AFGIFTEKANTOOR BRUSSEL X
P5 08820
Postbus 1212, 3000 Leuven 1

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Responsible editor:
Prof. F. HELLER (C.H. Jolimont)
Editorial staff: Prof. J. DUCOBU (CHU Tivoli)

Editorial

The new criteria for antilipemic drug reimbursement have arrived... However, there's some good news and some bad news... The good news is that these criteria are based on Belgian data, and therefore better match the everyday reality here in Belgium. The bad news is that these reimbursement criteria fail to match European recommendations and guidelines on the prevention of cardiovascular diseases in clinical practice. What's more, diabetic patients are not considered at risk until total cholesterol levels are 175 mg/dl or more, or when LDL-C is ≥ 100 mg/dl. Furthermore, factors such as extrapolation of risk to 60 years, triglyceride levels, family history of cardiovascular disease, Lp(a) and metabolic syndrome, must remain ignored. Whilst there is still much controversy surrounding metabolic syndrome, it nevertheless remains a current topic. For example, let us take the study by F. Desgardins, based at the Pharmacology and Therapy Unit headed by Prof. J.L. Balligand. Using an animal model, this study reveals that rosuvastatin has a beneficial effect on various parameters associated with metabolic syndrome and in particular on insulin resistance.

Prof. L. Annemans' macroeconomic analysis on the use of antilipidemics does a good job in highlighting situations where lipid-lowering drugs are effective, not only in terms of patient health, but also State finances! However, it does draw attention to the undesirable effects caused by irrational use of these drugs in Chapter I.

We shall endeavour to determine the impact of this reimbursement policy more precisely in our next issue.

Prof. F.R. Heller
President

Economic aspects of lipid-lowering drugs

Lieven Annemans (Univ. Gent)

The need for economic assessment in health care

The conflict between, on the one hand, what societies are able to pay for health care and, on the other, people's growing need for more and better-quality health care continues to increase.
Many countries apply different policies in order to meet this challenge, but with varying degrees of success. There is also a conflict in some countries between industrial policy, where the goal is to encourage innovative investments and employment in the pharmaceutical industry, and social policy, where the goal is to offer maximal health benefits to the population within limited budgetary means.

Economic assessment in health care may provide a solution. There would appear to be an increasing need for the assessment of new health-care technologies in order to help decide whether it is worth implementing them. The OECD (2004) states correctly that *"the growth norm cannot be a permanent instrument of health-care cost control since it has little if any relation to any notion of efficiency or optimality. It needs to be replaced by measures based on cost benefit analysis or appropriate incentives"*.

Economic assessment in health care (sometimes called cost-benefit studies, as in the OECD statement, and sometimes cost-effectiveness studies, because this is the most common type of health-care/health-economics assessment) is a comparative analysis of alternative courses of action in terms of their consequences BOTH for costs and health. The definition implies that a comparison is involved (Drug A versus Drug B; no drug versus drug therapy; prevention versus no prevention) and that in this comparison the consequences both for health and cost ("health-economic") are taken into consideration.
A key element in health-care policy, but one which is often forgotten by policy makers, is that cost-effectiveness is related not only to a health technology in itself but also to the way this health technology or drug is used in daily practice. In other words, a new drug or prevention strategy may be cost-effective if correctly used but may not be so if not applied to the appropriate patient population.

Economic assessments of cholesterol-lowering drugs

With regard to cholesterol-lowering drugs, the number of health-economic studies is legion and it is not the purpose of this paper to provide a complete overview. We shall simply give some examples in order to illustrate the concepts and current state of thinking regarding the economic status of statins in health care.

One of the first economic studies in this area was based on the 4S trial. Johannesson *et al* demonstrated that if 1000 men with characteristics of the 4S trial (therefore secondary prevention) were treated with simvastatin 40mg for 4 to 5 years, it would cost $ 2,242,000 but would save $718,000 because of the events prevented, and would therefore result in a net cost of $1,524,000. All in all, in this cohort of 1000 men, 280 life years would be saved. In other words, a net investment of $1,524,000 is made to "produce" or "gain" 280 life years. This corresponds to a cost-effectiveness ratio of $1,524,000/280 = $5,400 per life year gained.

Such a result can be considered as very cost-effective because many countries apply a "rule" to the effect that if a health-care programme or technology costs more than ± €30,000 to enable the gaining of one life year, investment in it is not justified. The reason for this is that, since the money available is limited, it is better to use our societal means on measures that yield the most health (life years) per euro invested. The threshold of €30,000 is related to the Gross National Product per inhabitant and reflects the societal value of a life year.

Having to spend only $5,400 to gain one life year is therefore a good economic result because it is much below the value that societies assign to a life year.

Caro *et al* (2000), in a study based on the WOSCOPS, concluded that primary prevention with pravastatin 40mg in high-risk patients gives a cost-effectiveness ratio of €12,400 per life year (the net investment was €3,870 to gain on average 0.3104 of a life year per patient 3870/0.3104 = +/-12400), again an acceptable result. Earlier, in 1998, Muls et al had concluded that the cost-effectiveness of secondary prevention gave acceptable cost-effectiveness results, but that these results were influenced by the number of risk factors present in the patient: Incremental Cost per Life Year Gained in the case of 1 risk factor = € 17,868, in the case of 2 risk factors: € 13,051; and in the case of 3 risk factors: € 9,736.

A better unit of expression of health gains is *quality-adjusted* life years (QALY). Figure 1 illustrates the concept. If a person lives for 10 years at a quality level of 0.5 (0 = death; 1 = perfect health), then this person has only 5 QALYs (10 x 0.5). If we can

increase the quality to 0.6, we gain (0.6-0.5) x 10 = 1 QALY. If we extend the life by 2 years (but with the quality level remaining at 0.5), we gain 0.5 x 2 = 1 QALY. Finally, if we extend life by 2 years and increase the quality to 0.6, then in the new situation the patient has 12 x 0.6 = 7.2 QALYs, which is 2.2 more compared with the initial situation.

Several health-economic assessments of statins express results in cost per QALY. Significantly, Prosser *et al* (2000) confirm what we have already observed with regard to the above "cost-per-life-year-gained" results in Belgian studies, namely that statins are very cost-effective in high-risk but less so in low-risk patients. For instance, treating (primary prevention) a 50-year-old male with high LDL cholesterol (>160 mg/DL) but without any other risk factor would be equivalent to spending almost €200,000 to gain one QALY. Treating a similar patient, but one with several risk factors, is equivalent to a cost-effectiveness ratio of <€30,000 per QALY gained.

Johannesson (2001) calculated threshold risk levels above which prevention with statins can be called cost-effective. If society were willing to pay $40,000 for a QALY gained, then the treatment of a 55-year-old male would be cost-effective only if he had a 5-year risk of coronary heart disease of more than 8.3%. In a 50-year-old male, this threshold decreases to 6.5%; in a 60-year-old man, the threshold increases to 11.6 %. So, to illustrate the last-mentioned case, if a 60-year-old man has no history of cardiovascular disease but does have a 5-year-risk of coronary heart disease > 11.6%, then it is cost-effective to treat him preventively with statins.

Given these figures, it would seem that the original guidelines of the European Joint Task force, setting the threshold for prevention with statins at a 20% coronary risk over 10 years, are quite acceptable from a health-economic point of view, at least for the relatively younger population.

A key conclusion from the above is that it cannot be said in a generalized way that statins are cost-effective. They can only be called cost-effective if they are used with the right patients. The definition of right patient depends mainly on the patient's risk profile, the effectiveness of the statin and its cost. With regard to the last mentioned, it should of course be recognized that if the average statin price decreases, these drugs become cost-effective in a larger number of patients.

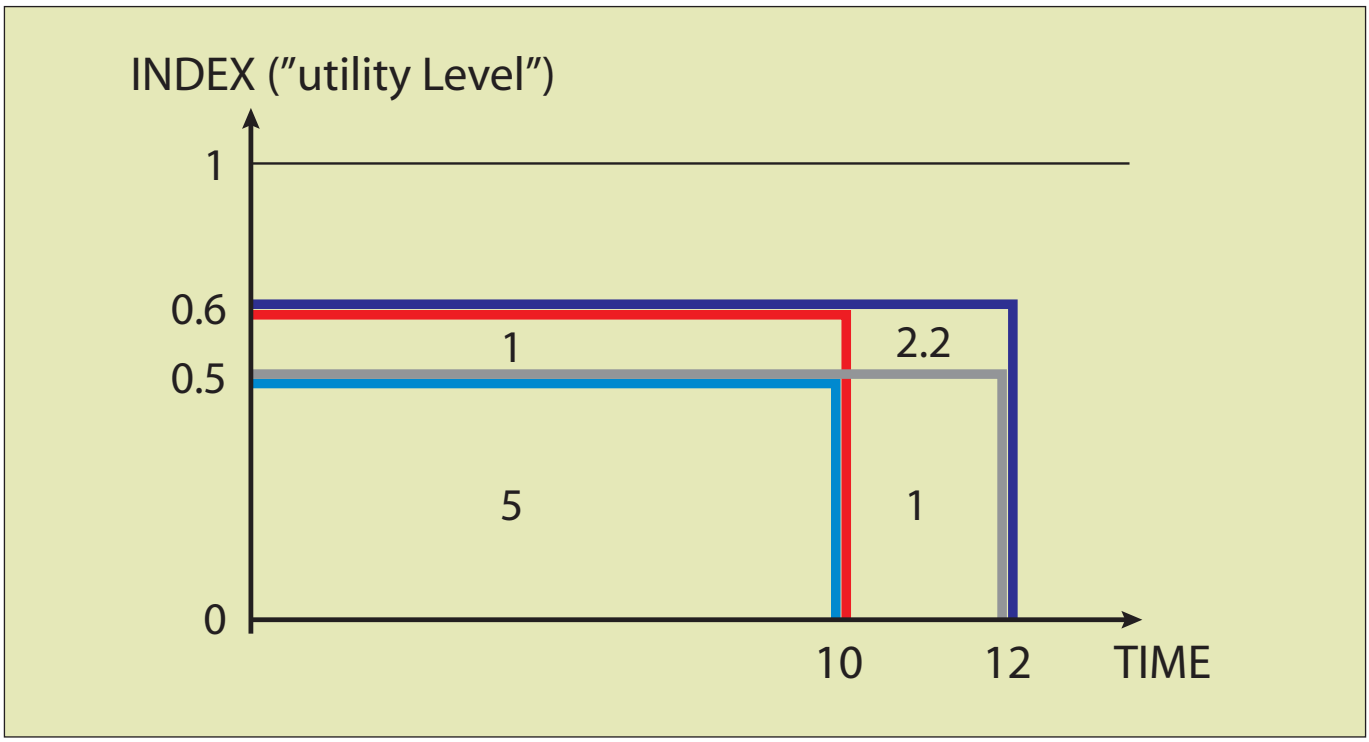
Issues concerning health-economic assessments in policy making

Many countries have developed guidelines to help researchers conduct better assessment studies and assist decision makers in appraising the quality of the studies. However, not all countries have the same approach to the assessment of technologies. In some, health-economic evaluations are mandatory, in others they are recommended and in others again they are not really regarded as important. All countries are confronted with several methodological issues.

For instance, what is the optimal time span of a health-economic evaluation? For example, the savings and health effects with statins will be relatively greater when a 10-year rather than a 3-year time span is applied.

There is also increasing awareness that valuations for QALYs may differ when the QALYs are gained by different patients. It has been shown that society is willing to pay more for a QALY if this QALY is gained in patients with more severe diseases.

Figure 1: illustration of the QALY concept; see text for explanation



Finally, even if a technology or drug is cost-effective, its budgetary impact may prevent it being adopted: e.g. if 70% of the population is eligible for a drug which is cost-effective but does not lead to net savings, then the budgetary impact of refunding the cost to patients would be prohibitive.

Toward a better health-care policy for cholesterol-lowering drugs?

It is exactly the above-mentioned budgetary-impact issue that has driven decision makers to revise the reimbursement conditions for cholesterol-lowering drugs. Figure 2 shows the development of the market in terms of the number of patients treated and the different reimbursement measures that have been taken. Clearly, the decision to reimburse for generics in accordance with what is called "Chapter I" (unconditional reimbursement) has boosted the generic market as well as the total number of patients treated.

It is estimated that currently about 800,000 patients are being treated with statins.

The question is: are they all being treated cost-effectively? A good policy would ensure that those patients in need of statins and in whom statin treatment is cost-effective do receive treatment, while those in whom treatment is not cost-effective do not. The latter should be given diet and lifestyle advice.

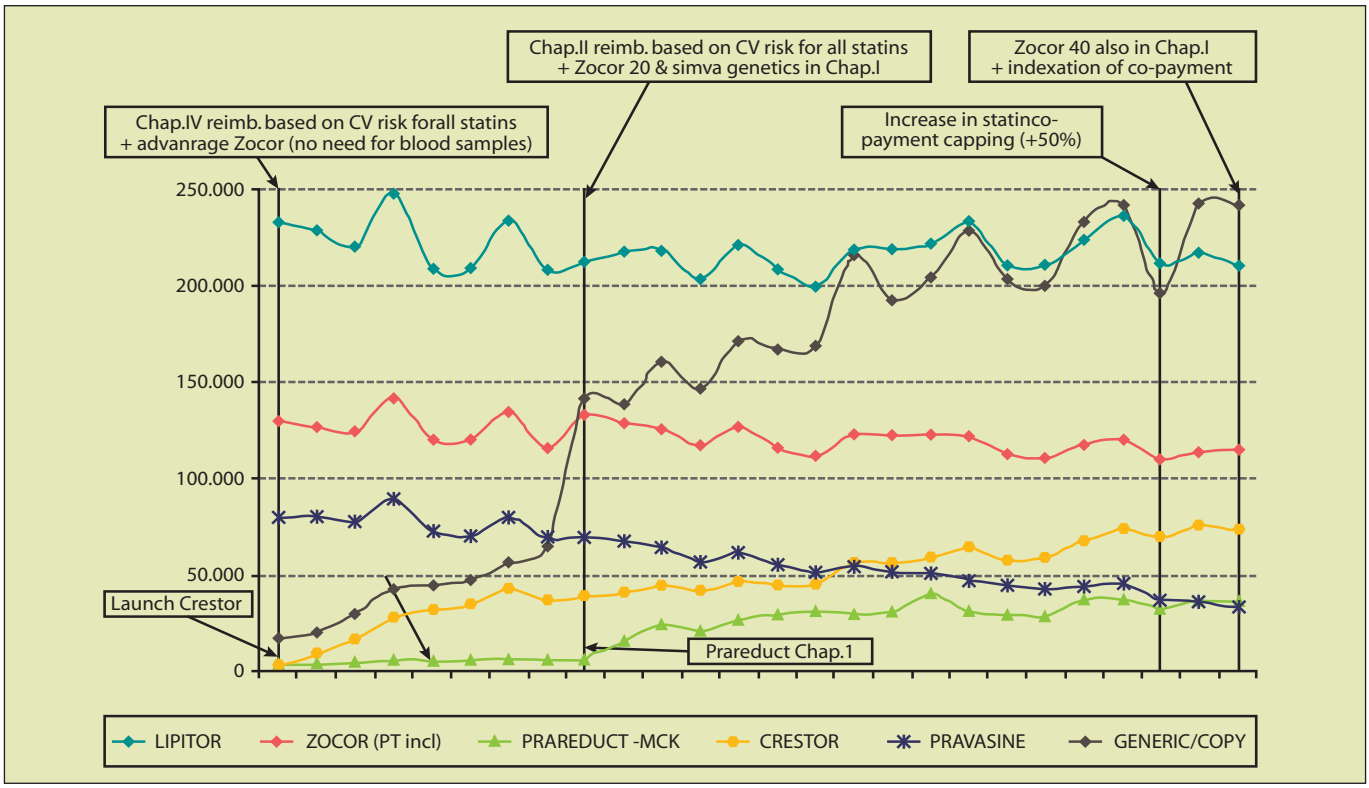
More than 300,000 patients already receive statins with unconditional reimbursement. It should be ascertained how many of these actually do not need statins.

To conclude, it is planned to revise reimbursement rules again and implement the European SCORE risk assessment. This risk assessment is more rigorous than that based on the Framingham cohort. Consequently, a better selection of high-risk patients will be possible. According to the current definitions of high risk following Framingham, 1.9 mln people would be eligible for statin therapy. With the implementation of the SCORE risk assessment, this figure would be reduced to 1.6 mln.

Discussion

The above illustrates a rather dualistic situation. On the one hand, the selection of high-risk patients will become stricter. Given the medical and health-economic grounds, this would appear to be justified. On the other hand, the door remains open to treating any high-cholesterol subject with cheaper statins. While the price reduction in itself is positive and can enable more people to be treated cost-effectively, even at low prices it will more than likely not be cost-effective to treat patients who only have a high cholesterol level. Physicians should be more aware of the value of prescribing statins for those patients with whom their use can be considered cost-effective.
In all of this, there is the additional element of the relative effectiveness of the different statins. It should be made clear at what dose and at what cost the different statins help to achieve therapeutic goals. In a health-economic perspective, these drugs definitely do not form one class. Finally, patient non-compliance and non-persistence with therapy has largely been overlooked. Incentives should be provided to encourage better compliance and persistence with therapy, otherwise many of our statin euros are likely to be wasted.

Figure 2: development of the statin market in number of patients



Use of statins in the treatment of the metabolic syndrome

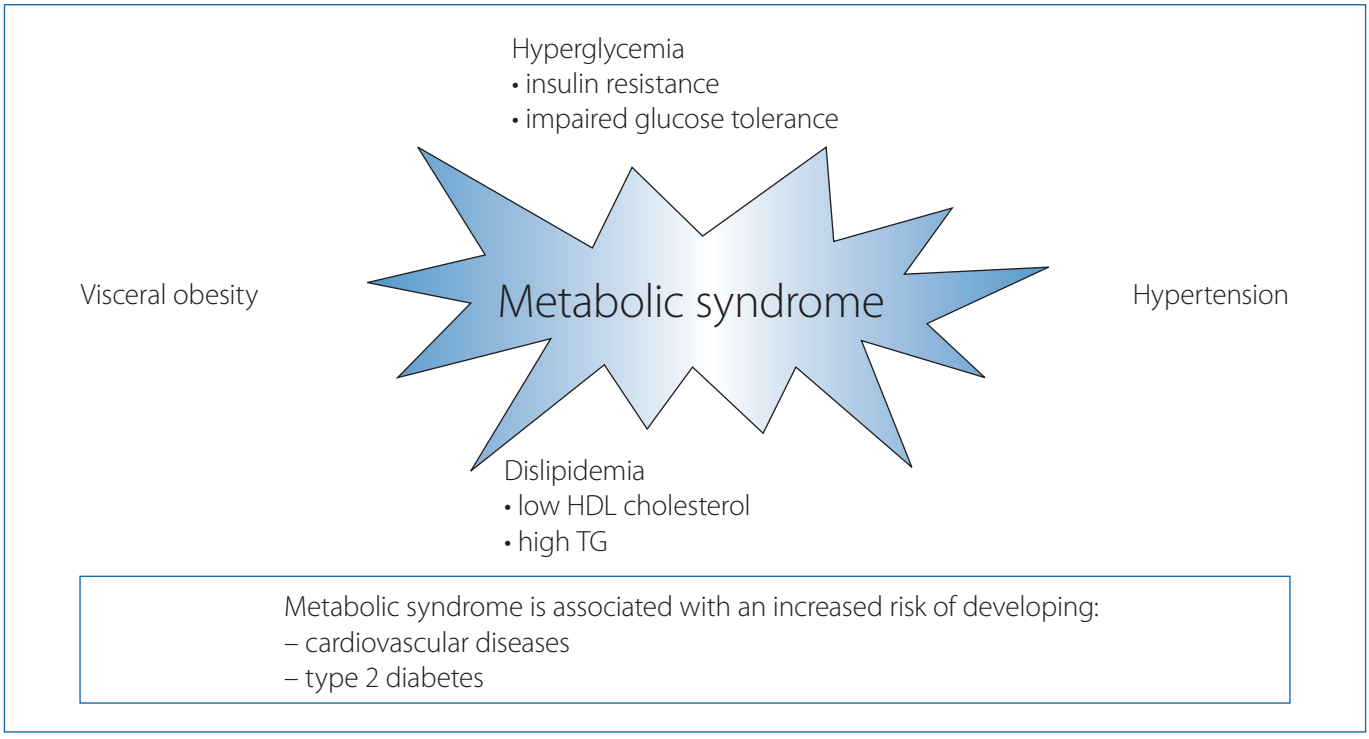
Fanny Desjardins - Pharmacology and Therapeutics Unit
University of Louvain Medical School
Promoter and Unit Director : Professeur Jean-Luc Balligand

The term metabolic syndrome is used to describe a group of metabolic disturbances associated with a strong predisposition toward the development and progression of atherosclerosis. Most of health organizations agree on abdominal obesity, systemic hypertension, hyperglycemia, high level of triglycerides and a reduced level of HDL cholesterol as being the main components of this syndrome (Figure 1). In the clinical setting, different combinations of these risk factors can be found, but the presence of at least three of them is necessary for a diagnosis of metabolic syndrome. In Europe, the prevalence of this pathology is around 15 % in the adult population[1] and in the course of the last few years, a significant increase in research on the association of systemic hypertension and diverse metabolic disturbances has been observed.

Many experimental models have been developed to understand the mechanisms underlying the development of atherosclerosis in the presence of the different components of the metabolic syndrome. Among those, mice deficient in leptin (ob/ob), in the receptor for LDL ($LDL^{-/-}$) and in apolipoprotein E ($ApoE^{-/-}$), are principally used. Leptin-deficient mice are largely used to study obesity, insulin resistance and diabetes, but they don't develop atherosclerosis under a normal diet, whereas $LDL^{-/-}$ and $ApoE^{-/-}$ mice have raised lipoprotein levels leading to the development of atherosclerotic lesions. Previous studies have shown that double knock-out mice for leptin and LDL-receptors (LDLR-/-/obob; DKO) are obese, develop all the characteristics of the human metabolic syndrome and present atherosclerotic lesions under a normal diet.[2] Even if genetic inheritance is one of the causes of this syndrome, the vast majority of clinical cases are linked to a sedentary lifestyle and bad eating habits. On the basis of this premise, we have recently demonstrated that weight loss caused by diet restriction, in the DKO mouse model, can restore the metabolic parameters and blood pressure, improve cardiac function and reduce atherosclerosis.[3]

In the clinical setting, inhibitors of the 3-hydroxyl-3-methylglutaryl coenzyme A (HMG-CoA) reductase (statins), the key enzyme in the synthesis of cholesterol, have been successfully used for a long time to reduce atherosclerosis in dyslipidemic patients, mainly by reducing cholesterol plasma levels. Fur-

Figure 1: The metabolic syndrome is a commonly occurring cluster of phenotypes, associated with an increased risk of developing Type 2 diabetes and cardiovascular disease



thermore, studies have shown the beneficial effect of statins in reducing the risk of cardiovascular death, independently of cholesterol lowering, in patients with the metabolic syndrome.[4] Next, we looked at the possible link between the positive effects of statins on the different components of the metabolic syndrome. We studied the effect of a rosuvastatin treatment, at low and high doses for 12 weeks, in comparison to a placebo in a model of obese and dyslipidemic mice, the LDLR$^{-/-}$/obob mice.

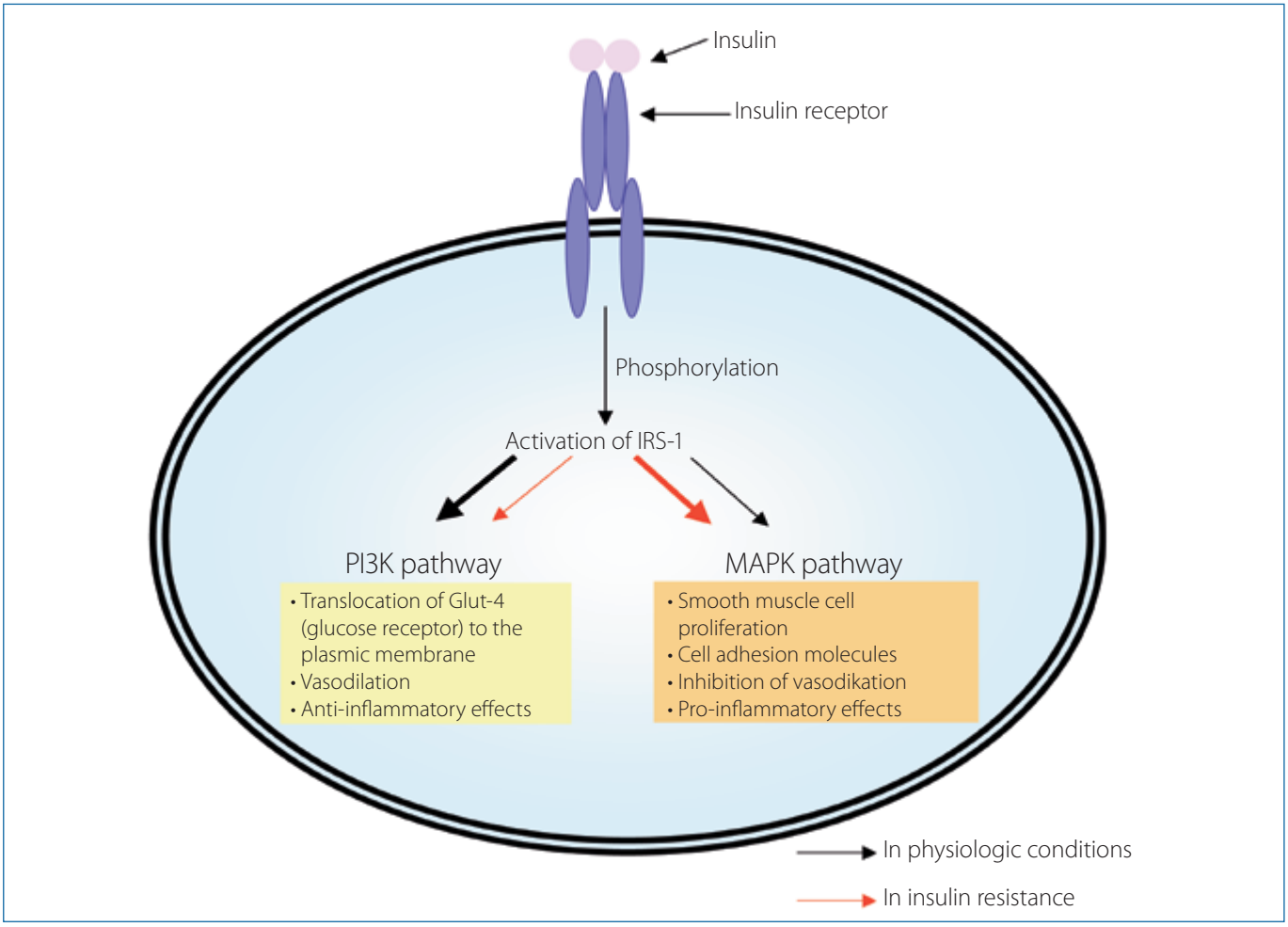
Rosuvastatin treatment did not have any effect on the weight gain of the animals during the study period but led, in a dose-dependent fashion, to the normalisation of the plasmatic levels of triglycerides, glucose and insulin, and even the insulin resistance, calculated in accordance with the HOMA *(homeostasis model assessment)* index. It is important to note that the above corrections were obtained in the absence of measurable differences in the plasma level of total cholesterol between the study groups, at least at the low statin dose (whereas a reduction of the post-treatment cholesterol levels was observed at the higher dose of rosuvastatin).

We then looked at the *in vivo* regulation of the blood pressure (BP) with an implanted, miniaturized telemetry system. The results demonstrated that rosuvastatin corrects the systemic hypertension associated with the development of the metabolic syndrome in our model, and also restores BP variability, dependent of nitric oxide (NO). Frequency analysis of the pressure readings using a Fourier transform revealed an effect of rosuvastatin in the *Very Low Frequency* (VLF; below 0.4Hz) area, an index of the effect of neurohumoral factors on the vascular tone (including NO).[5] Many research teams, including ours, have validated this parameter as an indicator of the buffering power of NO on the BP in mice.[5;6] Furthermore, epidemiologic data have substantiated that, in addition to the absolute BP value, its degree of variability (over both the short and the long term) is a predictor of end-organ damage in different animal models and also in humans.[7]

Finally, we compared cardiac function, evaluated by echocardiography, in our different groups. Our results have demonstrated that the DKO mice developed a left ventricular hypertrophy, associated with a reduction in ejection fraction and shortening fraction, two indicators suggesting an impaired left ventricular function. After 12 weeks of treatment with the high-dose regimen, cardiac function was significantly improved.

We then examined the relationship between the metabolic and hemodynamic parameters of cardiac function. Our results suggest a positive correlation between the HOMA and the BP, and also the variability of the BP. We also observed a negative correlation between HOMA and the shortening fraction.

Figure 2: Insulin signaling pathways in physiological conditions and in insulin resistance.



In our model, insulin resistance, that mostly arises from lipid storage disorders, seems to play a central role in the development of the metabolic syndrome, and more specifically in the deterioration of the hemodynamic and cardiac parameters. We then tried to find the mechanism by which statins could restore insulin sensitivity. In a previous transcriptomic profiling of mouse tissue in the same model, Pr P. Holvoet and his group had found the expression of the PPAR-γ gene *(Peroxisome Proliferator-Activated Receptor-gamma)* to be significantly increased after diet restriction.[3] Since the effect of rosuvastatin reproduced the effect of diet restriction (including on hemodynamics), we decided to study the involvement of PPAR-γ.

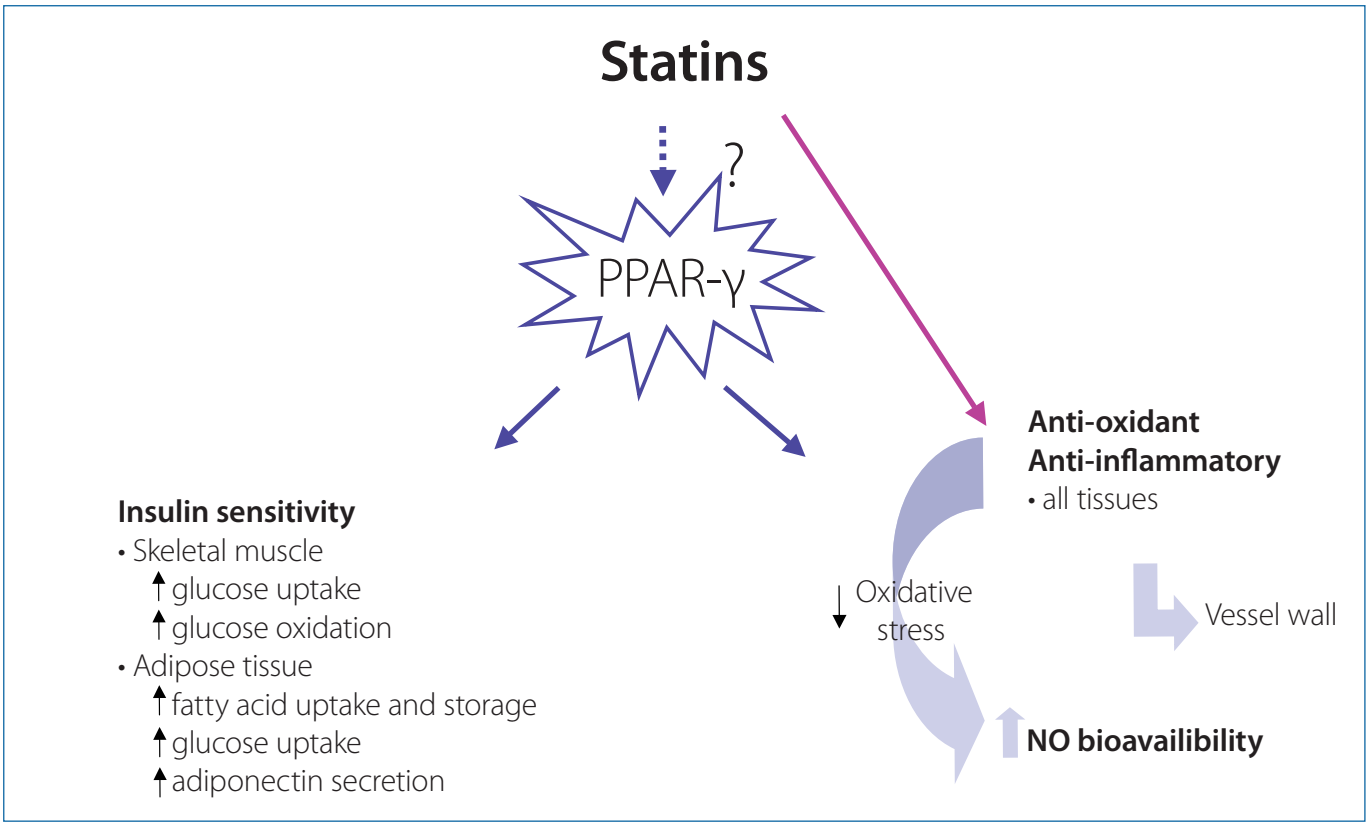
PPAR-γ is a nuclear transcription factor involved principally in insulin sensitivity. It improves glycemic control by increasing the peripheral utilisation of glucose and promotes adipocyte differentiation for proper lipid storage in subcutaneous adipose tissue. Furthermore, it exerts positive effects on the lipid profile by contributing to raise HDL levels and decrease triglycerides levels.[8] Recent studies have demonstrated that PPAR-γ also has an important anti-inflammatory role (figure 3). PPAR-γ ligands inhibit the expression of numerous pro-inflammatory genes (inducible NO synthase, metalloproteinase[9] of the extracellular matrix), via the repression of NF-κB, in macrophages and monocytes, but also the production of pro-inflammatory cytokines (TNF-α, IL-6).[8] It has also been demonstrated that the expression of PPAR-γ is regulated in part by a family of transcription factors named SREBP *(Sterol Regulatory Element Binding Protein)*, the activation of which is known to be sensitive to intracellular free cholesterol levels.[9] Statins could therefore increase the expression of PPAR-γ through this regulation mechanism.

The expression of the mRNA of PPAR-γ, measured by RT (Reverse Transcription)-quantitative PCR in the aortic wall of this mouse model, is significantly increased in the rosuvastatin treated group in comparison to the placebo group. Importantly, additional experiments in endothelial cells, and also in neo-natal cardiomyocytes, have confirmed this significant increase in mRNA expression after direct exposure to rosuvastatin in vitro . To determine if increased PPAR-γ manifests itself in transcriptional activation, we measured the expression of known target genes for this transcription factor in endothelial cells. Among these, the gene encoding superoxide dismutase 1 (SOD-1) contains one response element to PPAR in its promoter region. Our RT-PCR analysis confirmed a significant increase in the expression of SOD-1 in endothelial cells exposed to rosuvastatin, suggesting an increase in the activity of up-regulated PPAR-γ.

Insulin resistance contributes to the induction of deleterious changes in the vascular endothelium and the lipid profile, leading to the progression of atherosclerosis. Under physiological conditions, insulin has an anti-inflammatory and vasodilator role through increasing the expression, but also the activity, of the endothelial NO synthase (eNOS)[11;12] via the activation of the PI3 kinase pathway. When insulin resistance is established (in skeletal muscle cells principally), the activation of the MAP kinase pathway is favoured, inducing an increase in the pro-inflammatory activity and an inhibition of the vasodilation[10] (Figure 2).

A recent transcriptomic comparative analysis in adipocytes submitted to different stimuli known to produce insulin resistance has pointed to the key role of oxidant stress genes as

Figure 3: Proposed mechanism to explain the beneficial effect of statins on blood pressure regulation.



triggers for insulin resistance common to various pathophysiological states (e.g., from apparently unrelated conditions such as sepsis, burns or obesity) (REF). Defective or dysregulated mitochondria may play a key initiating role to promote both oxidant stress and insulin resistance, even before the appearance of significant obesity, as probably happens with aging (REF). In combination with overeating, the subsequent increase in visceral adipocytes volume, a characteristic of abdominal obesity, is associated with perturbation in the level of their cytokine secretion, a decrease of adiponectin, but also an increase in TNF-α. TNF-α is principally responsible for the further decrease in the action of insulin at the receptor level and, also, for the loss of its antilipolytic effect.[10] Free fatty acids released into the circulation are subsequently accumulated by other tissues, mainly hepatocytes and cardiomyocytes, where they may exert lipocytotoxic effects and further inhibit insulin signalling via the activation of PKC isoforms. At the heartlevel, this translates itself into a decreased ability to use glucose as an energy substrate, this being replaced by the almost exclusive utilisation of lipids. In diabetic and insulin-resistant rats, H. Tagtmeyer's group demonstrated that this excess in free fatty acid availability resulted in a striking reduction in the flexibility of the cardiac metabolism (capacity to use, alternatively, glucose and lipids or both simultaneously), leading to cardiac dysfunction.[13] Further, these authors showed that treatment with a PPAR-γ agonist allowed restoration of the heart metabolic flexibility and function.[13] Therefore, our demonstration of upregulated PPAR-γ expression and activity with rosuvastatin, paralleled with increased endothelial SOD-1 expression in isolated cells, may represent a supplementary effect of the drug which decreases oxidant stress and interrupts the initial move towards insulin resistance and ensuing adverse metabolic remodelling in the heart and vessels.

We cannot exclude other direct or indirect actions of statins that could also contribute to the regulation of BP in our model. Since LDL accumulation (e.g., oxidized LDL) is known to have adverse effects on the vascular wall (i.e. increase in the expression of endothelin-1 and the AT1 receptors of angiotensin II, adherence and infiltration of leucocytes, formation of foam cells), statins can also produce their effects by a reduction in plasma LDL levels. Statins decrease the expression of endothelin-1 and increase the experience of mRNA of eNOS via the inhibition of Rho kinase ; they also promote eNOS activation through downregulation of the inhibitory caveolin-1 (REF) and increase the phosphorylation of eNOS by activating the PI3 kinase and AKT pathways[7] Furthermore, by blocking the geranylgeranylation of Rac, they reduce the production of free radicals induced by angiotensin II.

The metabolic effects of rosuvastatin that we have observed in this model of DKO mice reproduce, in part, effects of statins similar to those observed in clinical practice. Even if the reduction in plasma levels of cholesterol is probably playing a role, other ancillary effects of rosuvastatin such as PPAR-γ and SOD-1 upregulation may represent key additional effects initiating the correction of insulin resistance and cardiovascular dysregulation.

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