficiency ratios (ICER) and, with the use of QALY, incremental cost utility ratios (ICUR) are used to evaluate the relation between effect and cost of a new comer compared to the standard. Usually, when economical models are applied to medicine, they are based on various assumptions around an average patient. Since empirical proof for such concepts is usually lacking, such models may create a *pseudo*reality about the constancy of such models through various patient populations. As a result, economical evaluations generate fixed thresholds that can be used and abused by policy makers to decide about acceptable confines. The effects of lipid interventions using standard and new comer therapies (PCSK9-Inhibitors, Ezetimibe) and the implicated costs can now be easily modeled, since relative risk reductions (RRR) are constant for LDL reductions[1]. All calculations are available at www.docfind.ch/QALYVarifo2016.xlsx.

Hypothesis

Cost-efficiency of lipid intervention is not constant. It varies with prior risk and prior LDL levels.

Introduction

The VARIFO risk calculator was originally developed to repeat the Swiss Medical Board Calculations on the cost/QALY of statins in primary care using differences in prior risks at the individual level. The results can be viewed on the sheet VARIFO QALY SMB CALCULATOR and shows that the assumptions of the SMB on cost/QALY have to be easily falsified, since they did not consider the prior of cardiovascular risk in the calculations. This creates the idea, that Statins are generally not cost effective in primary care. Since cost-efficiency increases with the time of exposition to the effect and the prior risk for a cardiovascular events, the assumptions of the SMB statin report pertain only to a small part of the Swiss population, e.g. those at the lowest risk for a cardiovascular event. Further, the SMB Model kept several variables constant (e.g. LDL levels), therefore not acknowledging that with higher LDL levels higher preventive effects are possible.

Statins are efficient in the prevention of cardiovascular diseases and interventions. In 2016, Ezetimibe and PCSK9-inhibitors come more and more into action. Based upon prizes and effects on LDL cholesterol, costs of such therapies can now be estimated for an individual patient. Further, the higher the risk, the higher the absolute risk reduction and hence the lower the number needed to treat (NNT). We aim to look at various degrees of pre-interventional risks and calculate cost/QALY based on the SMB/Felder model, published 2014[2] and cost/effect and their ratios for various priors of cardiovascular risk. By giving the direct and indirect cost of cardiovascular events in Switzerland, costs of therapy can be put into perspective with avoided costs without the need to use QALY.

Methods and Materials

Based upon the starting level of LDL in an individual patient, the efficiency of the intervention on the relative and absolute risk reduction, NNT included, is calculated. Per 1 mmol/l LDL reduction we uniformly calculated a relative risk reduction (RRR) of 21% [1,3]. We assume that these effects are also uniform in secondary prevention and irrespective of age, sex and previous diseases.

The absolute risk reduction (ARR) is derived from the prior risk (P) minus the expected RRR.

ARR = P – RRR

Based upon the literature, we use uniform percent LDL reductions:

Percent LDL reduction with Atorvastatin 40 mg 46%[4], high dose PCSK9-Inhibitor 60%, with 10 mg Ezetimibe 20%, Statin+PCSK9-Inhibitors 80%.

Based upon published prizes, we use the following *daily costs* for the medications

- Generic Atorvastatin 80 mg half tablet Sfr. 0.37
- Ezetimibe 10 mg Sfr 2.30
- PCSK9-Inhibitors Sfr. 19.91

Prior risk in *primary care* was calculated with the Framingham risk equation for cardiovascular disease risk (FRAM-CVD)[5]. Prior risk in *secondary care* was calculated using a *Utrecht risk equation* derived from the TNT[6] and the IDEAL[7] trials, published by Dorresteijn in 2013[8] and with a linear extrapolation from the original 5 to 10 years by doubling this prior risk.

Based on Framingham CHD (MACE), CVD adds another 40% to MACE. Therefore, CHD risk is (e.g. AGLA risk) is 60% of CVD risk multiplied by the AGLA factor 0.7[9]. If CVD risk is 13.0%, AGLA risk is estimated to be 7.8%x0.7=5.5%. For secondary prevention we assumed that the 10 year risk was about 25% for another cardiovascular event[8] or 2.5% per year.

Further, we used a Markov Model for the occurrence of a second event in those with a first event assuming a risk of 2.5% per year, which resulted in a factor 1.111 (for further details view: Excel sheet "*Markov2016*"). According to the medications and their combinations used, a total RRR was generated and the absolute risk reduction (ARR) was calculated.

NNR was calculated using the formula 100/ARR%.

Total cost per intervention is expressed for 10 years in Swiss Francs (SFr). Further, management costs were 10'000 for 10 years (fix cost assumption).

Direct and indirect costs of MACE and STROKE were assumed to be 191'494 per event, irrespective of additional cost over time after the event. Based on the final Swiss report on NCD costs 2014[10] for the year 2011:

- AMI cost estimates Sfr 4'798'000'000
- STROKE cost estimates SFr 3'168'000'000
- Swiss death registers for 2011 found 8'105 deaths due to ischemic heart disease.

Assuming that for every death there are 3 non-fatal AMI (again based on Framingham Data), we estimate the number of MACE to be 32'420. Assuming a ratio of MACE/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 costs per event are 191'494. In view of the fact that we calculate over a time of 10 years, these costs per event may even underestimate true event costs.

Cost-efficiency was calculated as event costs minus treatment cost.

ICER was calculated using standard cost-efficiency / new comer cost-efficiency.

ICER variability was calculated for prior risk of 10%, 20%, and 30% and varied prior LDL values with increments of 0.2 mmol/l covering the range from 2.0 to 6.0 mmol/l.

Results

The following calculations are made in the excel sheet "*Graph*".

Low risk setting:

At a CVD risk of 10.0% (AGLA risk 4.2%) cost of treatment exceed the case costs of SFr 191'494 for all LDL levels between 2.0 and 5.6 mmol/l for Atorvastatin, by a minimum of 22'200 for Atorvastatin+Ezetimibe, by a minimum of 558'777 for Atorvastatin+PCSK9-Inhibitors and by a minimum of 792'789 for PCSK9-Inhibitors alone.

At a CVD risk of 18.0% (AGLA risk 7.5%) Atorvastatin is cost-efficient for an LDL between 3.2 – 6.0 mol. (Atorvastatin+Ezetimibe: 3.8 – 6.0 mmol/l). The use of PCSK9-Inhibitors is not cost-efficient for the LDL range 2-0 – 6.0 mmol/l.

Intermediate risk setting:

At a CVD risk of 30.0% (AGLA risk 12.5%) Atorvastatin is cost-efficient for an LDL between 2.0 – 6.0 mol. (Atorvastatin+Ezetimibe: 2.4 – 6.0 mmol/l). The use of PCSK9-Inhibitors is not cost-efficient for the LDL range 2.0 – 6.0 mmol/l.

High risk setting:

At a CVD risk of 50.0% (AGLA risk 21.0%) Atorvastatin is cost-efficient for an LDL between 2.0 – 6.0 mol. (Atorvastatin+Ezetimibe: 2.0 – 6.0 mmol/l), Atorvastatin+PCSK9-Inhibitors 4.8 - 6.0 mmol/l, PCSK9-Inhibitors alone is not cost-efficient for LDL between 2.0 – 6.0 mmol/l.

ICER

Keeping prior risk constant at the levels 10%, 20%, and 30%, with allowing for LDL increments of 0.2 mmol/l, Atorvastatin compared to Atorvastatin+Ezetimibe can be described by the formula

- $y = -3E+05\ln(x) + 1E+06$ ($r^2 = 0.9879$)

Similar logarithmic curves are seen for the Atorvastatin and Atorvastatin+PCSK9-Inhibitors comparison and for the Atorvastatin and PCSK9-Inhibitors comparison. When comparing the logarithmic curves, we observe a linear association that is described with the formula

- $y = 0.5x$

Cost/QALY using the SMB Statin Model

Using the SMB Statin model, cost variability is observed with different prior risks (Excel sheet: "*VARIFO QALY SMB Calculator*"). The originally published cost/QALY by the SMB with SFr 210'000 pertains to a scenario of a 5 year observation time in 1000 people having a risk for 50 myocardial infarction, from which 11 fatal and non-fatal heart attacks could be prevented with a NNT of 91. From this, the SMB concluded erroneously, that Statins should be used in primary care only if the risk for a fatal ischemic heart attack exceeds 7.5% in 10 years. This scenario corresponds to the risk of 413 heart attacks in 10 years in 1000 persons at a cost/QALY of Sfr. 2'089 and an NNT of 11. For the scenario of an NNT of 25 (18% risk for fatal and non-fatal heart attacks in 10 years), cost/QALY would be 40'251 .

Cost/QALY using the SMB Statin Model applied to PCSK9-Inhibitors

Using the SMB Statin model, cost variability is observed with different prior risks (Excel sheet: "*PCSK9 SMB*"). Cost/QALY pertaining to a scenario of a 5 year observation time in 1000 people having a risk for 50 myocardial infarctions, from which 11 fatal and non-fatal heart attacks could be prevented with a NNT of 91 would result in costs of SFR 210'000 for Statins and of SFr 1'351'243 for PCSK9-Inhibitors. For the scenario fatal risk of 7.5% in 10 years, which corresponds to the risk of 413 heart attacks in 10 years in 1000 people at a cost/QALY of Sfr. 2'089 and an NNT of 11, cost/QALY for PCSK9-Inhibitors would be SFr 110'914. For the scenario of an NNT of 25 (18% risk for fatal and non-fatal heart attacks in 10 years), cost/QALY would be 40'251 for Statins and SFr 303'509 for PCSK9-Inhibitors.

PCSK9-Inhibitors Cost Modeling

We assume an average cost of a Statin to be SFr 1.00 per day (SMB assumption 2014). At a prior risk of CVD 20% (AGLA 8.4%), Statin+PCSK9-Inhibitors is comparable to the cost-efficiency of Statin alone at daily costs of SFr 6.90, if treated LDL are at least 4.4 mmol/l. At a prior risk of CVD 40% (AGLA 16.8%), Statin+PCSK9-Inhibitors is comparable to the cost-efficiency of Statin alone at daily costs of SFr 6.90, if treated LDL are at least 2.4 mmol/l. At a prior risk of CVD 60% (AGLA 25.2%), Statin+PCSK9-Inhibitors is comparable to the cost-efficiency of Statin alone at daily costs of SFr 6.90, if treated LDL are at least 2.2 mmol/l.

Discussion

Cost-efficiency analysis is used widely in order to receive an impression about cost and effects of standard and new comer therapies (or medical tests). In this individual based calculation of prior cardiovascular risk, varying levels of LDL cholesterol, a major and independent cardiovascular risk factor, have variable effects on the ratios of cost-efficiency (ICER). In this *e*-publication we used several accepted assumptions about the calculation of prior risk in primary and secondary prevention (risk variable), about the risk reduction per 1.0 mmol/l LDL cholesterol reduction (effect variable), and about daily medication and medical costs of lipid intervention for generic Atorvastatin 40 mg, Ezetimibe 10 mg and PCSK9-Inhibitors, and finally the costs, both direct and indirect, per event (cost variables).

We put effects and costs into perspective by calculating one event cost at the uniform price of SFr 191'494 over 10 years. These event costs were subtracted from the overall treatment costs in 10 years. Our model is not based on QALY but on the NNT. In fact, we were able to calculate costs per NNT and compare these costs with the event costs for various degrees of prior risks and prior LDL values.

By applying two major gradients to the ICER calculations, namely variations in prior risk and variation in amounts of LDL, we could test, whether the assumption of a constant ICER exists. We could demonstrate that, at the individual level, costly new comer therapies for LDL lowering, such as Ezetimibe and PCSK9-Inhibitors, have better ICER with higher prior risk *and* higher LDL levels. However, we were also able to show, that at a constant prior risk, ICER changes dramatically with various levels of LDL cholesterol. Therefore, there exists no constant ICER for the same comparator: Atorvastatin 40 mg at 10% CVD risk and an LDL level of 2.0 mmol/l would cost SFr 503'504 after the subtraction of SFr 191'494 event costs (LDL 6.0 mmol/l: 40'172). Therefore, the within Atorvastatin ICER is 12.5 (8.9 for Atorvastatin+Ezetimibe, and 3.9 for Atorvastatin+PCSK9-Inhibitors).

An NNT based model shows that ICER have per se no additional value in cost estimates when we look at *individual* patients with various degrees of prior risk *and* prior LDL cholesterol. This is due to the fact, that lipid medications have larger effects with higher prior risk *and* higher LDL at baseline, which therefore, has to be taken into account. Uniform *ICER's are therefore not clinically relevant* when we apply cost-efficiency calculations to different individuals in our model. For other clinically relevant models, similar results may be found, therefore questioning the clinical value of ICER.

Further we observed that the SMB cost/QALY model overestimates costs by a large quantity. As an example, at the level of 7.5% mortality risk (which corresponds to an AGLA risk of 34% and a FRAM-CVD risk of 80%), Statin cost/QALY is SFr 2'089, but cost/event based on the NNT calculation is SFr – 133'000 for LDL 3.0 mmol/l and Sfr -163'000 for LDL of 6.0 mmol/l; similarly, for such highest risks, Atorvastatin+PCSK9-Inhibitors cost/event and LDL 3.0 is SFr -34'000 and for LDL 6.0 mmol/l is SFr -113'000. The SMB would calculate a uniform cost/QALY of SFr 111'000. *Therefore, by individualizing cost-efficiency calculations, a non-cost efficient medication becomes highly cost efficient when cost/event instead of cost/QALY is used, a situation very likely to offer a high return-on-*investment. Further, by withholding effective therapies with such SMB calculations, important questions about legal and ethical issues arise[11].

Personalization of resource allocation is now possible with the addition of arterial age to the prior risk equations, e.g. by replacing chronological age by arterial age[12]. If a 50 year old patient has a total plaque area of 80 mm^2 (a coronary risk equivalent), which corresponds to an arterial age of 63 years, a 8% AGLA risk at an

LDL level of 3.0 mmol/l would result in costs per avoided event of SFr 52'000 using chronological age of 50%, however using arterial age of 63, AGLA risk would increase from 8% to 15% and costs per avoided event would be SFr – 64'000, a difference of SFr 116'000 Sfr per avoided cost.

Price modeling based on an average Statin cost of SFr 1.00 (SMB assumption 2014) showed an equivalent ICER irrespective of prior risk but largely dependent on prior LDL levels, if Statin+PCSK9-Inhibitors would be available at a daily cost of SFr 6.90. This is exactly three times the price of Ezetimibe. Since PCSK9-Inhibitors are three times more effective in LDL lowering when compared to Ezetimibe, this difference in daily costs appears justified for a new comer medication.

Our calculations are also in line with a new report about higher effects of lipid intervention in higher risk subjects[13].

Limitations

A limitation of our calculators is due to the assumptions made. However, it allows for a comparative analysis between generic Atorvastatin 40 mg and PCSK9-Inhibitors as well as Ezetimibe, because the assumptions made remain the same for all comparisons.

Further, it is acknowledged that AGLA are extended by CVD, which may include at instances heart failure, angina, coronary revascularization and others. Based on the CTT analysis, for 1 MACE (CHD), CVD is 1.91[1,3]. Instead, we used only 1.60 and therefore, we rather underestimate the effects lipid lowering for the prevention of all cardiovascular diseases with Statins.

A major limitation lies in the uniform allocation of event costs (SFr 191'494) to different events (AMI, Stroke, Revascularisation ecc).

Another limitation are the various cost assumptions. However, our calculator allows immediate corrections and liberal input at the all possible costs and even allows at the clinical individual level, to check expected effects with really obtained effects, e.g. if LDL goals are achieved or not and what then is the effect on the cost calculations.

Conclusions

Administrative limitations issued by statal health care authorities for PCSK9-Inhibitors and Ezetimibe are acceptable only in those, where the constellation of pre-intervention risk and LDL levels have been shown not to be cost-efficient at the individual level. Therefore, *general limitations in this scenario lead to rationing of effective medicine despite acceptable cost-efficiency. Global limitations are therefore legally, ethically and socially not acceptable for both PCSK9-Inhibitors and Ezetimibe and may seriously damage many people.*

An important finding lies in the improvement of cost efficiency, when the information from carotid plaque is incorporated into the risk prediction models (e.g. arterial age instead of chronological age). Such information should therefore be used to justify costly medical preventive interventions further.

If ICER are applied to decision making, especially with recurrence to QALY, severe overestimation of real costs for prevention of cardiovascular events at the individual level may occur. In general, uniform thresholds for reimbursements are hard to justify unless health economical models have clearly shown, that the ICER assumptions are equal for various individual priors and various individual clinical variables. Risk of withholding effective therapies is real with the SMB calculations and has legal and ethical implications. Future health technology assessments (HTA) have to take into account prior risk and clinical variables at the individual level, in order to be ethically and legally appropriate. *Average HTA calculations have a high risk to declassify effective therapies in a major part of the population.* We present individualized HTA for lipid lowering drugs, a method, that allows for precise resource

allocations: Since cost per prevented event are largely dependent on daily medication costs, the VARIFO calculator may help to find an acceptable threshold for Ezetimibe and PCSK9-Inhibitors. Although further research is needed to define ideal cost thresholds with more precision – e.g. cost which would lead to a maximum of prevented events –, such a threshold would be SFr 6.90 per day for PCSK9-Inhibitors, independent of prior risk but with higher LDL intervention levels in lower prior risk: cost per prevented event would be almost identical when compared to daily Statin cost of SFr 1.00 Therefore, a daily price of SFr 19.91 is not justified by our calculations.

Use of PCSK9-Inhibitors should be defined on risk and not on primary or secondary prevention situations, because under circumstances a person in secondary prevention may have a lower risk than a person in primary prevention. Similarly, a limitation to those with peripheral artery disease without the inclusion of carotid artery disease cannot be justified.

Figure 1: Primary Prevention Calculator Engine

This engine calculates the 10 year Framingham risk for cardiovascular disease. The input variables are highlighted in yellow. An additional feature is the arterial age input, where the calculator displays the arterial age attributed risk at the bottom of the Engine. Such a tool allows to immediately calculate the cost-efficiency of a lipid intervention, e.g. with generic statin, Ezetimibe, PCSK9-Inhibitors and the combinations.

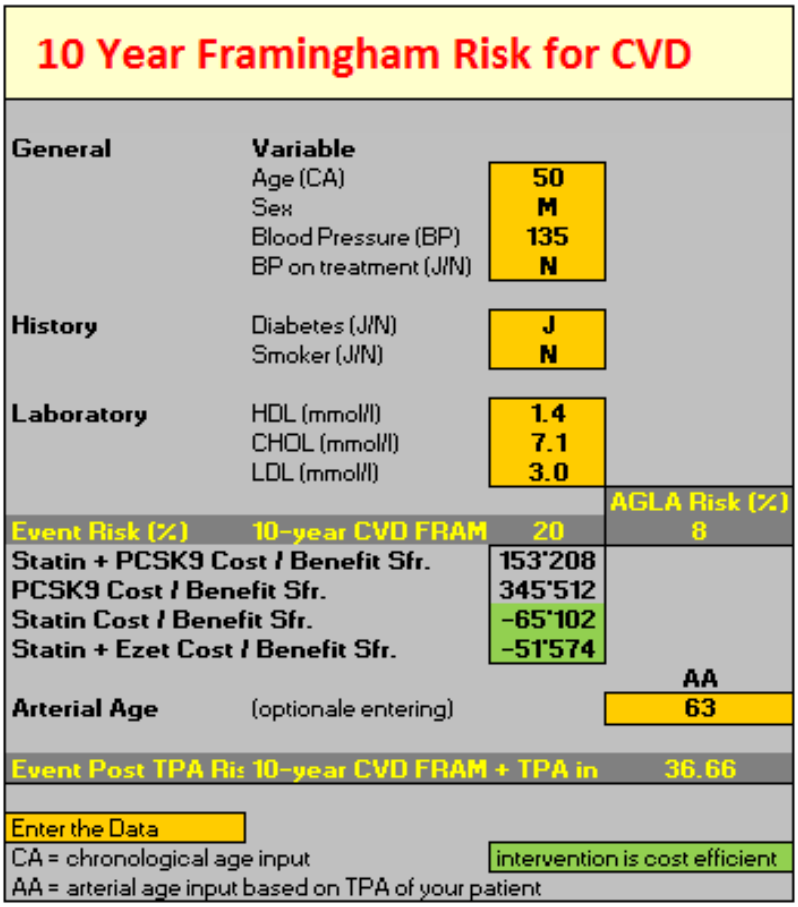
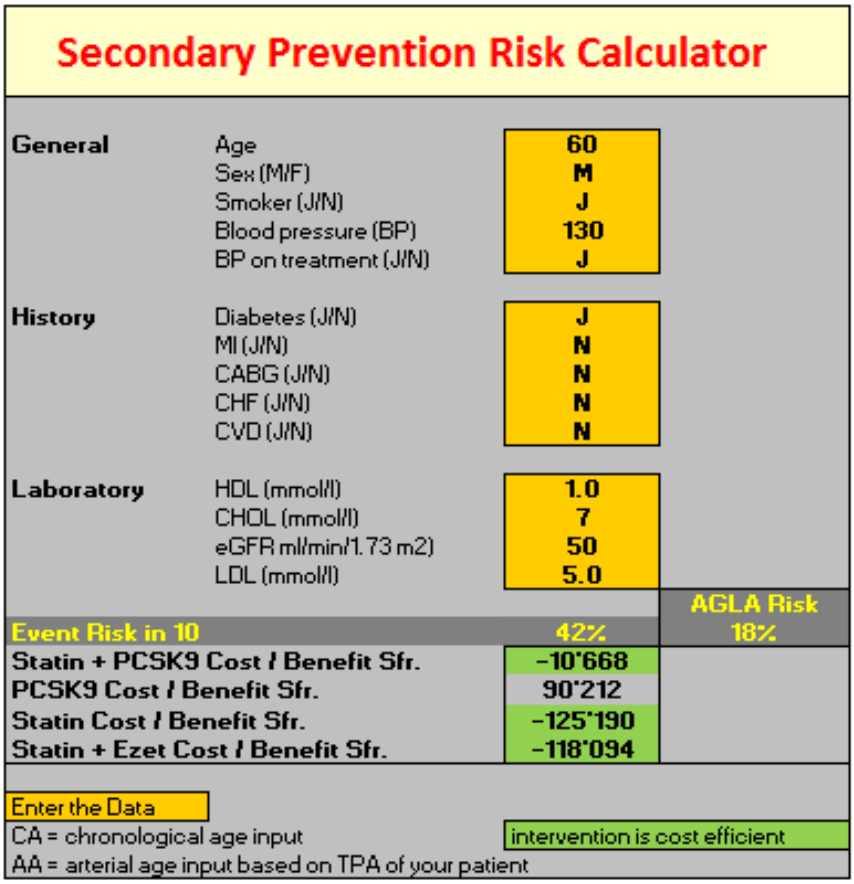


Figure 2: Secondary Prevention Calculator Engine

This engine calculates the 10 year "Utrecht" risk for cardiovascular disease in secondary prevention. The input variables are highlighted in yellow. Such a tool allows to immediately calculate the cost-efficiency of a lipid intervention, e.g. with generic statin, Ezetimibe, PCSK9-Inhibitors and the combinations.



Secondary Prevention Risk Calculator

General	Age	60	
	Sex (M/F)	M	
	Smoker (J/N)	J	
	Blood pressure (BP)	130	
	BP on treatment (J/N)	J	
History	Diabetes (J/N)	J	
	MI (J/N)	N	
	CABG (J/N)	N	
	CHF (J/N)	N	
	CVD (J/N)	N	
Laboratory	HDL (mmol/l)	1.0	
	CHOL (mmol/l)	7	
	eGFR ml/min/1.73 m2)	50	
	LDL (mmol/l)	5.0	
			AGLA Risk
Event Risk in 10		42%	18%
Statin + PCSK9 Cost / Benefit Sfr.		-10'668	
PCSK9 Cost / Benefit Sfr.		90'212	
Statin Cost / Benefit Sfr.		-125'190	
Statin + Ezet Cost / Benefit Sfr.		-118'094	

Enter the Data

CA = chronological age input

AA = arterial age input based on TPA of your patient

intervention is cost efficient

Figure 3: Example of the Calculation Engine

In this example on top left the daily medication cost and the avoidable cost per case. Prior risk of CVD is 20% in 10 years, corresponding to a AGLA risk of 8.4%. The engine calculates cost efficiency for every 0.2 mmol/l LDL increase between 2.0 and 6.0 mmol/l of LDL. The engine displays in green, at which LDL level the medical intervention becomes cost-efficient.

Enter Data		cost efficient		
0.37	Daily Statin Cost			
2.30	Daily Ezetimibe Cost			
6.90	Daily PCSK Cost			
191'494	10 year procedural and societal (indirect) costs of CVE			
Prior Risk CVD	AGLA RISK			
20	8.40			
LDL	Statin alone	Statin + Eze	Statin + PCSK9	PCSK9 alone
2.0	72'907	129'082	297'870	436'872
2.2	48'871	99'939	253'382	379'748
2.4	28'841	75'653	216'309	332'145
2.6	11'892	55'103	184'940	291'865
2.8	-2'636	37'489	158'051	257'339
3.0	-15'226	22'223	134'748	227'417
3.2	-26'243	8'866	114'358	201'235
3.4	-35'964	-2'920	96'367	178'133
3.6	-44'604	-13'396	80'375	157'598
3.8	-52'335	-22'770	66'066	139'225
4.0	-59'293	-31'206	53'188	122'689
4.2	-65'589	-38'839	41'536	107'728
4.4	-71'312	-45'778	30'944	94'127
4.6	-76'537	-52'113	21'273	81'709
4.8	-81'327	-57'921	12'408	70'325
5.0	-85'733	-63'264	4'251	59'853
5.2	-89'801	-68'196	-3'277	50'185
5.4	-93'568	-72'762	-10'248	41'234
5.6	-97'065	-77'003	-16'721	32'923
5.8	-100'321	-80'951	-22'748	25'184
6.0	-103'360	-84'635	-28'373	17'961

Part 2: Individual Effects and costs based on 5068 observations

Summary Part 2

Aim

Cost-efficiency of lipid interventions using Statins, Ezetimibe and PCSK9-Inhibitors are lacking for Switzerland. A QALY based approach, as performed for Statins by the Swiss Medical Board in 2014 may be misleading. We aim to look at individualized cost-efficiencies in 5068 primary care subjects with various degrees of cardiovascular risk.

Method

Prior 10 year risk for cardiovascular disease (CVD) is calculated with the Pooled Cohort Equation (PCE) and Bayes Theorem determined posterior risk based on carotid atherosclerosis total plaque area (TPA=PCE+) in each individual. Eligibility for lipid lowering was a) PCE ≥ 7.5% and b) absolute risk reduction of ≥ 2.3% with prior and with posterior risk. Event costs per 10 years were computed as CHF 191'494, which includes direct and indirect costs. Cost efficiency was defined by meeting a treatment cost below CHF 191'494. ICER was determined using a standardized cost per avoided event. Daily costs of medication was CHF 0.37 for generic Atorvastatin 40 mg, CHF 2.30 for Ezetimibe and CHF 19.91 for PCSK9-inhibitors. Additional treatment costs were computed with CHF 10'000 in 10 years. Measure of TPA was set to cost CHF 75.

Results

We assessed 5068 healthy subjects from Germany and Switzerland. Average age was 50.8±10.8 years, 61% were male, average LDL was 3.7±1.0 mmol/l, TPA was 43±51 mm^2, and average PCE risk was 7.9±11.5%, average Framingham CVD risk was 10.9±9.2%, average ESC-CVD risk was 1.6±2.1% and average AGLA risk was 4.3±5.1%. Atorvastatin versus Atorvastatin Ezetrol had an ICER of 1.40 for PCE ≥7.5 and an ICER of 1.32 for AAR ≥ 2.3%. Atorvastatin versus Atorvastatin PCSK9-I had an ICER of 5.55 for PCE ≥7.5 and an ICER of 6.20 for AAR ≥ 2.3%. The addition of TPA to Atorvastatin had an ICER of 0.65 and 0.58 respectively. Cost modeling showed maintained cost-efficiency for Ezetrol (CHF 2.30), however, PCSK9-Inhibitors were cost-efficient only for CHF 4.00 to 5.00 day.

Discussion

At the level of a general middle aged healthy population, TPA and Atorvastatin were highly cost-effective, and Ezetimibe had an acceptable cost-efficiency ICER. However, PCSK9-Inhibitors prices of CHF 19.91 cannot be justified by the effects on LDL and expected event reduction.

Conclusion

Adequate prizing of new medications such as PCSK9-Inhibitors should be based on expected effects, as long as the results from randomized controlled trials are not available. Actual PCSK9-Inhibitors prizing is likely to exclude many patients in primary care from an effective therapy. This also implies ethical problems due to administrative limitations of expensive new drugs, a direct consequence of exaggerated treatment costs. Prizes should be adopted to expected effects, whenever possible, and to expected direct and indirect costs.

Introduction

Cost-efficiency models are rarely tested in real patients. LDL cholesterol is an independent cardiovascular risk factor and it has been shown, that the relative risk reduction (RRR) is at least 21% per 1 mmol/l LDL reduction and RRR may even be higher in primary prevention[1]. Because such effects were observed not only with statins but also very recently with Ezetimibe[14], it can be anticipated, that the use of PCSK9-Inhibitors will have similar beneficial effects as statins.

LDL cholesterol has a dramatic effect on public health. LDL cholesterol reductions may therefore decrease the risk for many cardiovascular diseases such as myocardial infarction, stroke, revascularizations, and dementia due to cerebral ischemia.

The cost at which such beneficial effects can be obtained, however, depends largely on the magnitude of LDL effects of a drug and the costs to obtain such effects. In view of the problem of side effects and intolerance of statins, which may affect about 10% of statin users[15], alternatives are needed. Both Ezetimibe and PCSK9-Inhibitors are efficient in reducing LDL cholesterol and may be used in addition to statins.

Since beneficial effects for LDL lowering are proven even in low risk subjects for statins and can be expected to a similar extent Ezetimibe and for PCSK9-Inhibitors, supply of such drugs have to meet the demands for all subjects with LDL elevations, irrespective of base-line risk.

It has been shown that the number of subjects who might benefit from LDL lowering increases, when a treatment decision is based on an achievable absolute risk reduction of at least 2.3% instead of the pooled cohort equation (PCE) risk threshold of at least 7.5%[13]. In this study, another 9.5 million subjects not qualifying for statin treatments based on the PCE threshold would be eligible for statin treatments with an average number to treat (NNT) of 25 (instead of 21).

We aim to define the incremental cost-efficiency ratio (ICER) in 5068 healthy subjects for statins, Ezetimibe and PCSK9-Inhibitors for a cardiovascular risk of ≥ 7.5% defined by PCE, for subjects, in whom ARR of at least 2.3% can be obtained with lipid lowering drugs and to measure the ICER for the setting of using posterior risk derived from the extent of atherosclerosis in carotid arteries.

Methods

Subject selection

Groups of subjects were assessed at the practice based level as described elsewhere[12] and are collected in the working group of *"Arteris Cohort"*[16]. In the Swiss 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 Imaging Center in Koblenz, all subjects were referred within a working medicine setting[17]. Subjects had to be free of cardiovascular symptoms or diseases. Laboratory values, blood pressure and medical history were measured locally and entered into a data spread-sheet (Excel, Microsoft, Richmond, USA).

Carotid Imaging

Presence and burden of longitudinal carotid plaque surface was imaged with a high resolution ultrasound linear transducer using a 7.5–12.0 MHz probe, which identified all plaques defined by intimal thickening ≥1.0 mm. The longitudinal area of all plaques was summed up to compute the value for the total plaque area (TPA) in mm^2. All TPA measurements were made by A.A. in Koblenz and by M.R. in Olten. A TPA≥80 mm^2 (TPA80) defined a coronary risk equivalent (risk > 20% for fatal and non-fatal myocardial infarction in 10 years)[18].

Computation of Risk

Cardiovascular risk was computed using the published risk formulae in an Excel spread sheet. We used the European Society of Cardiology risk calculators for low risk populations (SCORE and SCORE-HDL[19]), the pooled risk equation (PCE) and the Framingham risk calculator for major cardiac (FRAM-CHD) and major cardiovascular events (FRAM-CVD). The PROCAM risk was calculated manually online, since the algorithm is not published. For Switzerland, PROCAM risk was multiplied by the factor 0.7 (according to the Swiss AGLA guidelines 2014[9]). The SCORE risk was calculated using the algorithm published by Conroy[20] and the SCORE-HDL[21] risks were calculated as previously described by Descamps[19].

Computation of Statin effects

Subjects recommended for statin therapy were based on a) the 2013 ACC/AHA cholesterol guideline[22], and b) if absolute risk reduction with LDL lowering drugs was calculated to be at least 2.3% in 10 years (NNT 44.5). LDL lowering capacity was 46% for Atorva 40 mg[4], 20% for Ezetimibe and 60% for PCSK9-Inhibitors; for the combinations we computed 66% for Atorva / Ezetimibe and 80% for Atorva / PCSK9-Inhibitors. Based upon each individuals LDL cholesterol, absolute expected LDL cholesterol reduction was calculated. Per 1 mmol/l LDL reduction a RRR of 21% was used and from this ARR calculated. Posterior risk was based on the total plaque area (TPA) of each individual using the Bayes theorem and sensitivities / specificities for incident myocardial infarction from the Tromso study[23]. These were adopted using the following formulas:

Female-Sensitivity" = - 0.268*LN(TPA) + 1.1551 "
Female-Specificity " = 0.144*LN(TPA) + 0.4142 "
Male-Sensitivity " = - 0.222*LN(TPA) + 1.0187 "
Male Specificity " = 0.1652*LN(TPA) + 0.2931 "

These formulas were validated externally for the London cohort originally described elsewhere[24] using ROC analyses: AUC original 0.743, AUC formulas 0.753 (p NS).

Computation of ICER

Total therapy cost was calculated for 10 years using 3650 days multiplied by the daily medication costs and adding CHF 10'000 for medical services associated with lipid therapy and adding CHF 75 for the TPA measurement. Costs per avoided event was calculated by total costs divided by the number of avoided events, which equals costs per avoided event (CEA). Respective CEA for Atorvastatin, Ezetimibe and PCSK9-Inhibitors were divided with Atorvastatin as the comparator, yielding the ICER. Direct and indirect costs per event was estimated to be CHF 191'494. Treatment costs exceeding this threshold were deemed not to be cost-efficient.

Statistics

We used MedCalc software (Version 13.3.3.0) [25]. Level of statistical significance was set at $p < 0.05$.

Results

We assessed 5068 healthy subjects from Germany and Switzerland. Average age was 50.8±10.8 years, 61% were male, average LDL was 3.7±1.0 mmol/l, TPA was 43±51 mm^2, and average PCE risk was 7.9±11.5%, average Framingham CVD risk was 10.9±9.2%, average ESC-CVD risk was 1.6±2.1% and average AGLA risk was 4.3±5.1% (Table 1).

Compared to the risk driven approach (PCE 7.5%), there were an additional 40% qualifying for a lipid intervention using the LDL driven approach (with TPA: 25%).

Costs per event are shown in Table 2 (without TPA) and in Table 3 (with TPA). Both Atorvastatin and the combination with Ezetimibe remained cost-efficient at the avoided event level (e.g. costs per event below CHF 191'494), but at higher costs for Atorvastatin / Ezetimibe (ICER 1.40 and 1.64, Table 4), whereas the use of PCSK9-Inhibitors showed excessively high costs and an ICER of 5.55 and 6.20 (Table 4) with

similar findings for the scenario with TPA (Tables 3 and 5).

The addition of TPA to Atorvastatin had an ICER of 0.65 and 0.58 respectively.

Cost modeling showed maintained cost-efficiency for Ezetrol using the risk driven approach (CHF 1.30 for the LDL driven approach), further, PCSK9-Inhibitors were cost-efficient only for CHF 4.50 (risk driven) and CHF 2.00 (LDL driven). Using TPA, cost modeling of PCSK9-Inhibitors was sufficient at CHF 6.00 and CHF 4.50 respectively (modeling can be made on www.docfind.ch/NNTVarifo2016.xls and on www.docfind.ch/NTTSwitchTableHelp.xlsx).

Discussion

We assessed 5068 healthy subjects from Germany and Switzerland, for whom baseline variables regarding cardiovascular risk factors and TPA, an independent risk measure for cardiovascular risk. The population was relatively young (mean age 50 years) and was mainly practice based, e.g. there, where medical decisions about lipid interventions are made.

Average LDL level in this population was 3.7 mmol/l, which gives room for cardiovascular risk reduction using lipid lowering drugs. The average risk of the population was low, e.g. < 10% risk for cardiovascular events and 1.6% for estimates about death due to myocardial infarction or stroke (ESC-CVD).

Subjects with a low coronary risk became a target for lipid intervention, as exemplified by the ACC / AHA guidelines 2013[22]. Using a fix target of PCE 7.5% or more may however exclude subjects with lower risk, who may benefit from lipid lowering interventions ("risk driven approach"). Using an individualized "LDL driven approach" in the primary prevention National Health and Nutrition Examination Survey for years 2005-2010, another 9.5 million U.S. citizens or another 35% of the population would qualify for lipid lowering interventions[13].

In our primary prevention population, we found that another 40% would qualify for lipid lowering, albeit being below the PCE risk threshold of 7.5%. Using TPA, this amount would be reduced to 25%. Both ways show the potential to target LDL levels in low risk subjects.

A TPA approach would further detect subjects with reclassification of cardiovascular risk using posterior probabilities. In fact, this approach led to a substantial increase in the number of subjects eligible for Statins. Of note, at the dose and cost of Atorvastatin chosen, it is expected that such a regimen is cost saving both for the risk and the LDL driven approach, when calculating 10 year cardiovascular event costs to be CHF 191'494. Using the LDL driven approach in combination with TPA would double the number of prevented cardiovascular events when compared to a risk driven approach without TPA (Table 2 and 3).

Ezetimibe has a cost per prevented threshold of CHF 191'494 only with the risk driven strategy, for the LDL driven strategy, daily Ezetimibe costs should be reduced to CHF 1.30. Similarly, PCSK9-Inhibitors are by far not cost efficient with ICER above 5.0 at a daily cost of CHF 19.91 (ex-factory costs, definitive costs might even be higher), appropriate daily costs, depending on the model used, should be between CHF 2.00 and 6.00 in order to keep ICER < 3.0.

Conclusion

Using a large sample of 5068 healthy practice based subjects, for whom we had information about cardiovascular risk factors and amounts of carotid atherosclerosis, we could show that the LDL driven approach allows more subjects for lipid interventions and a higher preventive effect, further reinforced by the use of TPA.

Since prevention of cardiovascular events with lipid lowering drugs, especially by the use of Statins, and LDL driven approach appears more appealing and in fact was calculated to further

improve the number of preventable cardiovascular events.

However, many subjects eligible for a LDL cholesterol intervention may not benefit because of high costs of Ezetimibe and PCSK9-Inhibitors. From a public health point of view, but also for ethical and parity reasons, pricing of lipid lowering drugs should be calculated based on expected effects and expected costs per avoided event, including direct and indirect costs. Asking for high prizes in conjunction with a limitation of the drug to a few, very high risk patients, is not likely to be effective at the population level.

Tables

Table 1: subjects baseline characteristics

N	5068	
Age (SD)	50.8	10.8
Male (%)	3073	61
LDL mmol/l (SD)	3.7	1.0
TPA mm2 (SD)	43	51
FRAM CVD % (SD)	10.9	9.2
PCE % (SD)	7.9	11.5
ESC CVD % (SD)	1.6	2.1
PROCAM % (SD)	5.1	6.7
AGLA % (SD)	4.3	5.1

Table 2: costs per avoided case in CHF without TPA

	A1 Ator	A2 Ator	B1 Eze	B2 Eze	C1 PCSK9	C2 PCSK9
PCE	>=7.5%	>=2.3	>=7.5%	>=2.3	>=7.5%	>=2.3
N	5068	5068	5068	5068	5068	5068
>=7.5%	1728	2902	1728	2902	1728	2902
N events	299	362	299	290	299	362
N prevented	188	228	233	241	251	272
Drug cost	0.37	0.37	2.67	2.67	20.28	20.28
Days	3650	3650	3650	3650	3650	3650
Add	10000	10000	10000	10000	10000	10000
Total Cost	19'613'664	32'939'151	34'120'224	57'301'441	145'190'016	243'831'844
Cost per Case	104'328	144'470	146'429	237'568	579'352	895'022

Table 3: costs per avoided case in CHF with TPA

	A1 Ator	A2 Ator	B1 Eze	B2 Eze	C1 PCSK9	C2 PCSK9
PCE	>=7.5%	>=2.3	>=7.5%	>=2.3	>=7.5%	>=2.3
N	5068	5068	5068	5068	5068	5068
>=7.5%	2459	3271	2459	3271	2459	3271
N events	672	715	672	290	672	715
N prevented	413	443	304	254	415	443
Drug cost	0.37	0.37	2.67	1.30	20.28	20.28
Days	3650	3650	3650	3650	3650	3650
Add	10075	10075	10075	10075	10075	10075
Total Cost	28'095'305	37'372'811	48'738'610	48'476'220	206'794'523	275'081'287
Cost per Case	68'026	84'336	160'369	190'477	498'180	620'752

Table 4: ICER without TPA

(A=Atorvastatin, B=Ezetimibe, C=PCSK9-Inhibitors, 1=PCE at least 7.5%, 2=ARR at least 2.3%)

B1/A1	B2/A2	C1/A1	C2/A2	C1/B1	C2/B2
1.40	1.64	5.55	6.20	3.96	3.77

Table 5: ICER with TPA

(A=Atorvastatin, B=Ezetimibe, C=PCSK9-Inhibitors, 1=PCE at least 7.5%, 2=ARR at least 2.3%)

B1/A1	B2/A2	C1/A1	C2/A2	C1/B1	C2/B2
2.36	3.02	7.32	7.36	3.11	2.44

Part 3: Estimate on Return on Investment

Based on the observation in 5068 individuals with an average age of 51 years (range 40-70) and the population in Switzerland in the year 2011 between age 40-70 (N=2'947'832) an attempt to calculate the return-on-investment can be made (Table): in the A1 column 188 cardiovascular events can be prevented with Atorvastatin with a return on investment of CHF -87'166 per case, if a case costs CHF 191'494. At the population level, in 10 years, 109'351 cases could be prevented with a return-on-investment of CHF 9.5 Mia. Adding Ezetimibe to Atorvastatin at usual prizes, 135'534 cases could be prevented with a return-on-investment of CHF 6.1 Mia. However, using a lipid driven approach, the addition of Ezetimibe would add costs of CHF 6.4 Mia. Use of PCSK9-Inhibitors at daily costs of CHF 19.91 would save another 40'000 subjects, but at an additional cost for all saved subjects of CHF 56.5 to 111.5 Mia. From this, at the population level, the far best option is Atorvastatin 40 mg/d at cost of CHF 0.37 per day, which would eliminate 132'618 cardiovascular event in Switzerland over a time period of 10 years. The addition of Ezetrol is cost saving, if PCE is at least 7.5%, but not for an absolute risk reduction of 2.3% or more. A comparison of such results with welfare calculations would be interesting[26].

	A1	A2	B1	B2	C1	C2
ICER	Ator	Ator	Eze	Eze	PCSK9	PCSK9
PCE	>=7.5%	>=2.3	>=7.5%	>=2.3	>=7.5%	>=2.3
N	5068	5068	5068	5068	5068	5068
>=7.5%	1728	2902	1728	2902	1728	2902
N events	299	362	299	290	299	362
N prevented	188	228	233	241	251	272
Atorva cost	0.37	0.37	2.67	2.67	20.28	20.28
Days	3650	3650	3650	3650	3650	3650
Add	10000	10000	10000	10000	10000	10000
Total Cost	19'613'664	32'939'151	34'120'224	57'301'441	145'190'016	243'831'844
Cost per Case	104'328	144'470	146'429	237'568	579'352	895'022
Cost per prev Case	191'494	191'494	191'494	191'494	191'494	191'494
Investment per prevented case	-87'166	-47'024	-45'065	46'074	387'858	703'528
Study population return on investment	-16'387'208	-10'721'481	-10'500'735	11'113'088	97'200'127	191'662'896
Population prevented cases	109'351	132'618	135'534	140'295	145'767	158'461
Population return on investment	-9'531'715'891	-6'236'212'466	-6'107'814'004	6'463'993'097	56'537'025'310	111'481'850'404

Part 4: Effects and costs of lipid lowering interventions: a comparison between derivation and verification

Executive Summary

We have described two cost-efficiency models for lipid lowering drugs at the individual level. First, we created a derivation model incorporating costs per avoid cardiovascular event. Second, we tested this approach in a large sample within relative young men and women within a primary prevention setting using a risk and an LDL driven approach in a verification attempt.

Our principle findings are: Ezetimibe has borderline cost-efficiency for cardiovascular event prevention. Especially using an LDL driven approach would make it more reasonable to downsize the daily costs to CHF 1.30; PCSK9-Inhibitors should be reduced below CHF 7.00, preferably to CHF 5.00 per day in order to be cost-effective at the population level. At the individual level, cost-efficiency largely depends on prior risk, posterior risk, and LDL level.

Our model is based on robust assumptions and measurements and is highly likely to reflect, what medical doctors encounter in daily clinical practice. If the goal is to achieve a maximum on preventable cardiovascular events at a reasonable cost based on expected but evidence based effects of newcomer drugs, then prizes should be reduced as evidenced by our calculators.

The distinction between primary and secondary prevention is not of a real clinical value, since risk may be grossly higher in certain subjects in primary than in secondary care. Also, re-imbursement limitations except for familial hypercholesterolemia, secondary prevention or for clinical atherosclerosis can hardly be justified, because a cardiovascular event may represent the same amount of suffering in those with and without clinical atherosclerosis.

The addition of imaging helps to further risk stratify subjects, e.g. those with atherosclerosis are likely to benefit even more from LDL lowering drugs. Further, we could show, that TPA has an excellent ICER both for a risk and an LDL driven approach.

Further, we have shown that QALY based models of the Swiss Medical Board exaggerate expected costs when compared to costs per avoided event and therefore needs some calibration. However, because QALY based effects may not sufficiently be evidence based, they may be subject to manipulation and erroneous results.

An important finding of our study is the variation of ICER when cardiovascular prevention is the issue, because of differences in prior, posterior and LDL level associated risks. Therefore, a unique ICER per drug and indication may be in conflict with individual rights and creates ethically problematic issues.

Based upon the Swiss constitution, excellency of the medical health care system is a societal obligation. We have tried to broaden the discussion about cost, effects and cost-efficiency ratios and hope that this work helps at the decisional level to find solutions that create a maximum benefit to the population.

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