

For personal use only. Not to be reproduced without permission of the publisher (editorial@gabi-journal.net).

Statin generics: no differences in efficacy after switching

Christoph Baumgärtel, MD

A study presented at the 2010 Congress of the European Society of Cardiology, had created a considerable stir. Its abstract allegedly showed that the originator drug Lipitor was more beneficial than any of its generic statin equivalents. But, in fact the study merely showed that the different potencies of statins were not taken adequately into consideration during the generics switch. The conclusions underscore that statin generics do have essentially the same safety and efficacy as Lipitor and may have implications for new atorvastatin generics that have recently entered the market and will increasingly be prescribed in future.

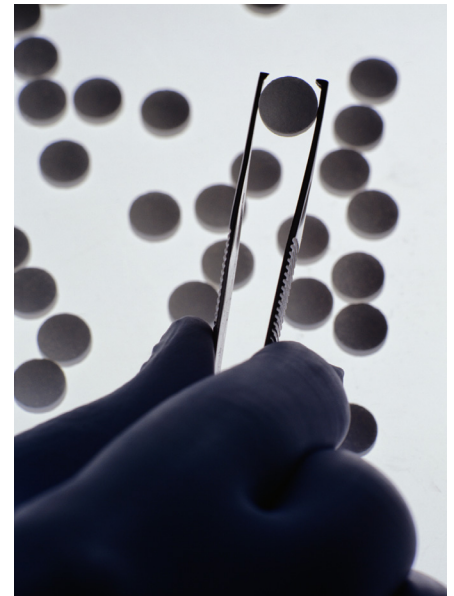
Keywords: Cardiovascular risk, generics, inferiority, potency, statins

A notable abstract on generics substitution of statins was presented at the 2010 Congress of the European Society of Cardiology [1]. Some of the resulting media coverage was equally interesting, stating, for example, that 'Patients should stay on Pfizer's Lipitor, and not switch to generics' [2]. What the abstract predicted was an increased potential risk for serious cardiovascular events following a switch to generic statins. Despite this interesting finding, the question of whether generic statins should be considered inferior to the atorvastatin brand leader, however, can be answered with a resounding 'No'.

Nonetheless, what may appear initially to be a paradoxical conclusion makes perfect sense when considering that the study's aim was not to see if generics act differently to branded products. Instead, the study showed that following a government-mandated switch to generic statins in The Netherlands, doctors—intentionally or unintentionally—prescribed inadequate doses

of the generic drug when switching. Notably, the Dutch doctors were not prescribing generics with the identical active pharmaceutical substance, but instead were switching from branded atorvastatin (Sortis/Lipitor) to various generic versions with simvastatin. This switch makes sense considering the high costs of originator atorvastatin and the remarkably lower costs of generic simvastatin. However, the change of active substances means that it was not a true generics switch because another active substance was prescribed. More importantly, the two active substances are not of equal potency: atorvastatin is more potent than the same molar quantity of simvastatin [3]. The dose equivalence therefore is set at a ratio of at least 1:2 to 1:4, as indicated in the product information leaflets.

Nevertheless, not all prescribing physicians are aware of this fact, and as a result, 20 mg atorvastatin is often substituted by just 20 mg simvastatin. An analysis of the Dutch database revealed, that out of 39,031 patients, more than a third (33.7%)



received less than an equipotent dose of simvastatin after the switch. These figures were calculated under the assumption of a potency ratio of 1:2. If the authors had used a ratio of 1:4, the numbers would have been even higher. Statistical models suggested that this inadequate dosing would lead to a 5.6% increase in LDL-cholesterol levels. This, together with the findings of a meta-regression study [4] showing that every 25 mg/dL (0.65 mmol/L) reduction in LDL-cholesterol lowers the risk of serious cardiovascular events by 14%, indicates that inadequate simvastatin dosing might increase cardiovascular risk by at least 5.5% [1].

It remains uncertain whether these dose reductions were intentional or not. But an intentional dose reduction is unlikely due to the high numbers of patients involved, which does not reflect everyday clinical practice. Worryingly, our conclusion is that a substantial number of switches in The Netherlands were performed by physicians who were unaware of the different potencies of statins. This occurred after a government-mandated change in policy in which physicians would have to justify their prescriptions of branded statins. The result was an economically beneficial increased switch to generics. At the time of the policy change, however,

Author: Christoph Baumgärtel, MD, Department Head, Department Safety and Efficacy Assessment of Medicinal Products, Institute Marketing Authorisation of Medicinal Products & LCM, AGES PharmMed—Austrian Medicines and Medical Devices Agency, and Austrian Federal Office for Safety in Health Care, European Expert in Pharmacokinetics Working Party and Safety Working Party of EMA, Member of Austrian Prescription Commission, 5 Traisengasse, AT-1200 Vienna, Austria

Submitted: 27 July 2012; Revised: 3 September 2012; Accepted: 3 September 2012; Published online first: 5 September 2012

atorvastatin generics were not yet licensed, and so patients were switched to generic simvastatin instead as the available alternative.

Fortunately, this situation has not occurred in Austria, for example. Here, the guideline for economic prescribing [5] stipulates that in the case of two equally effective treatments the cheaper one should be chosen. To do so, Austrian doctors can access an online 'Info-tool' [6] which indicates alternatives to an originator product and their prices. This tool takes the potency difference of statins into account correctly. A search for alternatives to atorvastatin, e.g. to Sortis 20 mg tablets, produces a list of several simvastatin generics, all at an appropriate dosage form of 80 mg tablets, some of them even with a score line. This takes into account dose equivalence in the range of 1:2 to 1:4. The product information leaflets affirm the difference in potency: the indicated dosage of atorvastatin for the prevention of cardiovascular disease is 10 mg per day, while for simvastatin it is 20–40 mg per day.

The Dutch study shows the importance of thoroughly checking product information and using additional info-tools. The erroneous switch to less than equivalent doses of simvastatin, two to four times below the recommended dosage, could have been detected and presumably avoided if the prescribing physicians had consulted these resources properly.

In conclusion, the media coverage that generic statins might be inferior per se, and that switching should be avoided, can be refuted. In support of this, a Korean study [7] examined the efficacy of atorvastatin generics to reduce LDL-cholesterol and total cholesterol compared to its atorvastatin originator. Reduction after eight weeks from baseline for LDL-cholesterol was about 44% for the generics and 46%

for the originator, showing no significant difference. Corresponding values for total cholesterol were about 30% and 31%, respectively, and not significantly different. In addition, a Slovenian trial [8] similarly revealed that generic atorvastatin leads to an equal reduction in LDL-cholesterol compared to the originator after 12 weeks (37.8% vs 38.4%, $p = ns$). Both drugs reduced the absolute coronary risk by 13% and 13.3% for the generic and reference atorvastatin, respectively.

These findings are important as a number of atorvastatin generics have recently entered the market that will increasingly be prescribed in future, as was already seen with other drug substances [9, 10], giving assurance to physicians that atorvastatin generics are equally as safe and effective as the originator. Physicians who choose to switch from atorvastatin to simvastatin may do so, but must consider the different potency of these two statins and take care to prescribe the correctly adjusted dose.

For patients

A misunderstood study about the statin drug Lipitor and its generic alternatives caused a media storm, with the notion that generics were inferior. A closer examination, however, reveals that physicians had mistakenly prescribed inadequate doses of the generic drug alternatives, putting patients at higher risk of cardiovascular disease.

Competing interests: None.

Provenance and peer review: Commissioned; externally peer reviewed.

References

- Liew D, et al. The cardiovascular consequences of switching from atorvastatin to generic simvastatin in the Netherlands. Abstract n° 3562. ESC; 2010 Aug 28–Sep 1; Stockholm, Sweden.
- Bloomberg News, 2010-08-20 [homepage on the Internet]. Patients should stay on Pfizer's Lipitor, not switch to generic, study say. [cited 2012 Sep 3]. Available from: www.bloomberg.com/news/2010-08-20/cholesterol-drug-study-shows-heart-risks-in-switch-to-generic-from-lipitor.html
- Rogers, et al. A dose-specific meta-analysis of lipid changes in randomized controlled trials of atorvastatin and simvastatin. *Clin Ther.* 2007 Feb; 29(2):242-52.
- Delahoy PJ, et al. The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. *Clin Ther.* 2009 Feb;31(2):236-44.
- Hauptverband der österreichischen Sozialversicherungsträger [homepage on the Internet]. [Austrian instructions on economic prescribing of medicines (RÖV)]. [cited 2012 Sep 3] German. Available from: www.hauptverband.at/portal27/portal/hvbportal/channel_content/cmsWindow?action=2&p_menuid=58307&p_tabid=4
- Hauptverband der österreichischen Sozialversicherungsträger [homepage on the Internet]. [Info-tool to the Austrian Reimbursement-Code]. [cited 2012 Sep 3] German. Available from: www.hauptverband.at/portal27/portal/hvbportal/emed/
- Kim SH, et al. Efficacy and tolerability of a generic and a branded formulation of atorvastatin 20 mg/d in hypercholesterolemic Korean adults at high risk for cardiovascular disease: a multicenter, prospective, randomized, double-blind, double-dummy clinical trial. *Clin Ther.* 2010 Oct; 32(11):1896-905.
- Boh M, et al. Therapeutic equivalence of the generic and the reference atorvastatin in patients with increased coronary risk. *Int Angiol.* 2011 Aug; 30(4):366-74.
- Baumgartel C, Godman B, Malmstrom R, et al. What lessons can be learned from the launch of generic clopidogrel? *Generics and Biosimilars Initiative Journal (GaBI Journal).* 2012;1(2): 58-68. doi:10.5639/gabij.2012.0102.016
- Baumgartel C. Generic clopidogrel—the medicines agency's perspective. *Generics and Biosimilars Initiative Journal (GaBI Journal).* 2012;1(2): 89-91. doi:10.5639/gabij.2012.0102.019