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EDITORIAL

The EVRA Trial: New Hope for People with Venous Leg Ulcers?

Although contemporary epidemiological data are lacking, it is widely cited that 1–2% of people over the age of 65 years will suffer leg ulceration.[1] Given ample evidence to show that chronic wounds are more difficult to heal,[2] and that treating leg ulcers (especially ineffectively) consumes considerable resources,[3,4] one would have thought that putting leg ulcer referral pathways in place, to ensure that an accurate diagnosis is reached as soon as possible, would be a priority for clinicians, purchasers, and policymakers. However, this approach has not been widely adopted, leading to clinically and cost-ineffective care for many patients.

Surprisingly, existing guidelines, including those published by the European Society for Vascular Surgery (ESVS) in 2015,[5] lack specific guidance regarding referral from community to specialist care. By contrast, UK National Institute for Health and Care Excellence (NICE) clinical guideline (CG) 168,[6] published in July 2013, recommends that patients with a leg ulcer (defined as a "break in the skin below the knee that has not healed within 2 weeks") should be referred to a "specialist vascular service" and undergo "duplex ultrasound to confirm the diagnosis of varicose veins and the extent of truncal reflux". Unfortunately, there is little evidence to show that these UK guidelines have resulted in a change in practice, with most UK National Health Service ulcer patients still waiting months to be referred, if, indeed, they are referred at all.[7,8]

While barriers to early referral, assessment, diagnosis, and treatment of leg ulcers probably vary between different healthcare systems, the following seem likely candidates: (i) to avoid additional short-term expenditure, purchasers of health care will find every excuse not to refer patients to secondary care (even when there is good evidence that this is likely to reduce expenditure in the longer term); (ii) lack of education and empowerment means that patients are largely unaware of, and unable to demand, evidence based care; (iii) suboptimal training, education, and awareness among community practitioners; (iv) lack of "level 1" evidence from randomised controlled trials showing that early intervention for venous ulceration is clinically and cost-effective.

With regard to the last point, although the ESCHAR trial,[9] published almost 15 years ago, demonstrated conventional surgery to ablate superficial venous reflux reduced ulcer recurrence, it did not improve healing. Furthermore, many patients with venous leg ulcers were considered unsuitable for, and/or declined, surgery. Therefore, many colleagues remained unconvinced that early surgical intervention conferred additional benefit over conservative treatment with compression.[10]

Venous intervention has advanced considerably since ESCHAR. ESVS and NICE CG168 recognise that the majority of patients with symptomatic superficial venous reflux are best treated by endovenous methods (particularly endothermal ablation and ultrasound guided foam sclerotherapy [UGFS]) rather than conventional surgery. This is especially true for elderly and frail patients. As a result, there has been a growing trend towards offering endovenous intervention under local anaesthesia to most patients with active venous leg ulcers rather than the historical management of compression and subsequent conventional surgery to a selected group of patients to reduce recurrence.

Strictly speaking, this change in practice has not been evidenced based and the "belief" among vascular specialists that this was the correct approach has clearly not been enough to convince many community practitioners to refer leg ulcer patients.[11–13] Fortunately, the evidence base has been transformed by the recent publication of the UK National Institute for Health Research, Health Technology Assessment funded Early Venous Reflux Ablation (EVRA) trial.[14] This UK based trial randomised 450 venous leg ulcer patients presenting to 20 specialist vascular centres to either early (within 2 weeks) or delayed (after 6 months) endovenous ablation of superficial truncal reflux in addition to standard compression management. Early endovenous ablation was associated with a reduction in healing time from a median of 82 to 56 days. The hazard ratio for ulcer healing was 1.38 (95% confidence interval 1.13–1.68; $p = .001$) and the rate of ulcer healing at 24 weeks was 85.6% and 76.3% in the early and deferred interventions groups, respectively. Early ablation was associated with a significant increase in ulcer free time over the first 12 months (306 days [interquartile range {IQR} 240–328] vs. 278 [IQR 175–324]), along with significant reduction in venous clinical severity score, improvement in quality of life, and was highly cost-effective. Clinicians were permitted to use their preferred endovenous technique, most commonly UGFS, which was used either alone or in combination with other methods in $> 50\%$.

This landmark trial should herald a major change in thinking and practice regarding the management of leg ulcers. Many guidelines, including those of the ESVS, still recommend compression as the cornerstone of management for C6 venous disease. ESCHAR provided "level 1" evidence that surgically ablating superficial venous reflux

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reduces ulcer recurrence rates, and EVRA now provides clear evidence that early endovenous ablation accelerates ulcer healing and reduces recurrence, at least out to 12 months. Existing European and UK guidelines will have to be rewritten to ensure that such early referral and assessment occurs, as well as recommending early intervention over compression alone. Furthermore, at least in the UK, it seems unlikely that the excellent healing rates (just over 75% at 24 weeks) observed in EVRA with compression in the participating specialist centres will be reproducible in most community settings. So, in the real world, the added benefit of early endovenous ablation is likely to be much greater than was observed in the trial.

One would hope this trial would change practice, giving new hope to tens of thousands of patients who hitherto have been denied access to evidence based treatment. However, despite the compelling evidence that early endovenous ablation is clinically and cost-effective, it is possible that there may still be resistance from purchasers and community providers as EVRA has not yet shown early ablation to be associated with sustained long-term benefit; and only a relatively small proportion of patients were considered suitable for randomisation. While 6555 patients were assessed for eligibility, only 450 (about 7%) were randomised. Most commonly, patients were excluded for ulceration duration $>$ 6 months (27%) and significant arterial disease (ankle brachial index $<$ 0.8) (13%); another 610 patients had healed their ulcer by the time of randomisation, and 568 patients were deemed not to have an ulcer. So, while EVRA is undoubtedly an important, landmark trial, longer-term follow up data are required so that the full impact of early endovenous intervention in recurrence can be determined. Further trials are required to better define evidence based care for patients with leg ulcers who were not the subject of the EVRA trials, including patients with more chronic (over 6 months) venous ulcers (although with early referral and intervention such ulcers should largely be a thing of the past); and those with arterial disease, in whom early endovenous intervention may be even more effective because full compression is contra-indicated.

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Huw O.B. Davies, Andrew W. Bradbury*

University Department of Vascular Surgery, University of Birmingham, Netherwood House, Solihull Hospital, Birmingham, B91 2JL, UK

*Corresponding author. University Department of Vascular Surgery, University of Birmingham, Netherwood House, Solihull Hospital, Birmingham B91 2JL, UK.

Email-address: andrew.bradbury@btinternet.com (Andrew W. Bradbury)