Health Technology Assessment of Generic Statins and Generic Ezetimibe:

Cost-Efficiency for the prevention of cardiovascular events.

Vascular Risk Foundation, Switzerland

Author: Michel Romanens, MD

Questions, discussion and contact: michel.romanens@hin.ch

Funding: Varifo / Fairfond

Project: 11.04.2018, 17:35 – 13.04.2018, 17:50

Introduction

Morbidity and mortality due to atherosclerosis is highly prevalent worldwide (1,2) and could be prevented by up to 90%, if all risk factors were treated (3). Moreover, atherosclerosis detected by imaging is a marker of all-cause mortality (4,5) and should therefore be integrated into risk prediction models in order to improve the appropriateness of preventive therapies (6). One major and independent risk factor is cholesterol (7) and lowering of LDL cholesterol with statins and Ezetimibe reduces the risk of cardiovascular events by a relative risk of 22%-30% per 1 mmol/l LDL reduction achieved (8–10).

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 (11). If indicated by cardiovascular risk estimates – especially when documented through the presence of atherosclerosis assessed by carotid plaque imaging – any attempt should be made to lower LDL cholesterol (12,13). While statins are now available as a generic at relatively low costs (0.50 SFr. per day), cost-efficiency of Ezetimibe has not been formally tested for the current daily costs of SFr. 1.23 in Switzerland. Quality of life measurements integrated into QALY have been criticized for subjective and ethical considerations (14). Calculations of value-based prices are difficult (15) and the results of *fixed pricing* are dependent on the average risk levels and the chosen cutoff of cost per QALY gained (16,17).

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 (18) at the 150’000/QALY SFr. gained level and compare this with results with a value-based *individual pricing of the Vascular Risk Foundation* (Varifo) in cardiovascular prevention using risk estimates for cardiovascular events and base-line LDL levels.

Methods

1. The Varifo cost-efficiency model (individual price model)

Calculation of absolute risk reduction over 10 years: Per 1 mmol/l LDL reduction we calculated for statins a relative risk reduction (RRR) of 30% for the combined CTT outcome (19). Atorvastatin 40 mg/d reduces LDL by 46% and Rosuvastatin 20 mg/d reduces LDL by 50% (20), Ezetimibe 10 mg reduces LDL by 22% (10). The effective RRR (RRRe) is therefore given by the multiplication of RRR with the LDL reduction achieved. The absolute risk reduction AAR is baseline risk (R) multiplied by RRRe.

Calculation of direct and indirect medical costs: Direct and indirect costs of fatal and non-fatal myocardial infarction and stroke are estimated. Based on the final Swiss report on NCD costs 2014 (21) 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 7’003 deaths due to ischemic heart disease.

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 30’812 in Switzerland for the year 2011. The incidence of stroke in Switzerland is about 150:100’000, which corresponds to 11805 strokes in 2011, of which 2’360 are fatal and 9’490 are non-fatal. Those with an event will experience a second event with a probability of 6.8% per year for myocardial infarction and 4.8% per year for stroke (22). Over a 10-year period, events occur on average after 5 years with a probability of 34% for myocardial infarction and 24% for stroke in the same individual. Therefore, in 30’812 non-fatal myocardial infarctions estimated in 2011, 34% were assumed to be repeated events, therefore 20’336 individuals were affected (stroke: 9’572 affected individuals). Direct and indirect cost per individual is 171’119 SFr. for myocardial infarction and 330’961 SFr.per stroke, which amounts to an average amount of 251’035 for cardiovascular events. For the ease of calculation, we used avoidable direct and indirect medical costs of 200’000 SFr. per event, which is accounts for additional costs due to coronary revascularization performed in individuals without myocardial infarction and thus represents a conservative cost-estimate.

Individual price model (Varifo) for Ideal costs were calculated as follows: based on the calculated absolute risk reduction obtained by the individually expected magnitude of treatment on LDL reduction, an NNT was calculated for a 10-year period. The price of the drug was customized in such a way that treatment costs equal 200’000 SFr. (which is the expected direct and indirect cost of a prevented cardiovascular event (www.docfind.ch/pepqalyeze.xlsx). Further, for every increment in risk or LDL, ideal daily costs can be calculated.

2. The SMB cost-efficiency model (fixed price model)

Calculation of cost/QALY using the cost-efficiency model of the SMB

According to the Swiss Medical Board, cost-efficiency for cardiovascular events can be calculated based upon an effect model developed for statins (18). 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 8500 SFr. per fatal event and 25'000 SFr. per nonfatal event in the first year and 8'000 SFr. 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 365 SFr. for statins and 170 SFr. for medical monitoring (Total 470 SFr.). 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 × 2.5 ×1 = 5.0 QALY for fatal events and 9 × 2.5 × 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 × 5 × 1 = 20 QALY for fatal and 18 × 5 × 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 compared to 5 years. For this analysis, we evaluated annual costs for the Atorvastatin, Rosuvastatin and Ezetimibe in order to obtain a threshold of 150'000 SFr./QALY gain at various 10-year risk levels. Further, we used the same relative and absolute risk reduction effects of the drugs as in the *Individual price model.* Over a 10-year period, the SMB model calculates direct cost of 57'000 SFr. for one non-fatal cardiovascular event and 8'500 SFr. for one fatal cardiovascular event. Indirect costs are not calculated in the SMB cost-efficiency model.

Results

Daily cost of Atorvastatin is 0.37 SFr., for Rosuvastatin 0.68 SFr., and for Ezetimibe is 1.23 SFr. RRR is 30% for statins (19) and 24% for Ezetimibe (10). RRRe is dependent from baseline LDL.

Cost-efficiency thresholds

- *Varifo-Model:* Cost-efficiency, where the costs of preventive therapy equal the costs of a prevented event (200'000 SFr. in 10 years for direct and indirect costs) is achieved with Atorvastatin for a risk of 3% and a baseline LDL of 3.0 mmol/l (Rosuvastatin 4.0% risk, Ezetimibe 17.7%).
- *SMB-Model:* Cost-efficiency at the 150'000/QALY threshold is reached for Atorvastatin at 1.9% risk (for Rosuvastatin 2.7%, for Ezetimibe 32.9%).

Cost-Efficiency at various risk threshold

- *Varifo-Model:* at the 7.5% risk threshold with LDL 3.0 mmol/l, Atorvastatin is cost-efficient for a daily price of 1.45 SFr, (Rosuvastatin 1.52 SFr, Ezetimibe 0.33 SFr.)
- *SMB-Model:* at the 7.5% risk threshold with LDL 3.0 mmol/l, Atorvastatin achieves 17'697 SFr./QALY (Rosuvastatin 35'266 SFr./QALY, Ezetimibe 277'750 SFr./QALY). Ezetimibe would be cost-efficient for daily costs of 0.59 SFr.

Tables with various thresholds for CVD risk and Cost/QALY calculator are attached in the Appendix and are available electronically (www.docfind.ch/pepgalyeze.xlsx).

Discussion

Individual price models are useful to negotiate prices with manufacturers based on individual risk information. Prices may be reduced for lower risk subjects, allowing for a broader range of patients to receive preventive therapies.

The *individual price* model is based on evidence from controlled randomized trials. In order to eliminate the poor reproducibility and subjectivity inherent to QALY based price models, which are used to determine *fixed prices* (14,23), we developed *individual price model* by replacing QALY with preventive and evidence-based effects of the relative risk reduction inherent to LDL lowering drugs (24).

Using the value-based model of VARIFO of *individual pricing*, generic Atorvastatin and Rosuvastatin at current daily costs are *very cost-efficient* at CVD risk of only 7.5% and LDL of 3.0 mmol/l. This finding is in line with our calculation of the cost-efficiency of statins in primary care (18) and reveals again the errors made in the SMB Statin report issued in 2014 (25). These problems arose because the SMB QALY model was using excessive statin costs and cardiovascular risk, which was too low and calculated over too short of a treatment period (only 5 instead of 10 years). Especially the latter point is noteworthy, in that the SMB QALY model efficacy increases by a factor 4 if treatment time is doubled. Due to these shortcomings and a mathematically incomprehensible projection of the SMB results concerning an indication of statins only if cardiovascular risk is 7.5% for mortality (which corresponds to a cardiovascular risk for fatal and nonfatal events of 32.5%). the conclusions of the SMB Statin report are scientifically inaccurate and the report should be adjusted or withdrawn. Our calculations also show, that a fixed price per QALY is subject to misinterpretation and can lead to rationing of effective preventive therapies.

Ezetimibe is only cost-efficient for individuals with a CVD risk of at least 30% using the *individual price model*. Ezetimibe daily cost should be 0.10 SFr. instead of 1.23 SFr. for a CVD risk of 7.5% and an LDL as high as 5.0 mmol/l. Equally, regarding the SMB Cost/QALY Model, Atorvastatin and Rosuvastatin are highly cost-efficient for a CVD risk of 3% and an LDL of 3.0 mmol/l, while Ezetimibe is cost-efficient for a CVD risk of 13% and an LDL of 3.0 mmol/l.

Therefore, using an evidence-based model such as *individual pricing* reflects medical and societal value directly and appears more appropriate to calculate cost-efficiency, because it contains only reproducible data. Regarding Ezetimibe, costs/QALY estimates using the SMB assumptions has a tendency to overestimate the clinical and societal value of the drug at current prices.

Ezetimibe has only a modest effect on LDL lowering (22%), but the relative risk reduction is similar to statins. The clinical effect of Ezetimibe is at least 50% lower compared to 40 mg Atorvastatin or 20 mg Rosuvastatin. Therefore, in theory, cost-efficient pricing of Ezetimibe compared to the named

statins should be less than 50% of the statin prices. The current daily cost of Ezetimibe cannot be justified by superior clinical efficacy are therefore not value-based.

The difference between the demanded cost from producers and the value-based price derived from our cost-efficiency model is at least 1.0 SFr. A broader application including individuals with a cardiovascular risk as low as to 10% in 10 years of the drug can be achieved (for exact comparison refer to the tables in the Appendix). In view of the very high direct and indirect costs of cardiovascular diseases in Switzerland (21), an increase of preventive efficacy is mandatory and Ezetimibe should remain available for all patients requiring further LDL-lowering in primary and secondary prevention.

On behalf of value-based calculations it also becomes evident, that *fixed price models* cannot adequately reflect the value of a drug at the individual level. Future price negotiations might therefore include individual price models based on baseline risk.

The amount of 200’000 SFr. as a result direct medical and indirect cost is open to debate. Changes of such estimates will not significantly change our results in a sensitivity analysis, if a range between 150’000 - 250’000 SFr. should be used. For statins, event costs of 150’000 SFr, still produce acceptable daily costs above the current market price of generic Atorvastatin and Rosuvastatin (0.95 and 1.06 SFr. respectively), while cost-efficiency for Ezetimibe is found to be 0.17 SFr. for a threshold of 7.5% cardiovascular risk and an LDL of 3.0 mmol/l.

Recommendation

The use of generic Atorvastatin and Rosuvastatin can be recommended without any restriction.

Generic Ezetimibe is largely overpriced at current daily costs of 1.23 SFr. It is recommended to negotiate daily costs of this drug down to at least the costs of generic Statins, e.g. 0.20 to 0.50 SFr. per day, where it can be used in intermediate or high-risk patients in a cost-efficient way.

Ezetimibe is an important additional cardiovascular risk reducer that should not be limited for cost issues. It should remain widely available, in order to increase the efficiency of medical prevention.

More statistical and epidemiological efforts are needed to determine direct and indirect costs of chronic diseases in Switzerland more accurately in order to improve the cost-efficiency calculations in the *individual price model*.

The SMB Report on Statins published 2014 contains scientifically inaccurate conclusions, has created a lot of confusion and has sent problematic signals to the public and the medical community. Swiss health care authorities should request a withdrawal of this report.

Appendix

(all calculations are available at www.docfind.ch/pepqalyeze.xlsx)

Table 1: Cost/QALY calculator using the SMB assumptions allows to compare cost-efficiency of lipid lowering drugs.

Cost/QALY calculator

	Enter values	Read Result Cost/QALY		
		Atorva	Rosuva	Ezetimibe
CVD Risk	10.00			
LDL	4.00	-2259	7633	144030

Table 2: acceptable daily costs of Atorvastatin in relation to baseline cardiovascular risk and baseline LDL for event costs of 200'000 SFr.

Atorva	LDL			
Risk	**5.0**	**4.0**	**3.0**	**2.0**
7.5	2.51	1.94	1.37	0.81
15.0	5.34	4.21	3.07	1.94
20.0	7.23	5.72	4.21	2.70
25.0	9.12	7.23	5.34	3.45
30.0	11.01	8.75	6.48	4.21
35.0	12.90	10.26	7.61	4.96
40.0	14.79	11.77	8.75	5.72
45.0	16.68	13.28	9.88	6.48
50.0	18.58	14.79	11.01	7.23
55.0	20.47	16.31	12.15	7.99
60.0	22.36	17.82	13.28	8.75
65.0	24.25	19.33	14.42	9.50
70.0	26.14	20.84	15.55	10.26
75.0	28.03	22.36	16.68	11.01
80.0	29.92	23.87	17.82	11.77
85.0	31.81	25.38	18.95	12.53
90.0	33.70	26.89	20.09	13.28
95.0	35.59	28.41	21.22	14.04
100.0	37.48	29.92	22.36	14.79

Table 3: acceptable daily costs of Rosuvastatin in relation to baseline cardiovascular risk and baseline LDL for event costs of 200'000 SFr.

Rosuva	LDL			
Risk	**5.0**	**4.0**	**3.0**	**2.0**
7.5	2.75	2.14	1.52	0.90
15.0	5.84	4.60	3.37	2.14
20.0	7.89	6.25	4.60	2.96
25.0	9.95	7.89	5.84	3.78
30.0	12.00	9.53	7.07	4.60
35.0	14.05	11.18	8.30	5.42
40.0	16.11	12.82	9.53	6.25
45.0	18.16	14.47	10.77	7.07
50.0	20.22	16.11	12.00	7.89
55.0	22.27	17.75	13.23	8.71
60.0	24.33	19.40	14.47	9.53
65.0	26.38	21.04	15.70	10.36
70.0	28.44	22.68	16.93	11.18
75.0	30.49	24.33	18.16	12.00
80.0	32.55	25.97	19.40	12.82
85.0	34.60	27.62	20.63	13.64
90.0	36.66	29.26	21.86	14.47
95.0	38.71	30.90	23.10	15.29
100.0	40.77	32.55	24.33	16.11

Table 4: acceptable daily costs of Ezetimibe in relation to baseline cardiovascular risk and baseline LDL for event costs of 200'000 SFr.

Ezetimibe	LDL			
Risk	**5.0**	**4.0**	**3.0**	**2.0**
7.5	0.10	0.01	-0.07	-0.16
15.0	0.53	0.36	0.19	0.01
20.0	0.81	0.58	0.36	0.13
25.0	1.10	0.81	0.53	0.24
30.0	1.38	1.04	0.70	0.36
35.0	1.67	1.27	0.87	0.47
40.0	1.96	1.50	1.04	0.58
45.0	2.24	1.73	1.21	0.70
50.0	2.53	1.96	1.38	0.81
55.0	2.81	2.18	1.56	0.93
60.0	3.10	2.41	1.73	1.04
65.0	3.38	2.64	1.90	1.16
70.0	3.67	2.87	2.07	1.27
75.0	3.95	3.10	2.24	1.38
80.0	4.24	3.33	2.41	1.50
85.0	4.53	3.55	2.58	1.61
90.0	4.81	3.78	2.76	1.73
95.0	5.10	4.01	2.93	1.84
100.0	5.38	4.24	3.10	1.96

References

1. Mancia G., De Backer G., Dominiczak A., 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;28:1462–536.
2. WHO. Global status report on noncommunicable diseases 2014. 2014.
3. Yusuf S., Hawken S., Ounpuu S., 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.
4. Cao JJ., Arnold AM., Manolio TA., 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.
5. Störk S., Feelders RA., van den Beld AW., et al. Prediction of Mortality Risk in the Elderly. Am J Med 2006;119:519–25.
6. Romanens M., Ackermann F., Spence JD., 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;17:18–23.
7. D'Agostino RB., Vasan RS., Pencina MJ., et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation 2008;117:743–53.
8. Mihaylova B., Emberson J., Blackwell L., et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;6736:1–10.
9. Nanchen D., Pletcher MJ., Cornuz J., et al. Public health impact of statin prescribing strategies based on JUPITER. Prev Med (Baltim) n.d.;2011;52:159–63.
10. Cannon CP., Blazing MA., Giugliano RP., et al. Ezetimibe Added to Statin Therapy after Acute Coronary Syndromes. N Engl J Med 2015;372(25):2387–97. Doi: 10.1056/NEJMoa1410489.
11. Romanens M., Mortensen MB., Sudano I., et al. Extensive carotid atherosclerosis and the diagnostic accuracy of coronary risk calculators. Prev Med Reports 2017;6:182–6.
12. Mancia G., Fagard R., Narkiewicz K., 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.
13. Piepoli MF., Hoes AW., Agewall S., et al. 2016 European Guidelines on cardiovascular

disease prevention in clinical practice. Eur Heart J 2016;37:2315–81.

14. Beresniak A., Medina-Lara A., Auray JP., 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.
15. 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.
16. Fonarow GC., Keech AC., Pedersen TR., et al. Cost-effectiveness of evolocumab therapy for reducing cardiovascular events in patients with atherosclerotic cardiovascular disease. JAMA Cardiol 2017;2:1069–78.
17. 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.
18. Romanens M., Sudano I., Szucs T., Adams A. Medical costs per QALY of statins based on Swiss Medical Board assumptions. Cardiovasc Med 2017;17:96–100.
19. Cholesterol Treatment Trialists' Ctt Collaborators. CTT Appendix Online 2012. Append Online n.d.
20. Karlson BW., Palmer MK., Nicholls SJ., Lundman P., Barter PJ. Doses of rosuvastatin, atorvastatin and simvastatin that induce equal reductions in LDL-C and non-HDL-C: Results from the VOYAGER meta-analysis. Eur J Prev Cardiol 2015;23:744–7.
21. Wieser S., Tomonaga Y., Riguzzi M., et al. Die Kosten der nicht übertragbaren Krankheiten in der Schweiz 2014:195.
22. Rea TD., Heckbert SR., Kaplan RC., Smith NL., Lemaitre RN., Psaty BM. Smoking status and risk for recurrent coronary events after myocardial infarction. Ann Intern Med 2002;137(6):494–500.
23. 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.
24. Sabatine MS., Giugliano RP., Keech AC., et al. Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med 2017;376:1–10.
25. Felder S., Jüni P., Meier CA., et al. SMB Statin Recommendation. Available at: http://www.medical-board.ch/fileadmin/docs/public/mb/fachberichte/2014-07-21_bericht_statine_final_anpassung.pdf.