How much do we pay for a benefit? A Descriptive Cost Analysis of the Use of Statins. The Need for a National Cost-Effectiveness Analysis

José Luiz da Costa Vieira, Vera Lúcia Portal, Emílio H. Moriguchi

Porto Alegre, RS - Brazil

The role of the elevation of serum cholesterol levels as a cause in the genesis of atherosclerosis and its clinical sequels, mainly coronary heart disease, was well established several decades ago by means of a number of large cohort studies [1-3], after cross-sectional studies had shown an association between hypercholesterolemia and ischemic heart disease.

Ever since, the acknowledgement of this role has encouraged many randomized studies designed to test the hypothesis that the lowering of cholesterol levels might bring about a reduction in morbidity and mortality caused by cardiovascular disease. Over the last few years, a number of such studies have shown an important decline in the incidence of ischemic heart disease events, and some of them have shown that with the use of statins a reduction in both cardiovascular disease and total mortality occurrs [4-8].

Based on these findings, it became a consensus among cardiologists that a need existed to increase the prescription of drugs to lower cholesterol levels. Several papers have reported concern about the small use of these drugs and the resulting damage suffered by patients who do not receive this treatment [9-11], even in the USA and in Europe. In Great Britain, a recent study showed that only in 17% of patients with indication of secondary prevention presented lipid concentrations, according to the official guidelines [11]. In our environment, the situation is more critical yet, because the socioeconomic situation in Brazil prevents the correct use of statins, even when the cardiologists are absolutely sure about its indication.

With the purpose of drawing attention to the need for carrying out a nationwide cost-effectiveness study concerning the use of statins in primary and secondary prevention, we made a descriptive cost analysis of these drugs, in relation to the benefits they bring about, based on the large randomized clinical trials of primary and secondary prevention.

In the cost-effectiveness ratio of an intervention, the absolute risk reduction is more important than the relative reduction obtained. The absolute benefits of the treatment tend to be greater and the cost-effectiveness ratio more favorable in groups of patients at higher absolute risk [12]. Thus, at the beginning, a greater absolute benefit and a better cost-effectiveness ratio are expected in secondary prevention, as compared with that in primary prevention. Moreover, even considering the primary and secondary prevention groups separately, within each one of them, higher risk patient groups like those with lower HDL-cholesterol levels, a higher total or LDL-cholesterol level, older age, or history of diabetes or smoking, have a higher risk and consequently a greater absolute benefit for the same relative risk reduction [8,12-15]. This means that, even though the relative benefit may be similar for different initial risk levels, a greater absolute benefit, and a better cost-effectiveness ratio in the groups at higher risk will exist.

Looking at the issue from this angle, we can predict a better cost-effectiveness ratio in the studies on secondary prevention – *Scandinavian Simvastatin Survival Study* (4S) [4], *Cholesterol and Recurrent Events Trial* (CARE) [6], and *Long-Term Intervention with Pravastatin in Ischaemic Disease Study* (LIPID) [8] – than in those on primary prevention – *West of Scotland Coronary Prevention Study* (WOSCOPS) [5] and *Air Force/Texas Coronary Atherosclerosis Prevention Study* (AFCAPS/TexCAPS) [7]. In the primary prevention group, the WOSCOPS [5] analyzed patients at higher risk (men with total cholesterol above 252mg/dL and mean total cholesterol of 272mg/dL) than the AFCAPS/TexCAPS [7] (men and women with total cholesterol ranging from 180 to 264mg/dL, HDL-cholesterol below 45mg/dL in men and 47mg/dL in women, and mean total cholesterol of 221mg/dL). In the secondary prevention studies, the profile of patients in 4S [4] (men and women after an acute myocardial infarction or unstable angina with total cholesterol between

Instituto de Cardiologia do Rio Grande do Sul/Fundação Universitária de Cardiologia - Porto Alegre
Mailing address: José Luiz da Costa Vieira – IC/FUC – Av. Princesa Isabel 395 – 90620-001 Porto Alegre, RS, Brazil

213 and 330mg/dL) was of a higher risk group than in the patients in CARE [6] (men and women after an acute myocardial infarction with total cholesterol below 240mg/dL) and of LIPID [8] (men or women after an acute myocardial infarction or unstable angina with total cholesterol between 155 and 271mg/dL).

In addition to the previous risk profile of patients (previous absolute risk) and the intrinsic effect of the intervention (relative risk reduction), which will give us the absolute risk reduction, the cost of this intervention will also affect the cost-effectiveness ratio. As compared with Brazilian cost tables [17], the cost of the used intervention was higher in WOSCOPS [5], CARE [6], and LIPID [8] than in 4S [4] and in AFCAPS/TexCAPS [7] (Table I). It is important to point out that the drug doses used to obtain the benefits reported in the different studies were considerably higher than those that are usual in our country for routine care. From the point of view of an evidence-based medical practice, to obtain the same benefits, we should use the same doses as in the clinical trials.

The cost of the treatment was calculated based on the cheapest commercial product available on the Brazilian market, according to the prices listed in *Guia Farmacêutico Brasíndice* of 20/12/2000 [17]. The commercial exchange rate then was 1 US$ = 1.91 R$.

As expected, we found in the descriptive cost analysis that, in primary prevention, the relation with the benefits was less favorable than in secondary prevention. In WOSCOPS [5], the absolute reduction of total mortality, although not significant, was 0.9% in five years, ie, an absolute reduction of two deaths per one thousand treated patients per year, corresponding to 556 patients that would need to be treated (NNT) during one year (556 patients would have to be treated during one year to prevent one death). So, according to the cost of this intervention (40mg pravastatin/day) on the Brazilian market [17], one prevented death would cost about R$ 672,000.00. According to the results of the same study, the reduction of one event of primary outcome (death from coronary cause or a nonfatal acute myocardial infarct), with a yearly NNT of 208 (208 patients would have to be treated during one year to prevent one death due to a coronary cause or one nonfatal acute myocardial infarct), would cost about R$ 252,000.00. One prevented death from a coronary artery disease (NNT during one year of 1,000, corresponding to an absolute risk reduction of 0.5% in five years) would cost about R$ 1.210,000.00, whereas to prevent one death from any cardiovascular cause would cost R$ 864,000.00 (NNT during one year: 714 patients). To prevent

Table II – Descriptive cost analysis of WOSCOPS

Evaluated outcome (simple or combined)	RAR/1000 treated/year	NNT during 1 year	Cost in R$/ prevented outcome
AMI or death from CAD*	5	208	252.000
Nonfatal AMI	4	263	318.000
Death from CAD	1	1.000	1.210.000
Death from cardiovascular cause	1	714	864.000
Total mortality	2	556	672.000
MR	2	625	756.000

* primary objective of the study; ARR- absolute risk reduction; NNT during 1 year- number of patients needing treatment during one year (to obtain the benefit of preventing an outcome or an event of the outcome); CAD- coronary artery disease; AMI- acute myocardial infarct; MR- myocardial revascularization procedure, including surgery or angioplasty. 1 U$$= 1.91 R$.

Table I – Characteristics of the large randomized clinical trials in dyslipidemia

Study	Patient Characteristics	Drug used/ Average dose	Mean monthly cost (R$)*
Primary prevention			
WOSCOPS	6,595 men with TC above 252mg/dL (average of 272mg/dL)	Pravastatin/ 40 mg/day	101
AFCAPS/TexCAPS	5,608 men with c-LDH-below 45mg/dL and 997 women with c-LDH -below 47mg/dL both with TC between 180 and 264mg/dL(average: 221mg/dL)	Lovastatin/ 30mg/day**	81
Secondary prevention			
4S	3,617 men and 827 women after AMI or UA with TC between330mg/dL(average: (médio	Simvastatin/ 27mg/day***	76
CARE	Men and women after AMI with TC below 240mg/dL	Pravastatin/ 40mg/day	101
LIPID	Men and women after AMI or UA with TC between 155 and 271mg/dL	Pravastatin/ 40mg/day	101

* according to the price of *Guia Farmacêutico Brasíndice*[17], considering the product with the most cost-effective presentation for the indicated doses of each drug; ** mean dose, with 50% of patients using 20mg/day and 50% using 40mg/day; *** mean dose, with 63% of patients using 20mg/day and 37% using 40mg/day; TC- total cholesterol; AMI- acute myocardial infarct; UA- unstable angina. 1 U$$= 1.91 R$.

one nonfatal acute myocardial infarct, it would be necessary to treat 263 patients during one year (NNT during one year: 263) at a cost of R$ 318,000.00 (Table II).

According to AFCAPS/TexCAPS [7], the cost of preventing one primary outcome event represented by an acute myocardial infarct, an angina destabilization, or a sudden death of cardiac origin would be R$ 237,000.00, based on the cost of 30mg of lovastatin, the average dose used [17], on the Brazilian market and on an absolute risk reduction of four events per 1,000 patients treated during one year, or a NNT/year of 244 patients. In the same study, one prevented acute myocardial infarct (NNT/year of 435 patients) would cost R$ 422,000.00, and the cost of one prevented revascularization procedure (myocardial revascularization surgery or coronary angioplasty – NNT/year of 323 patients) would be R$ 313,000.00. The costs of preventing one death from coronary artery disease or one death from any cardiovascular cause would be R$ 3,236,000.00 and R$ 2,427,00.00, respectively, based on reductions of 0.3 and 0.4 deaths per 1,000 patients treated during one year (NNT/year of 3,300 and 2,500 patients). Considering the acute myocardial infarcts, angina instabilizations, sudden death, or myocardial revasculari–zation all together, the benefit of reducing any one of these events individually would cost R$ 136,000.00 on average (Table III).

In the 4S study [4], with patients after an acute myocardial infarct or unstable angina with higher mean cholesterol levels and consequently, at least theoretically, at higher absolute risk, the absolute mortality reduction was 3.3% in 5.4 years, or 6 per 1,000 patients treated during one year. This corresponds to a NNT/year of 164 (164 patients would have to be treated during one year to prevent one death). The cost of one saved life among patients with this profile, considering an average dose of 27mg simvastatin (since 37% of patients used a daily dose of 40mg and 63% used a daily dose of 20mg), would amount to about R$ 150,000.00. As for the cost of preventing one major coronary event, considering an absolute benefit of 16 per 1,000 patients treated during one year and a NNT/year of 81 (81 patients would have to be treated during one year to prevent one major cardiovascular event), it would amount to about R$ 74,000.00. Adding the benefits of reducing both mortality and cardiovascular events in general, the cost of one prevented event would drop to R$ 50,000.00 (Table IV).

The absolute reduction of in the composite outcome of coronary events or non-fatal myocardial infarcts in CARE [6] was 3% in five years, which corresponds to an NNT/year of 167 (167 patients would have to be treated during one year to prevent one death from a coronary cause or a nonfatal myocardial infarct). Taking into account that a 40mg pravastatin dose was used, the conclusion is that the prevention of one death or nonfatal myocardial infarct would cost over R$ 202,000.00. One prevented death from coronary artery disease (NNT/year of 455 patients) would cost R$ 550,000.00, whereas one prevented revascularization procedure (surgery or angioplasty – NNT/year of 106) would cost R$ 129,000.00. When analyzed jointly, the cost of preventing one primary outcome event (acute myocardial infarct or death from coronary artery disease) or one myocardial revascularization procedure would amount to R$ 79,000.00 (NNT/year of 65 patients). However, one prevented death of any cause would cost R$ 774,000.00, the value of an

Table III – Descriptive cost analysis of AFCAPS/TexCAPS

Evaluated outcome (simple or combined)	RAR/1000 treated/year	NNT during 1 year	Cost in R$/ prevented outcome
AMI or UA or SD*	4	244	237.000
AMI or UA	4	256	249.000
AMI	2	435	422.000
MR	3	323	313.000
AMI or UA or SD or MR	7	140	136.000
Death from CAD	0,3	3.333	3.236.000
Death from cardiovascular cause	0,4	2.500	2.427.000

* primary objective of the study; ARR- absolute risk reduction; NNT during 1 year = number of patients needing treatment during one year (to obtain the benefit of preventing an outcome or an event of the outcome); CAD- coronary artery disease; AMI- acute myocardial infarct; UA- unstable angina; SD- sudden cardiac death; MR- myocardial revascularization procedure, including surgery or angioplasty. 1 U$$= 1.91 R$.

Tabela IV - Descriptive cost analusis of 4S

Evaluated outcome (simple or combined)	RAR/1000 treated/year	patients NNT during 1 year	Cost in R$/ prevented outcome
Total mortality*	6	164	150.000
Major coronary event	12	81	74.000
AMI	9	115	125.000
MR	11	92	84.000
Death or any atherosclerotic cardiovascular event	18	55	50.000

* primary objective of the study; ARR- absolute risk reduction; NNT during 1 year = number of patients needing treatment during one year (to obtain the benefit of preventing an outcome or an event of the outcome); AMI- acute myocardial infarct; MR- myocardial revascularization procedure, including surgery or angioplasty. 1 U$$= 1.91 R$.

Tabela V - Descriptive cost analusis of *CARE*

Evaluated outcome (simple or combined)	RAR/1.000 treated/year	patients NNT during 1 year	Cost in R$/ prevented outcome
AMI or death from CAD*	6	167	202.000
Death from CAD	2	455	550.000
AMI or UA	9	111	134.000
MR	9	106	129.000
AMI or death from CAD or MR	15	65	79.000
First cardiovascular event	10	98	119.000
Total mortality	1	639	774.000

* primary objective of the study; ARR- absolute risk reduction; NNT during 1 year = number of patients needing treatment during one year (to obtain the benefit of preventing an outcome or an event of the outcome); CAD- coronary artery disease; AMI- acute myocardial infarct; UA- unstable angina; SD- sudden cardiac death; MR- myocardial revascularization procedure, including surgery or angioplasty. 1 U$$= 1.91 R$.

NNT/year of 639 patients (Table V). These number are higher than those for 4S [4] because the evaluation was made on patients with lower cholesterol levels therefore with a lower expected absolute risk.

According to the LIPID [8] results, 197 patients would have to be treated during one year (NNT of 197) with 40mg of pravastatin to prevent one death (which corresponds to a 3.1% reduction in the absolute mortality observed in 6.1 years). Thus, in secondary prevention with patients of this profile (men and women after an acute myocardial infarct or angina destabilization, with total cholesterol between 155 and 271mg/dL and HDL-cholesterol below 45mg/dL in men and 47mg/dL in women), the cost of one life would amount to approximately R$ 232,000.00. Adding these events (death from coronary artery disease or nonfatal acute myocardial infarct), the cost of preventing one of them would drop to R$ 205,000.00 (NNT/year of 169). The benefit of preventing one acute myocardial infarct would cost R$ 254,000.00 (NNT/year of 210 patients), and the cost of avoiding one revascularization procedure would be R$ 273,000.00 (NNT/year of 226 patients, with a reduction of five revascularization surgeries and three angioplasties per 1,000 treated patients per year). However, taking into account the general benefit of preventing the occurrence of a first new cardiovascular event (death, nonfatal acute myocardial infarct, or stroke) in these patients after an acute myocardial infarct or an angina unstabilization, treated with 40mg pravastatin daily, the cost becomes somewhat more favorable, amounting to around R$ 154,000.00 per patient who remained free of any event, corresponding to a NNT/year of 127 patients (Table VI).

Note that we define our cost-effectiveness analysis partial because we made only the evaluation of the drug cost, as compared with the prevented outcomes. A complete cost-effectiveness analysis should encompass the entire amount of expenses, including the increase in medical visits and laboratory tests required by the treatment, along with the decrease in hospitalization and procedure expenses associated with the benefits of the treatment. Attempts to carry out this kind of more complete analysis were made in Europe with the participation of organizers of large clinical trials, showing a much more favorable cost-effectiveness ratio [18,19], although some of them were severely criticized [20,21] for methodological reasons. In one of these analyses, it was assumed that, on primary prevention, patients with moderate hypercholesterolemia, in which the development of heart disease was avoided by the use of pravastatin, would have the same life expectancy as the general population, after discontinuation of treatment (the costs of maintaining the treatment were not included in the calculation!) [18], which is really hard to accept. An attempt to carry out a complete cost-effectiveness analysis with Brazilian costs (including medical and laboratory expenses and the reduction in hospitalizations and procedures) seems vital to us at this point. Such studies were carried out in countries where the entire situation and costs of medical practice are very different from ours, thus making it impossible to simply transpose their values. A practical example of this is a European study (WOSCOPS), where ocurred less absolute prevention of myocardial revascularization procedures than in an American study (AFCAPS/TexCAPS), in spite of pharmacological intervention in patients at higher risk, probably associated with the fact that American cardiology practice is usually more interventional than the British.

Table VI – Descriptive cost analysis of LIPID

Evaluated outcome (simple or combined)	RAR/1.000 treated/year	NNT during 1 year	Cost in R$/ prevented outcome
Death from CAD*	3	321	389.000
Total mortality	5	197	238.000
AMI	5	210	254.000
Death from CAD or AMI	6	169	205.000
MR	4	226	273.000
First cardiovascular event	8	127	154.000

* primary objective of the study; ARR- absolute risk reduction; NNT during 1 year = number of patients needing treatment during one year (to obtain the benefit of preventing an outcome or an event of the outcome); CAD- coronary artery disease; AMI- acute myocardial infarct; MR- myocardial revascularization procedure, including surgery or angioplasty. 1 U$$= 1.91 R$.

The cost of each statin on the Brazilian market had a direct influence on the cost of each prevented event. Thus, a statin treatment schedule with a higher monthly cost, like the one used in WOSCOPS, CARE, and LIPID (pravastatin with a fixed dose of 40mg/day), enters the study already with a disadvantage regarding its cost-benefit ratio, even if the NNT to avoid one event was the same as in less expensive schedules, such as those used in 4S (simvastatin in doses of 20 or 40mg/day – average of 27mg/day) or in AFSCAPS/TexCAPS (lovastatin in doses of 20 or 40mg/day – average of 30mg/day).

The currently available information about statins is better than that about most of the new drugs, and we have no doubt about the fact that their intervention in cases of hypercholesterolemia or even sometimes of medium cholesterol levels can reduce the risk of cardiovascular events, at the level of both secondary and primary prevention. And so we raise the question: what is the final cost of this benefit?

The risk levels considered as thresholds above which pharmacological intervention on the cholesterol levels should take place, as well as the concern of doctors about patient noncompliance, have already been criticized a lot, even in places with greater resources than ours [22,23]. An interesting calculation based on the 4S [4] and on a meta-analysis of over a hundred randomized clinical trials of antiplatelet therapy [24] showed that, if all bad events were taken into consideration, both acetylsalicylic acid (in the first five weeks after acute myocardial infarct) and simvastatin would prevent one bad event in a projection of every 30 to 40 years of drug use by the patient. Yet, with 100,000 pounds Sterling (approximately R$ 215,000.00) of acetylsalicylic acid, about 1,300 events would be prevented, whereas the same value of simvastatin would prevent only eight [23].

The point is not "not to treat the patient because it is

expensive". What we think is important is that the doctor, to help make the best possible therapeutic decision, should not ignore the patient's socioeconomic situation or system in which he or she lives. The technical decision is not the hardest one to make, and the doctor should not be a mere technician of medicine. His action should be a responsible and holistic one, within the context of his environment.

So, it is our purpose to draw attention to the need for greater reflection on the medical act in every situation and in every area, mainly when it involves expensive treatments, which also applies to invasive cardiology procedures. Good medical practice is not the mere application of medicine based on evidence.

Currently we cannot dissociate our acts from the socioeconomic context of our patients, or from the system in which we live. In this descriptive cost analysis, we see only one side of the coin: the cost of the treatment. For society as a whole, it is also crucial to evaluate the cost of not treating (more events, more hospitalizations, more procedures, more suffering and disability of patients, and more deaths). Only a complete Brazilian cost-effectiveness study could help us evaluate, from which risk level for coronary artery disease does the treatment with statins becomes cost-effective within our reality.

We believe that the way to do this, starting from such a complete evaluation, is to perform risk stratification [25,26] of patients to allow us to detect those who would benefit most from this intervention. Patients with clinical manifestations of coronary artery disease are already at high risk for subsequent coronary events. The risk of a coronary event within 10 years is usually over 20% and, for many patients, over 40%. To this kind of patients, an intensive modification of risk factors is recommended, in general including the use of statins. In primary prevention, even individuals at low risk should be advised to keep their risk at a low level. Directions should be intensified as the risk increases and, in case the risk level exceeds 20% over 10 years, the modification of risk factors has to be intensive, including the possible use of statins, even in asymptomatic patients.

This procedure would allow nationwide application of public health actions on a collective level for the prevention of coronary artery disease and, on the individual level, also to help solve the difficult question of when and how to give this treatment to patients, considering the economic situation of the majority of our population.

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