



REVIEW

The Seriousness of Chronic Venous Disease: A Review of Real-World Evidence

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ABSTRACT

Chronic venous disease (CVD) is a prevalent condition that tends to worsen with age. Patients initially seek treatment to relieve symptoms of leg pain, discomfort, heaviness and swelling, all of which impact their quality of life. As the disease increases in severity to include varicose veins, skin changes, and venous ulcer, the demand for treatment increases while the quality of life further diminishes. The prevalence of CVD is highest in Western countries where it already consumes up to 2% of healthcare budgets. With the aging of the global population, the prevalences of CVD and severe CVD are projected to increase substantially, foretelling unsustainably large increases in the healthcare resources and costs needed to treat CVD patients in the coming decades. Effective venoactive drug treatments and ablation procedures are available that provide symptom relief, improve quality of life, slow disease progression, and promote ulcer healing. In addition, venoactive drug

treatments may be highly cost-effective. However, there is evidence that physician awareness of CVD is suboptimal and that many patients with CVD are not being treated or referred to specialists according to established guidelines. To decrease this treatment gap and prevent unnecessary disease progression, international guidelines are available to help physicians consider CVD treatment options and refer patients when warranted. Improved disease awareness and appropriate early treatment may help reduce the coming burden of CVD.

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Keywords: Cardiology; Chronic venous disease; Chronic venous insufficiency; Epidemiology; Treatment guidelines; Venoactive drugs; Venoactive drug therapy

INTRODUCTION

Patients with chronic venous disease (CVD) seek treatment for a variety of symptoms and signs that may substantially impact their quality of life (QoL). Symptoms include leg pain, discomfort, and heaviness, whereas the clinical signs of CVD are varicose veins (VVs), oedema, skin discolouration, lipodermatosclerosis, and, in severe cases, venous ulceration. Based on the presence of specific clinical signs, which may or may not be symptomatic but are associated with

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increasing clinical severity, CVD can be classified from C0 (no signs) to C6 (venous ulceration) (Table 1). Some of the principal issues facing the medical community are: why CVD develops, why it progresses in certain individuals but not in others, and how many people have CVD. In addition, despite the existence of national referral guidelines in the UK, and international guidelines for the diagnosis and treatment of CVD, the management of CVD is variable. A 2013 survey of general practitioners in the UK indicated that less than 50% were aware of referral guidelines for CVD patients and would refer patients with moderate to severe disease (C4 or C5) to a vein specialist, and only about 10% were aware of clinical venous scoring systems [1]. These findings indicate that a substantial knowledge gap needs to be bridged to ensure that CVD patients of all severities receive appropriate treatment according to international guidelines [2]. In addition, the National Institute for Health and Care Excellence (NICE) in the UK also provides comprehensive guidance for the diagnosis and management of varicose veins [3].

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by the author.

Table 1 Clinical classification of chronic venous disease

CEAP classification of CVD	Clinical classification
C0	No visible or palpable signs of venous disease
C1	Telangiectasies or reticular veins
C2	Varicose veins
C3	Oedema
C4a	Pigmentation or eczema
C4b	Lipodermatosclerosis or atrophie blanche
C5	Healed venous ulcer
C6	Active venous ulcer

CVD chronic venous disease

EPIDEMIOLOGY OF CVD

Thirty years ago in an analysis of 3822 adults in the Framingham Study cohort, it was recognised that the incidence of VVs was higher in women than in men [4]. New VV case rates in the cohort over 2 years were 51.9 per 1000 women and 39.4 per 1000 men. More recent evidence supports these trends but also shows that the prevalence of CVD and VV vary widely by region, though they are highest in Western countries [5]. Risk factors confirmed in subsequent studies were: excess body mass index (BMI) and obesity, low physical activity, and high systolic blood pressure for both sexes; older age at menopause, and sedentary occupations for women; and smoking for men [4]. Following a systematic review performed 20 years after the Framingham Study, Robertson et al. proposed a variety of risk factors for primary CVD, including increasing age, positive family history, gender, pregnancy, obesity, reduced mobility at work, smoking, low fibre intake, and constipation [6].

Venous reflux is a known precursor for CVD. In the Edinburgh Vein Study cohort, which is a prospective random population-based cohort of 1566 adult patients, a follow-up at 13 years after baseline found the annual incidence of venous reflux to be 1% [7]. Risk factors associated with venous reflux were being overweight [odds ratio (OR) 2.1, 95% confidence interval (CI) 1.0–4.4] and a history of deep vein thrombosis (OR 11.3, 95% CI 1.0–132.3), whereas pregnancy and smoking were not significant risk factors. The 13-year incidence of VV was two-fold higher in participants who had venous reflux at baseline than in those who did not.

An epidemiological survey of 6009 adult patients (mean age 53.4 years) conducted by general practitioners in Belgium and Luxembourg found the overall prevalence of CVD (class C1–C6) to be high (61.3%) and underestimated by general practitioners, who considered that only 45.9% of these patients had CVD [8]. This study also reported the C-class to be significantly higher in women than in men, and that CVD severity was associated with high BMI, absence of regular exercise, number of

pregnancies, a family history of CVD, and increasing age. QoL decreased with the appearance of the first symptoms of CVD and further decreased as the cumulative number of symptoms increased. CVD symptoms also led to losses in productivity as 10.4% of patients with CVD reported a loss of working days. This study was conducted as part of the Vein Consult Program, which is an extensive international prospective epidemiological survey supported by the *Union Internationale de Phlebologie* with the goal to improve understanding of the worldwide prevalence of CVD. The epidemiology of CVD has also been reported for a much larger international population of 91,545 adult patients in the Vein Consult Program cohort across diverse geographic regions, including Europe, Latin America, the Middle East, and the Far East [9]. Overall, 41.4% of these patients had early stage CVD (C0s–C1) and 84% had any class of CVD greater than C0s. These results confirm that CVD is a widespread global problem. It is also widely under-recognised because general practitioners considered that only 51% of the patients diagnosed with C0s–C1 patients had CVD. Although referrals to specialists tended to increase with CVD severity, referral rates by general practitioners varied by region and were lowest in the Far East.

As the age of the global population is increasing due to medical advances and longer lifespans, the numbers of patients with CVD are also growing. Barnes et al. reported that US outpatient visits for venous disease, including deep vein thrombosis, increased significantly from 4 million visits in 1997 to nearly 6 million visits in 2006, providing some evidence of the growing burden of venous disease, although some of this increase might be due to improvements in CVD patient management [10]. Disease severity and treatment requirements also increase with age. In a retrospective study of 38,750 CVD patients in the US, the initial presenting symptoms of pain, heaviness, fatigue, and aching were more common in patients under 65 years of age. The symptoms and signs of more severe CVD, such as swelling, skin discolouration, and venous ulceration, as

well as venous ablations, were more common patients older than 65 [11].

A systematic review of epidemiological studies showed that the burden of VVs (57.1–90.4%) and treatment practices varies across European countries [12]. Comparisons of the predicted numbers of CVD patients (with CVD > C2) to the actual number of patients being treated for venous disease indicated that some countries are not treating all patients with C2-level disease, while others may be treating excessive numbers of patients. The numbers of procedures performed for VVs per million people across these countries differed by up to four-fold, indicating that there are marked treatment gaps in some countries.

The prevalence of CVD and other venous diseases are predicted to increase because the prevalence of the main risk factors for them, age and obesity, are increasing rapidly. In the UK, which is contributing to the current global obesity epidemic, the population of adults over age 85 has been predicted to grow to over 1.4 million men and 1.94 million women by 2033. In the US, the number of venous thromboembolism cases has been projected to increase from 1 million in 2010 to 1.8 million in 2050 [13], while VV procedures are projected to increase by over 60% in the US and Europe between 2013 and 2021 [14].

With the rising prevalence of venous diseases, QoL in an increasing number of patients can also be expected to decline. The QoL of patients with C6/venous ulceration has been reported to be comparable to that of patients with congestive heart failure or chronic lung disease, suggesting that, if CVD is allowed to progress to severe stages, the QoL of CVD patients can become very poor [15]. Indeed, QoL is lower in patients with recurrent VVs than in the general population, and patients with recurrent VVs scored lower than normal in all eight scales of the short-form health survey (SF-36) [16]. However, interventions to treat VVs have been shown to significantly and substantially improve QoL in these patients [17–19].

CVD PROGRESSION

Patients with CVD are prone to disease progression, in which patients progress to a higher clinical class over time or develop venous reflux and/or VVs in veins not previously affected. Disease progression is distinct from treatment failure, neovascularisation following surgical removal of VVs, or incomplete removal of varicosities. Progression can occur despite treatment or surgical removal of afflicted veins [20].

Annual progression rates of approximately 4% have been reported for the Edinburgh Vein Study, the Bonn Vein Study, and from reviews of other epidemiological studies [21–23]. In the Edinburgh Vein Study, the overall progression rate was 58% after a follow-up of 13 years [21]. The main risk factors for progression in patients with VVs at baseline were an age greater than 55 years (OR 3.9, 95% CI 1.1–14.3), being overweight/obese (BMI \geq 25; OR 1.9, 95% CI 1.1–3.1), and a family history of VV (OR 1.9, 95% CI 1.20–3.04) [21]. Additional risk factors included female gender and superficial venous reflux.

Following endovenous ablation of VVs, 15–47% of patients experience clinical recurrence, with a new area of truncal reflux occurring in 16% of patients as a result of disease progression [24]. In another study, new truncal reflux developed in 16–24% of patients after thermal ablation [25]. Recurrence can arise from neovascularisation, disease progression and incomplete ablation, either alone or in combination [20].

TREATMENTS

Pharmacological treatment can improve CVD symptoms and QoL [2, 26, 27]. Among the venoactive drugs available, Daflon® (micronised purified flavonoid fraction, MPFF) has been the most widely studied and has accumulated the most evidence for its efficacy [28–34]. In one recent study, MPFF treatment reduced the frequency of night cramps, pain, leg heaviness, and situational (evening) reflux in the great saphenous vein [34]. Other venoactive drugs

may also be effective for specific applications [26]. Pentoxifylline is a useful adjunct to compression therapy for patients with venous ulcers; oxerutins and calcium dobesilate may help reduce oedema; and rutosides may provide symptom relief for varicose veins in pregnancy. However, in a recent update of treatment guidelines, Daflon/MPFF was the only venoactive drug to receive strong recommendations for relief of CVD symptoms and for venous ulcer healing [2]. Physicians should refer to these guidelines to identify the most appropriate pharmacological treatments for their CVD patients.

Clearly, CVD is a complex chronic disease that will progress and substantially impact patient QoL if improperly treated. For this reason, perhaps the key recommendation for general practitioners is to refer to a vascular service specialist those patients who present with symptomatic or recurrent varicose veins or with lower limb skin changes (e.g. pigmentation or eczema) assumed to be caused by chronic venous insufficiency. Additionally, the CEAP classification is not recommended for referral guidance in the UK by NICE, as patients may not be referred despite having symptoms due to C2-level disease.

Treatment options have improved in recent years, and include venoactive drug therapy, surgery, and endovenous ablation of VVs using lasers, radiofrequency, or sclerotherapy. There is general agreement among physicians in the US and Europe that all of these strategies are more effective than compression alone [3, 35, 36]. In addition, virtually all of these strategies have been shown to be cost-effective [37–40].

CVD IS A GROWING ECONOMIC BURDEN

The Millenium Research Group has estimated that, by 2021, VV treatments will have increased twofold over 2011 levels [41]. At US\$2000 per treatment, total costs have been projected to reach US\$8 trillion by 2021. Further, 1 in 65 people have a VV treatment every year and, with life expectancies increasing, this means that virtually every person who attains

the age of 80–85 years will have had at least one vein treatment.

The global varicose vein treatment market, which was US\$290.59 million in 2016, has been estimated to reach over US\$396 million by 2021. Currently, care and treatment for CVD patients consumes 2% of national healthcare budgets [42, 43]. Treatments and care strategies that can prevent or slow disease progression, or VV recurrence, are likely to reduce these substantial costs.

VENOUS LEG ULCERS

Currently, venous leg ulcers affect 1% of the adult population [44]. In the US, accumulated annual costs of prescription drugs, emergency department visits, home healthcare, outpatient visits, and hospitalisations in the 12 months after initial ulceration have been estimated to be US\$2611 for Medicare-insured patients and US\$3066 for privately-insured patients [44]. Total costs were estimated to reach US\$15 billion annually [44].

Treatments that speed ulcer healing could help reduce these costs. As an example, adding pentoxifylline treatment to compression therapy significantly improves venous ulcer healing rates versus compression therapy alone or if combined with placebo, and also reduces treatment costs [45]. A cost-effectiveness analysis of this adjunct pentoxifylline treatment, which costs GB£6 per month, suggested that the combined treatment costs only GB£98 (95% CI – 49.2 to 245.0) per quality-adjusted life year (QALY) gained [45]. As a point of reference, the cost-effectiveness threshold in the UK is considered to be GB£20,000 per QALY gained, so adjunct pentoxifylline therapy is likely to be extremely cost-effective. Even with rising costs of pharmaceuticals, any venoactive drug that significantly reduces ulcer healing time is likely to be cost-effective.

In a contrasting example, surgical treatments for post-thrombotic syndrome, such as deep vein angioplasty and stents, are quite expensive but there is little evidence from randomised controlled clinical trials to show that they are

effective. Thus, the use of such treatments should be evaluated with caution.

CONCLUSIONS

The burdens of VV, CVD, and venous ulcers are great for patients and healthcare systems. Because these conditions are complex, are prone to worsening, and can substantially impact patient QoL, it is critical that patients receive appropriate treatment to prevent disease progression and recurrence. Thus, referral of these patients to a specialist may be warranted. Further, it is important for physicians to consider the options and costs of available CVD treatments. Pharmacological treatments with venoactive drugs alone, or as adjuncts to compression therapy, offer patient benefits that are likely to be cost-effective. However, more cost-benefit studies are needed, as treatments not proven to be cost-effective will not be available for reimbursement.

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