What further evidence do we need before NICE Clinical Guideline (CG) 168 actually changes UK practice?

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What has been the impact of CG 168?

Original Article

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SAGE

Impact of UK NICE Clinical Guidelines 168 and social deprivation on access to interventional treatment for symptomatic varicose vein and specialist referral for leg ulceration

Huw OB Davies, Matthew Popplewell, Gareth Bate, Lisa Kelly, Andreas Koutsoumpelis and Andrew W Bradbury

Abstract

Background: UK National Institute for Health and Care Excellence (NICE) clinical guidelines (CG) 168, published in July 2013, aimed to improve the management of lower limb venous disease by newly recommending interventional treatment for all people affected by symptomatic varicose veins (VV) and specialist vascular referral for all people suffering from a leg ulcer (LU) that had been present for ≥2 weeks. This study aims to determine if CG168 has increased access to vascular services, particularly for the socially deprived, who might be expected to have greater need for such services.

Methods: The study was performed in a highly multi-cultural, socio-economically diverse, mixed urban/suburban population of approximately 1.2 million people living in and around East Birmingham, UK. Index of multiple deprivation quintile (IMD-Q) was used as a measure of social deprivation to compare levels of social deprivation of people undergoing interventions for symptomatic VV or referred with an LU during 18-month periods before and after the publication of CG168. The referring general practitioner practices (GPPs) were also recorded.

Results: There was no change in overall IMD-Q distribution before and after CG168 in terms of VV interventions. However, there was a non-significant increase in proportions of people classified as IMD-Q5 (the most deprived quintile). After CG168, fewer IMD-Q5 people with LU were referred, with a shift in referrals towards those from less socially deprived areas. More GPP referred people with both VV and LU after CG168, and those that referred patients before and after CG168 tended to refer more after CG168.

Conclusions: CG168 has increased VV interventions as well as the number referred with LU. However, this improvement in access to treatment and referral may have disproportionately favoured the more socio-economic privileged. Professional and public education is required to ensure that the beneficial impact of the CG168 recommendations are maximised and that those with the greatest health needs have equal access to evidence-based management of their venous disease.

Keywords

Varicose veins, leg ulceration, endovenous, index of multiple deprivation, IMD, social

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Publication of UK NICE Clinical Guidelines 168 has not significantly changed the management of leg ulcers in primary care: An analysis of The Health Improvement Network database

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Abstract

Background: NICE Clinical Guidelines (CG) 168, published in July 2013, recommend specialist vascular referral for all leg ulcers, defined as a break in the skin below the knee that has not healed within two weeks.

Aim: To examine the impact of CG168 on the primary care management of leg ulcers using The Health Improvement Network database.

Methods: An eligible population of approximately two million adult patients was analysed over two 18-month periods before and after publication of CG168. Those with a new diagnosis of leg ulcers in each time period were analysed in terms of demographics, specialist referral and superficial venous ablation.

Results: We identified 7532 and 7462 new diagnoses of leg ulcers in the pre- and post-CG168 cohorts, respectively. Patients with a new diagnosis of leg ulcers were elderly (median age: 77 years both cohorts) and less likely to be male (47% both cohorts). There were 2259 (30.0%) and 2329 (31.2%) vascular service referrals in the pre- and post-CG168 cohorts, respectively (hazard ratio, 1.05, 95% CI: 0.99, 1.11, p = 0.096). The median interval between general practitioner diagnosis and referral was 1.5 days in both cohorts. Patients from both cohorts who were referred for a new diagnosis of leg ulcers were equally likely to receive superficial venous ablation.

Conclusions: Disappointingly, we have been unable to demonstrate that publication of NICE CG168 has been associated with a meaningful change in leg ulcer management in primary care in line with guideline recommendations.

Keywords

Leg ulceration, ulcer, The Health Improvement Network, primary care, NICE, guidelines

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Impact of UK NICE clinical guidelines 168 on referrals to a specialist academic leg ulcer service

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Abstract

Background: Leg ulcers are a common cause of morbidity and disability and result in significant health and social care expenditure. The UK National Institute for Health and Care Excellence (NICE) Clinical Guideline (CG)168, published in July 2013, sought to improve care of patients with leg ulcers, recommending that patients with a break in the skin below the knee that had not healed within two weeks be referred to a specialist vascular service for diagnosis and management.

Aim: Determine the impact of CG168 on referrals to a leg ulcer service.

Methods: Patients referred with leg ulceration during an 18-month period prior to CG168 (January 2012–June 2013) and an 18-month period commencing six months after (January 2014–June 2015) publication of CG168 were compared.

Results: There was a two-fold increase in referrals (181 patients, 220 legs vs. 385 patients, 453 legs) but no change in mean age, gender or median-duration of ulcer at referral (16.6 vs. 16.2 weeks). Mean-time from referral to specialist appointment increased (4.8 vs. 6 weeks, $p = 0.0001$), as did legs with superficial venous insufficiency (SVI) (36% vs. 44%, $p = 0.05$). There was a trend towards more SVI endovenous interventions (32% vs. 39%, $p = 0.271$) with an increase in endothermal (2 vs. 32 legs, $p = 0.001$) but no change in sclerotherapy (24 vs. 51 legs) treatments. In both groups, 62% legs had compression. There was a reduction in legs treated conservatively with simple dressings (26% vs. 15%, $p = 0.0006$).

Conclusions: Since CG168, there has been a considerable increase in leg ulcer referrals. However, patients are still not referred until ulceration has been present for many months. Although many ulcers are multi-factorial and the mainstay of treatment remains compression, there has been an increase in SVI endovenous intervention. Further efforts are required to persuade community practitioners to refer patients earlier, to educate patients and encourage further investment in chronically underfunded leg ulcer services.

Keywords

Varicose veins, leg ulcers, ulcer treatment, NICE, guidelines

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The impact of 2013 UK NICE guidelines on the management of varicose veins at the Heart of England NHS Foundation Trust, Birmingham, UK

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Abstract

Objective: Although varicose veins are a common cause of morbidity, the UK National Health Service and private medical insurers have previously sought to ration their treatment in a non-evidence based manner in order to limit health-care expenditure and reimbursement. In July 2013, the UK National Institute for Health and Care Excellence published new national Clinical Guidelines (CG168) to promote evidence-based commissioning and management of varicose veins. The aim of this study was to evaluate the impact of CG168 on the referral and management of varicose veins at the Heart of England NHS Foundation Trust, Birmingham, UK.

Methods: Interrogation of a prospectively gathered database, provided by the Heart of England NHS Foundation Trust Performance Unit, of patients undergoing interventions for varicose veins since 1 January 2012. Patients treated before (group 1) and after (group 2) publication of CG168 were compared.

Results: There were 253 patients, 286 legs (48% male, mean (range) age 54 (20–91) years) treated in group 1, and 417 patients, 452 legs, (46% male, mean (range) age 54 (14–90) years) treated in group 2, an increase of 65%. CG168 was associated with a significant reduction in the use of surgery (131 patients (52%) group 1 vs. 127 patients (30%) group 2, $p = 0.0003$, χ^2), no change in endothermal ablation (30 patients (12%) group 1 vs. 45 patients (11%) group 2), a significant increase in ultrasound-guided foam sclerotherapy (92 patients (36%) group 1 and 245 patients (59%) group 2, $p = 0.0001$, χ^2) and an increase in treatment for C2/3 disease (53% group 1 and 65.2% group 2, $p = 0.0022$, χ^2).

Conclusions: Publication of National Institute for Health and Care Excellence CG168 has been associated with a significant increase (65%) in the number of patients treated, referral at an earlier (CEAP C) stage and increased use of endovenous treatment. CG 168 has been highly effective in improving access to, and quality of care, for varicose veins at Heart of England NHS Foundation Trust.

Huw Davies, MD Thesis

What is the impact of CG 168?

Five years on, sadly, we have found no evidence that CG 168 has had a positive impact on NHS practice or outcomes for patients with C2-6 disease

Varicose veins: diagnosis and management

Clinical guideline [CG168] Published date: July 2013 Uptake of this guidance

Waste of time and money? (c. £500K [FoI])

Why is there not more concordance between the evidence base and UK vascular practice?

Condition	Venous ulcer	Intermittent Claudication	AAA (EVAR2)	AAA (EVAR1)
Intervention	Surgical and Endovenous Intervention	Supervised Exercise	EVAR	EVAR
Trials	ESCHAR EVRA	Many!!!	EVAR-2	EVAR-1
ICER	< 6K	< 2K	£300-400K	Infinity
Clinically and cost-effective	Very	Very	Nowhere near	Dominated
NICE	**YES**	**YES**	**NO**	**NO**

Is it really a matter of evidence?

CG 168 – response to consultation

Varicose veins: diagnosis and management

Clinical guideline [CG168] Published date: July 2013 Uptake of this guidance

Draft AAA guidelines - 2018
Response to consultation

Varicose Veins – a lost cause?

Early Venous Reflux Ablation

EVRA

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on behalf of the EVRA trial investigators

NHS

National Institute for Health Research

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Early Endovenous Ablation in Venous Ulceration

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ABSTRACT

BACKGROUND

Venous disease is the most common cause of leg ulceration. Although compression therapy improves venous ulcer healing, it does not treat the underlying causes of venous hypertension. Treatment of superficial venous reflux has been shown to reduce the rate of ulcer recurrence, but the effect of early endovenous ablation of superficial venous reflux on ulcer healing remains unclear.

METHODS

In a trial conducted at 20 centers in the United Kingdom, we randomly assigned 450 patients with venous leg ulcers to receive compression therapy and undergo early endovenous ablation of superficial venous reflux within 2 weeks after randomization (early-intervention group) or to receive compression therapy alone, with consideration of endovenous ablation deferred until after the ulcer was healed or until 6 months after randomization if the ulcer was unhealed (deferred-intervention group). The primary outcome was the time to ulcer healing. Secondary outcomes were the rate of ulcer healing at 24 weeks, the rate of ulcer recurrence, the length of time free from ulcers (ulcer-free time) during the first year after randomization, and patient-reported health-related quality of life.

RESULTS

Patient and clinical characteristics at baseline were similar in the two treatment groups. The time to ulcer healing was shorter in the early-intervention group than in the deferred-intervention group; more patients had healed ulcers with early intervention (hazard ratio for ulcer healing, 1.38; 95% confidence interval [CI], 1.13 to 1.68; P=0.001). The median time to ulcer healing was 56 days (95% CI, 49 to 66) in the early-intervention group and 82 days (95% CI, 69 to 92) in the deferred-intervention group. The rate of ulcer healing at 24 weeks was 85.6% in the early-intervention group and 76.3% in the deferred-intervention group. The median ulcer-free time during the first year after trial enrollment was 306 days (interquartile range, 240 to 328) in the early-intervention group and 278 days (interquartile range, 175 to 324) in the deferred-intervention group (P=0.002). The most common procedural complications of endovenous ablation were pain and deep-vein thrombosis.

CONCLUSIONS

Early endovenous ablation of superficial venous reflux resulted in faster healing of venous leg ulcers and more time free from ulcers than deferred endovenous ablation. (Funded by the National Institute for Health Research Health Technology Assessment Program; EVRA Current Controlled Trials number, ISRCTN02335796.)

From Cambridge University Hospitals NHS Foundation Trust, Cambridge (M.S.G.), the Department of Surgery and Cancer (M.S.G., F.H., A.H.D.) and Imperial Clinical Trials Unit (X.L., J.W.), Imperial College London, London, University of Birmingham, Birmingham (A.B.), Gloucestershire Hospitals NHS Foundation Trust, Gloucester (R.B., K.R.P.), the Medical Research Council Population Health Research Unit and the Clinical Trial Service Unit and Epidemiological Studies Unit, Nuffield Department of Population Health, University of Oxford, Oxford (R.B.), University of Manchester, Manchester (N.C.), Worcestershire Acute Hospitals NHS Trust, Worcester (I.N.), North West London Hospitals NHS Trust, Harrow (S.R.), and University of Warwick, Coventry (J.W.) — all in the United Kingdom; and the University of Granada, Granada, Spain (D.M.E.). Address reprint requests to Dr. Davies at the Section of Vascular Surgery, Department of Surgery and Cancer, Imperial College London, Charing Cross Hospital, London W6 8RF, United Kingdom, or at a.h.davies@imperial.ac.uk.

*A complete list of the Early Venous Reflux Ablation (EVRA) trial investigators is provided in the Supplementary Appendix, available at NEJM.org.

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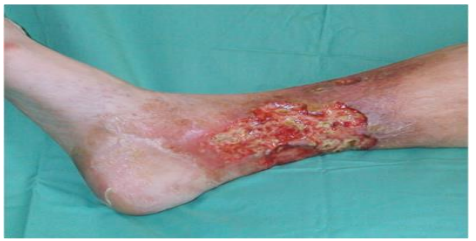
Conclusions

Early endovenous ablation plus compression vs. compression alone was associated with:

- shorter time to healing
- greater ulcer free time
- better VCSS and HRQL



And was highly cost-effective

Surely this should be enough to ensure the CG 168 CVU ulcer recommendations are followed?

- BUT WILL IT? ….. AND IF NOT, WHY NOT?

Recruitment was difficult!

Oct 2013 – Sep 2016
6555 Screened

EXCLUSIONS (n = 6105)
1772 Ulcer >6 months
873 ABPI < 0.8
610 Ulcer healed
568 Not an ulcer
496 Clinician decision
434 Patient declined
378 No venous reflux
974 Other reason
Inclusion rate 7%

450 Randomised

224 Early

226 Deferred

31 lost to follow-up / withdrew
12 died
387 (6%) – per protocol

1) Generalisability?

Two important exclusions (**40%** of 6555 screened)

- 27%: 1772 ulcer present for **> 6 months**
- 13%: 873 **ABPI < 0.8**

We still see lots of patients with ulcers > 6/12

We still ablate them – but non-evidence based?

Only a minority of patients we see in our leg ulcer clinic are suitable for endovenous ablation

- Co-morbidity (immobility, no capacity, stockings)
- Not venous
- Multifactorial (deep venous, arterial disease)
- Phlebesity (correct BMI cut-off?)

2) Have we addressed the correct cost-effectiveness question to impact CG 168?

We have shown early endovenous ablation to be clinically and cost-effective from the starting point of "**do we or do we not offer early ablation once we have seen the patient in our vascular clinics, scanned them, and deemed them suitable for such ablation?**"

Most venous specialists already believed this to be true and have been treating people accordingly for many years

But is that the CG 168 cost-effectiveness question?

Playing Devil's Advocate, I suggest not …

Cost-effectiveness?

Data on only 387 patients out to 12 months

Only 28 additional ulcer free days at 1 year

Currently no long-term recurrence data

So, cost-effectiveness at the 'case finding' decision making point in primary care (vs. vascular clinic) is much less certain

Very large numbers of patients would have to be **referred** and **scanned** (at considerable expense) to find a (very?) small proportion of people (6-7%) who are suitable for, likely to benefit from, and would accept early endovenous ablation

So the cost per 'EVRA-like patient' may be considerable

(6105 x £250 = c. £1.5m ÷ 450 = **£3392 per patient**)

Arguably, unlikely to negate the savings gained from early ablation once people get to the point of randomisation?

EVRA-1+ ?

Long-term follow-up of current cohort

5 years?

Relatively inexpensive (telephone?)

And potential for much larger

- Reduction in health care costs
- Improvement in HRQL (QALYs)

But, loss to follow-up?

Do we have enough patients?

EVRA-2 ?

Repeat EVRA with patients who have an **ABPI < 0.8 (0.6?)**

Probably reasonable to hypothesise that the additional benefit of endovenous ablation over reduced compression would be greater than that observed with endovenous ablation in EVRA against full compression only?

However, are there enough patients out there?

Only 873 in the EVRA screened population

Older, with more co-morbidity?

Would there be more other exclusions in this group than was found in EVRA?

Greater loss to follow-up (sample size)?

Would intervening to correct their ABPI so they can have full compression +/- endovenous ablation be more clinically and cost-effective?

EVRA-3 ?

Repeat EVRA with patients who have an a **leg ulcer for more than 6 months**

But are they different:

- Clinically?
- Pathophysiologically?
- Biologically?

So, would it be reasonable to hypothesise that the additional benefit of endovenous ablation over full compression only would be same as that observed in EVRA?

Also, are there enough patients out there? (1772 in EVRA)

There shouldn't be! Seeking funding for a trial in a group of patients who (in theory) should not exist

How do you deal with prior treatment confounding (e.g. those that have compression and those that have not?)

EVRA-4 ?

Cluster RCT by geography at a suitable level of granularity

Strategy 1 - refer all leg ulcer patients to a specialist vascular service as per NICE guidelines

- What happens to them (investigations, treatments etc.)?
- what are outcomes (ulcer free time as the primary end-point + all the usual stuff, HRQL etc.)?
- what are the associated costs (the EVRA-like patients will be a small proportion of this patient group)?

Strategy 2 - don't refer until a clinician decides to refer for whatever reason

What happens now for the most part and what will probably continue despite EVRA)

- ditto as above (the EVRA-like patients will be an even smaller proportion of this patient group?)

EVRA: New Hope?

Eur J Vasc Endovasc Surg (2018) ■, 1–2

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"

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evidence that surgically ablating superficial venous reflux 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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