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Statin therapy for venous ulcers

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Dear Editor, The recent paper by Evangelista *et al.*[1] seems to offer the promise of an inexpensive, readily available, easy to administer and highly efficacious adjunctive therapy for the treatment of chronic venous leg ulcers. We congratulate the authors on this very provocative study in which subjects were randomized to receive either simvastatin 40 mg daily or a placebo pill, in addition to standard compression therapy.

As with any surprisingly positive finding, the potential benefit of added simvastatin will require independent confirmation, which should address some potentially important methodological issues. Firstly, this was a small single-centre trial. Regulatory agencies require multicentre trials for confirmation of efficacy in order to prevent unintentional or conscious bias, outlier outcomes or other idiosyncratic site effects from significantly influencing overall results. A single-centre study has none of these safeguards in place and therefore can only be considered exploratory.

Secondly, it would be difficult to imagine more favourable outcomes than those achieved in this trial. The authors report healing rates of 67% at 10 weeks for ulcers > 20 cm^2 (> 5 cm in diameter) and 100% for ulcers ≤ 20 cm^2. This result is compared with the placebo group where 0% and 50% achieved closure, respectively.

These results are particularly surprising when one considers that these ulcers were not small and not young; the mean size for ulcers that closed was 12 cm^2 and 31 cm^2 for placebo and simvastatin groups with average chronicity of 2·4 years and 3·3 years, respectively. According to Margolis *et al.*,[2] a wound > 10 cm^2 and > 12 months old has only a 22% chance of healing after 24 weeks of good therapy with compression. If one compares the outcomes achieved for the placebo group with those from other studies with a compression-only group, it is apparent that the proportion healed is unusually high. Kirsner *et al.*[3] reported 46% healed at 12 weeks for ulcers treated with four-layer compression. Although this seems similar to the 50% reported for the smaller ulcers (≤ 20 cm^2) in the Evangelista *et al.* study, these ulcers were all < 12 cm^2 (mean = 5·6 cm^2) and ≤ 2 years old. As Evangelista *et al.* point out, larger longer-duration ulcers are more difficult to heal. Why were these large, long-duration ulcers healed with such comparative facility? It is possible that this study represented the first application of good care (i.e. consistent, good-quality compression, infection control, control of oedema). The study did not employ a run-in period to exclude those who would heal under standard care alone.

It is also not clear from their paper whether subjects were required to be either statin naive, or to have discontinued prestudy statin usage and undergone a 'washout'. This is important because subjects with hypercholesterolaemia were allowed to enrol. While the number of affected subjects is not given, it would be reasonable to assume based on previous work[4] that at least 12–20% had serum cholesterol of ≥ 240 mg dL^{-1} and would be categorized as having hypercholesterolaemia. If those subjects with 'high-borderline' serum cholesterol (200–239 mg dL^{-1}) and ≥ 2 risk factors are included, it is likely to be closer to 30% of subjects.[4] Presumably, most (if not all) subjects were under statin treatment prior to the study. Were subjects allowed to continue taking their prestudy statins or were they required to discontinue use? Allowing subjects to continue these medications would introduce several difficulties, including nonstandardized dosing in the active treatment group and a serious confounding variable for those randomized to the placebo group. The alternative, requiring cessation of statins before enrolling, would present challenges, particularly for those randomized to the placebo group. From a practical standpoint it would also put a serious limitation on the generalizability of these results as statins are in widespread common usage, particularly in this target population.

Moreover, a subject undergoing chronic statin therapy who develops a venous ulcer would seem to be in some sense a 'nonresponder' to statin treatment, at least in regard to venous ulcers. From our own phase II trial comparing HP802-247 with compression alone,[3] we know that of those subjects enrolling who were concomitantly undergoing statin therapy ($n = 48$, mean duration prestudy = 50·5 months), the overall healing rate at 12 weeks was only modestly higher than for those not on a statin (65% vs. 59%, not significant). If those subjects who were randomized to compression only and not treated with HP802-247 are considered, the difference is even smaller (50% vs. 45%, not significant). Several other important factors affecting healing were identified including ulcer area, chronicity and bacterial load.[5]

An inexpensive, highly efficacious, adjunctive treatment for venous leg ulcers, which could be administered as a once-daily tablet, is surely a very exciting prospect. Confirmation will require replicating these results in larger multicentre studies

with appropriate inclusion and exclusion criteria, study design and complete transparency of these key trial design components.

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Requests for dermatology specialist consultations show an inverse correlation with waiting time: an analysis of waiting time to access dermatology specialist health care in Bolzano, South Tyrol, Italy

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Dear Editor, Accessibility and waiting times represent a general problem in public-financed healthcare systems.[1] The Italian National Health Service (NHS) provides free healthcare access to every Italian citizen, and is funded through direct and indirect taxation. Patients are assigned a general practitioner (GP), who is entirely paid by the NHS. Specialist consultations or diagnostic tests are provided by public hospitals or ambulatories only if prescribed by the GP.

Skin diseases are among the main reasons for seeking primary healthcare advice; Schofield *et al.*[2] have shown that in England and Wales in 2006, about the 24% of the population consulted their GP for skin problems. Notoriously, skin problems generate long waiting lists in secondary care structures with a specialized dermatology unit; moreover, the demand for dermatology assistance has shown a steady increase over the years.[3] In Italy, waiting times for dermatology specialist consultations and requests for dermatology specialist care are monitored centrally by the local government in the north Italian province of South Tyrol. A provincially agreed prioritization triage system according to urgency is in place in order to not dismiss patients with severe or urgent dermatology disease.[4] The average waiting time for any specialist consultation is available without restriction on the hospitals' website.

Evidence of whether there is an increase or decrease in specialist consultation requests with regard to the availability of specialist consultations is scarce. By creating a lottery for uninsured, low-income adults, Taubman *et al.*[5] analysed the effects of Medicaid coverage on emergency department use. The authors found that Medicaid coverage increased the use of health care. In particular, Medicaid coverage increased self-reported access to and use of primary care, as well as the self-reported use of prescription drugs and preventive care.

We performed a retrospective study to investigate the correlation between monthly waiting time in days and number of dermatology specialist access requests for the city of Bolzano, comprising approximately 250 000 inhabitants. The monitored time included data from January 2007 (start of the monitoring of waiting times) to July 2013 for monthly waiting times in days, and from November 2007 (start of the monitoring of monthly requests) to July 2013 for the number of monthly dermatological access requests, all provided by the central monitoring agency. The results of the analysis showed that the median waiting time for a nonurgent dermatology referral was 57 days in the first year of the monitoring and was slowly increasing, from 30 days at the beginning of the first year to 61 days by the end of that year. Owing to staff shortage, waiting time increased sharply at the end of 2010, reaching a peak of 224 days in January 2011. With the allocation of new physicians, waiting time decreased to 49 days in July 2013 (see Fig. 1). This change in waiting time, with a sharp peak increase and rapid reduction of waiting time thereafter, provided us with the opportunity to analyse the relationship between waiting time and the number of requests for specialist health care in dermatology.

Mean monthly requests for dermatology specialist consultations was lowest in the 6-month period from September 2010 to February 2011, with the longest waiting time being over 200 days (mean 568 requests per month), and highest in the 8-month period from December 2012 to July 2013, with the shortest waiting time being less than 50 days (mean 987 requests per month); this difference was statistically significant ($P < 0{\cdot}01$). In addition, a strong negative correlation between waiting time and request for access was noted (Pearson's $r = -0{\cdot}67$; $P < 0{\cdot}01$) (Fig. 2).