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ORIGINAL RESEARCH

Effectiveness of Conservative Treatment on Chronic Venous Disease Symptoms and Quality of Life in Patients with Type 2 Diabetes: Results from a Subanalysis of the VEIN STEP Observational Study

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Background: This post-hoc subanalysis of the VEIN STEP study assessed the effectiveness of conservative treatment, particularly venoactive drugs (VAD), in reducing chronic venous disease (CVD) signs and symptoms and improving quality of life (QoL) for patients with type 2 diabetes (T2D) in a real-life setting.

Methods: VEIN STEP was an observational, prospective study conducted in adult outpatients who consulted for symptomatic CVD (NCT04574375). CVD symptoms (10-cm Visual Analog Scale and Patient Global Impression of Change), disease severity (Venous Clinical Severity Score), and QoL (Chronic Venous Insufficiency Questionnaire [CIVIQ-14]) were assessed.

Results: Overall, 6084 patients were analyzed, of whom 702 (11.5%) had T2D. These patients were more likely to be older, present with a more advanced CEAP class, have a higher body mass index, greater symptom severity and reduced QoL scores than those without T2D ($p<0.001$ for all). Almost all patients with T2D (97.3%) received VAD-based treatment, mainly micronized purified flavonoid fraction (MPFF, 72.2%) or diosmin (24.6%). After 4 weeks, conservative therapy was associated with significant improvements in CVD symptoms and QoL ($p<0.001$). Physicians also noted a significant improvement in disease severity ($p<0.001$). The decrease in global symptom intensity was significantly greater among patients treated with MPFF than in those treated with diosmin (mean −2.7±1.8 vs −2.0±1.8, $p=0.004$). Greater reductions in symptom intensity were also observed in patients treated with MPFF for pain ($p=0.011$), leg heaviness ($p=0.006$), and swelling ($p=0.014$), with a tendency for greater improvement of cramps. QoL improved for patients receiving MPFF and those receiving diosmin, with changes in CIVIQ-14 global index score of −21.3±15.8 and −15.5 ±14.6, respectively.

Conclusion: These findings indicate that patients with concomitant CVD and T2D are more likely to have greater symptom severity and disease burden. In such patients, VAD-based conservative therapy, particularly MPFF, was associated with significant improvements in CVD-related symptoms and QoL.

Plain Language Summary: Chronic venous disease (CVD) is a common condition that often coexists with type 2 diabetes (T2D), with which it shares many risk factors such as aging, obesity, and inactive lifestyles. The VEIN STEP observational study included over 6,000 patients with CVD, 11.5% of whom also had T2D. Subjects with both conditions had worse symptoms, more severe disease, and lower quality of life than those with CVD alone. For the majority, interventions consisted of non-surgical treatments such as compression therapy and venoactive drugs, especially micronized purified flavonoid fraction (MPFF) and diosmin. There is a strong connection between CVD and T2D and the presence of one condition should prompt physicians to examine the patient for the other.

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This study shows that early diagnosis and treatment can significantly reduce CVD symptoms and improve quality of life. It also calls for more attention to managing CVD in people with T2D to reduce complications and improve outcomes.

Keywords: chronic venous disease, conservative therapy, micronized purified flavonoid fraction, observational study, type 2 diabetes, venoactive drug

Introduction

Chronic venous disease (CVD) is a prevalent condition worldwide with high healthcare costs and significant impacts on patients' physical and psychological levels.[1] Common symptoms include leg pain or discomfort, leg heaviness, cramps, and a sensation of swelling. CVD is also associated with a range of clinical signs, that may or may not be symptomatic, classified by the Clinical Etiology Anatomy Pathophysiology (CEAP) system.[2] A recent systematic review pooling data across six continents showed prevalence estimates ranging from 0.4% for the most severe form of CVD (C6 CEAP class) to 26% (C1) and 19% (C2) for milder CVD forms.[3]

Risk factors for the development and progression of CVD are common in most populations and include advanced age, excess body weight, sedentary lifestyles and occupations, and family history of the disease.[4,5] Many of these risk factors are associated with unhealthy lifestyle and nutritional habits including physical inactivity and consumption of energy-dense, nutrient-poor diets.[6] They are also risk factors for other noncommunicable diseases, such as type 2 diabetes (T2D).[7] According to the 2025 International Diabetes Federation (IDF) guidelines, it was estimated that, by 2024, more than one in nine adults worldwide would have diabetes, with the highest prevalence (81%) occurring in the middle-income countries.[8] Notably, CVD and T2D prevalence, and their related morbidities and socioeconomic costs, is set to increase in the following decades.[1,8,9]

CVD is related to primary venous valve failure, which is often due to venous hypertension and inflammation.[10] T2D is a complex metabolic disorder associated with insulin resistance, β-cell dysfunction, and abnormal glucose levels. It is also linked to subclinical inflammation and increased oxidative stress.[11] This altered disease state ultimately leads to long-term outcomes in T2D, including microvascular complications that share some similarities with the microvascular inflammatory abnormalities occurring in CVD.[12]

While several studies suggest a higher prevalence of CVD and greater symptom severity among patients with T2D,[13–16] there is a lack of evidence regarding the optimal management of CVD in patients with both conditions. The international VEIN STEP observational study was one of the largest studies to collect data on patients with symptomatic CVD and their management through conservative therapy in daily clinical practice.[17] The present subanalysis is the first large-scale observational study to compare patients' characteristics and the outcomes of conservative therapy on CVD symptoms and quality of life (QoL), among CVD patients with and without concomitant T2D.

Materials and Methods

Study Design

Details of the study design, data collection process, baseline characteristics, and findings for the VEIN STEP study (NCT04574375) have been previously reported.[17] VEIN STEP was an international, observational, prospective study conducted to gather data on the conservative treatment of patients with venous disorders in routine clinical practice. To ensure that the study population was representative of the real-life community of patients with CVD, the study involved physicians from different specialties (general practitioners, phlebologists, dermatologists, and surgeons) working in various clinical settings (clinics, private practices, or hospitals) across different countries.

Between June and December 2020, physicians selected consecutive outpatients who consulted spontaneously or were referred for treatment of symptomatic CVD not requiring surgical treatment. Patients had to be ≥18 years and able to provide written informed consent. Exclusion criteria were current treatment for CVD either with a VAD or compression therapy; lower limb arterial disease; presence of concomitant disease or treatment that may interfere with lower limb pain or edema; any procedure or surgery planned during the study for CVD; and pregnancy or breastfeeding.

At the inclusion visit (V0), patients were prescribed conservative treatment, according to the physician's usual practice. This could include pharmacological or nonpharmacological treatment (such as compression therapy, oral VAD, painkillers, topical treatment). The provision of lifestyle advice was also left to the discretion of the physician. The intensity of symptoms and their improvement with treatment as well as impact on quality of life was assessed using patient-reported outcomes (10-cm Visual Analog Scale [VAS], Patient Global Impression of Change [PGIC], 14-item ChronIc Venous Insufficiency Questionnaire [CIVIQ-14]).[18–20] Only fully completed CIVIQ-14 questionnaires were analyzed. PGIC scores were collected at a week-2 telephone call (V1), week-4 on-site visit (V2), and an optional week-8 telephone call (V3). CVD severity was assessed by physicians using the Venous Clinical Severity Score (VCSS)[21,22] at V0 and V2.

The primary objective of the study was to assess, in a real-life setting, the effectiveness of conservative treatment on CVD symptoms and signs and improvement of patient's QoL. This subanalysis of the VEIN STEP study focuses on CVD patients with and without concomitant T2D.

VEIN STEP was a non-interventional study thus physicians were instructed to continue management and treatment of participants according to their usual practice. All data from the patient electronic case report forms were collected anonymously. The study was conducted in accordance with the principles of the Declaration of Helsinki. Ethics Committee approval was obtained in each country.

Statistical Analysis

Continuous variables were described using mean ± standard deviation (SD). Categorical variables were described using proportions and percentages. Missing data were not replaced.

At baseline, patient characteristics were compared between those with and without T2D using a Chi-square test for categorical variables and a Wilcoxon test for continuous variables. Within-group treatment differences were evaluated with a paired *t*-test or Wilcoxon signed-rank test, for continuous variables with normal or skewed distribution, respectively. McNemar's test or Cochran's Q test were used for categorical variables, depending on the number of modalities. Effectiveness parameters of the most commonly used treatment, MPFF and diosmin, were compared using ranked ANCOVA. Quade's method was used to transform the rank of the response variable and the covariate (baseline). The model was adjusted for country, CEAP class, and baseline characteristics.

Statistical significance was assumed when $p<0.05$ (two-sided). All statistical analyses were performed with the SAS® software version 9.4 or higher.

Results

VEIN STEP investigators enrolled a total of 6236 patients from nine different countries (China, Costa Rica, Dominican Republic, Honduras, Mexico, Morocco, Panama, Romania, and Ukraine). The full analysis set comprised 6084 (97.6%) patients with available data for the main variables (age, sex, weight, height, and CEAP class) and at least one follow-up visit. Of these, 702 (11.5%) had CVD with concomitant T2D and 5382 (88.5%) had CVD without T2D.

Baseline Characteristics

Most patients were female, ranging from 74.8% in patients with T2D to 78.4% in patients without ($p=0.029$). Patients with T2D were older than those without, with mean age of 58.8±11.2 vs 49.6±13.8 years; $p<0.001$, with about a third (31.6%) of patients in the older age category (≥ 65 years) vs 15.4% of patients without T2D. The mean body mass index (BMI) was also higher among patients with concomitant T2D than those without (30.0±4.4 vs 27.7±4.9 kg/m^2, $p<0.001$), with 49.6% and 27.9% of patients, respectively classified as obese (BMI≥30kg/m^2). A higher proportion of female patients with concomitant T2D had given birth than those without T2D (84.6% vs 68%) with a mean number of births of 3.9±2.0 vs 2.6±1.5, respectively (all $p<0.001$). Patients with T2D reported more frequently concomitant hypertension than those without the disease (43.9% vs 17.1%, $p<0.001$). No significant differences were observed in the proportion of patients suffering from other venous disorders such as deep vein thrombosis, post-thrombotic syndrome, pelvic congestion syndrome, and hemorrhoidal disease between the two groups. Notably, more than 85% of patients reported concomitant hemorrhoidal disease (Table 1).

Table 1 Patients' Demographics and Baseline Characteristics According to the Presence of Type 2 Diabetes (T2D)

Characteristics	CVD Patients with T2D n=702	CVD Patients Without T2D n=5382	P value
Male/female, n (%)	177/525 (25.2/74.8)	1162/4220 (21.6/78.4)	p=0.029
Mean age (SD) years	58.8 (11.2)	49.6 (13.8)	p<0.001
Number (%) per age group (years)			
[18–35]	10 (1.4)	786 (14.6)	p<0.001
[35–50]	118 (16.8)	1987 (36.9)	p<0.001
[50–65]	352 (50.1)	1784 (33.1)	p<0.001
[65–80]	198 (28.2)	719 (13.4)	p<0.001
≥80	24 (3.4)	106 (2.0)	p=0.013
Mean BMI (SD) kg/m^2	30.0 (4.4)	27.7 (4.9)	p<0.001
Number (%) per BMI category (kg/m^2)			
<18.5	4 (0.6)	58 (1.1)	p=0.208
[18.5–25]	81 (11.5)	1478 (27.5)	p<0.001
[25–30]	269 (38.3)	2344 (43.6)	p=0.008
≥30	348 (49.6)	1502 (27.9)	p<0.001
Sedentary lifestyle, n (%)	407 (58.0)	2025 (37.6)	p<0.001
Current/former smoker, n (%)	140 (19.9)	920 (17.1)	p=0.061
Family history of CVD, n (%)	228 (32.5)	1910 (35.5)	p=0.116
Females having given birth, n (%)	444 (84.6)	2871 (68.0)	p<0.001
Mean number of births (SD)	3.9 (2.0)	2.6 (1.5)	p<0.001
Other venous disorders, n (%)	131 (18.7)	989 (18.4)	p=0.855
DVT	9 (6.9)	96 (9.7)	p=0.295
PTS	6 (4.6)	39 (3.9)	p=0.727
PCS	1 (0.8)	17 (1.7)	p=0.712
HD	120 (91.6)	864 (87.4)	p=0.162
Hypertension, n (%)	308 (43.9)	922 (17.1)	p<0.001

Abbreviations: BMI, body mass index. CVD, chronic venous disease. DVT, deep vein thrombosis. HD, hemorrhoidal disease. PCS, pelvic congestion syndrome. PTS, post-thrombotic syndrome. SD, standard deviation. T2D, type 2 diabetes.

Compared to patients without T2D, patients with the concomitant disease were more likely to present with advanced CEAP classes (C3 and above: 62.0% vs 41.2%) (Figure 1).

At the time of enrolment, none of the patients were undergoing treatment for CVD either with a VAD or compression therapy. Over half the patients had never previously received a treatment for CVD (54.7% with T2D and 67.2% without T2D). A previous treatment for venous leg disorders had been received by 38.2% of patients with T2D and 26% without. It consisted mainly of oral VADs (67.0%), topical therapy (58.6%), and compression (26.5%) in patients with concomitant T2D. For those without T2D, the respective figures were 80.5%, 54.8%, and 30.5%. Only a small number had previously undergone a procedure or surgery for venous diseases in both groups (3.1% with T2D and 4.3% without).

At baseline, most patients reported pain, heaviness, swelling sensation and cramps, ranging from 91.6% (swelling) to 96.3% (pain) of those with concomitant T2D and from 82.4% (cramps) to 94.2% (pain) of those without the disease. The intensity of these symptoms was significantly greater in patients with T2D than in those without (p<0.001) (Figure 2A). Consequently, these patients reported worse QoL, with a mean CIVIQ-14 global index score of 41.7±21.5 vs 32.1±19.9

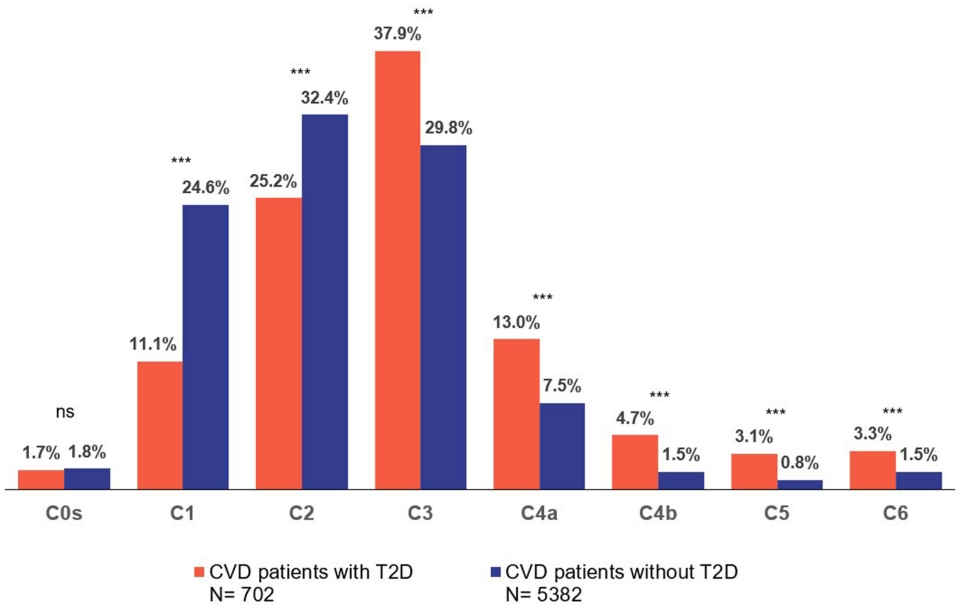

Figure 1 The distribution of CEAP (Clinical Etiology Anatomy Pathophysiology) classes among patients with chronic venous disease (CVD), with and without type 2 diabetes (T2D). Chi-square tests were performed. ***p<0.001 between patients with and without T2D.
Abbreviation: ns, non significant.

for those without T2D, p<0.001 (Figure 2B). They also had more severe CVD than patients without T2D, as assessed by their physicians (mean VCSS score of 7.3±4.4 vs 5.4±3.7, respectively; p<0.001) (Figure 2C).

Lifestyle Advice and Conservative Treatments Prescribed at Inclusion

At inclusion, nearly all patients (with or without concomitant T2D) received lifestyle recommendations (96.9% and 95.0%, respectively) and were prescribed at least one conservative treatment (98.9% and 98.3%, respectively) including compression and/or pharmacological treatment (VAD, painkiller, topical treatment) (Figure 3). Oral VADs were the most commonly prescribed conservative therapy (97.3% [n=683/702] and 95.6% [5145/5382] respectively), either as mono or combination therapy. The percentage of patients prescribed with compression, painkillers and topical treatments were significantly higher for those with concomitant T2D (56.7%, 53.4% and 41.5%, respectively) than for those without T2D (51.4%, 31.9% and 30.2%). A higher proportion of patients with T2D were prescribed a combination of conservative treatments, compared with those without T2D (22.9% vs 8.7%, p<0.001), while VADs alone were only prescribed to 17.9% patients with T2D versus 26.5% patients without T2D (p<0.001) (Figure 3).

Among patients receiving oral VADs, MPFF was the most widely used. It was prescribed to 72.2% of patients with T2D and 75.9% of those without (13.8% and 21.5% as monotherapy, respectively). The second most prescribed drug was diosmin, which was prescribed in 24.6% of patients with T2D and 18.1% without T2D.

Patient-Reported Outcomes in Patients Treated with VAD-Based Therapy

Symptom Intensity

Compared to baseline, the global symptom intensity score showed improvement after 4 weeks treatment, with a mean change of −2.6±1.8 cm (p<0.001) in patients with concomitant T2D receiving VAD-based treatment (n=641). A similar improvement was observed for each symptom individually, with mean changes of −2.5±1.8 for pain, −2.5±1.9 for leg heaviness, −2.3±1.9 for cramps, and −2.3±2.0 for sensation of swelling (all p<0.001). In patients without T2D receiving VAD-based treatment (n=4853), changes in individual and global symptom intensity were also significant versus baseline (all p<0.001) and were of similar magnitudes to those observed in patient with T2D (not significant).

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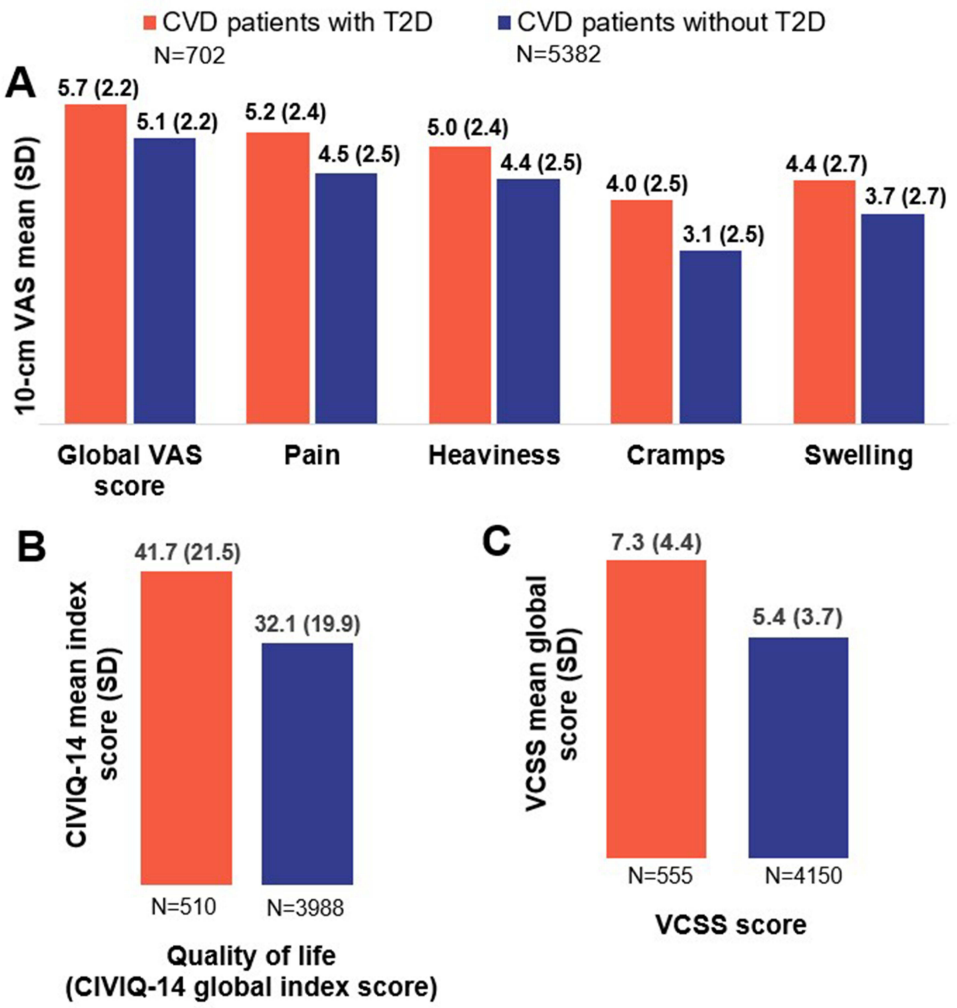

Figure 2 Chronic venous disease intensity, quality of life, and severity at baseline: (**A**) Symptom intensity assessed by patients using a 10-cm visual analog scale (VAS); (**B**) Quality of life assessed by the global index score using the ChronIc Venous Insufficiency quality of life Questionnaire (CIVIQ-14); (**C**) Symptom severity assessed by physicians using the Venous Clinical Severity Score (VCSS). The differences between CVD patients with and without T2D were statistically significant ($p<0.001$) in all graphs.
Abbreviations: CVD, chronic venous disease; T2D, type 2 diabetes.

Global Symptom Improvement

Improvements in symptoms as assessed by PGIC, were observed after 2 weeks among the majority of patients receiving VAD-based therapy (85.8% of those with concomitant T2D [n=506/590] and 91.6% of those without T2D [4214/4599]). This had increased to 97% of patients, both with and without T2D, by 4 weeks and was maintained in those who attended the optional week 8 visit.

Quality of Life

Compared with baseline, QoL was significantly improved after 4 weeks in patients with concomitant T2D receiving VAD-based treatment (n=488) with a mean change in CIVIQ-14 global index score of −19.5±15.6, and scores for pain, physical and psychological dimensions of −23.6±17.8, −20.7±17.8, and −16.5±17.1, respectively (all $p<0.001$). In patients without T2D (n=3702), the reduction in global index score observed with VAD-based treatment was also statistically significant after 4 weeks (−16.1±13.6; $p<0.001$). However, the magnitude of this reduction was lower than that observed in patients with concomitant T2D ($p=0.022$).

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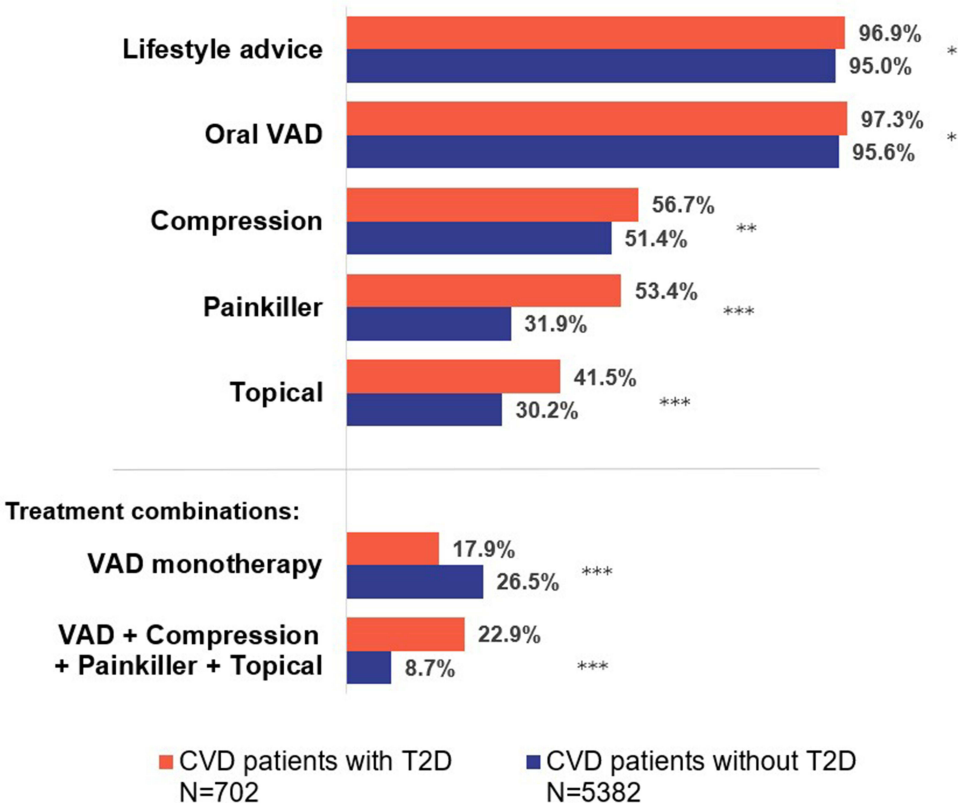

Figure 3 Recommendations and treatments prescribed at baseline. * p<0.05, ** p<0.01, *** p<0.001 between patients with and without T2D. The number of patients varies between categories.
Abbreviations: CVD, chronic venous disease; T2D, type 2 diabetes; VAD, venoactive drug.

Disease Severity

Compared with baseline, patients receiving VAD-based treatment showed a significant decrease in VCSS at V2, with a reduction in VCSS score of −2.8±3.5 in patients with T2D (n=489) and −1.8±2.7 in patients without T2D (n=3504) (all p<0.001). Notably, there was no statistically significant difference in the score reductions between patients with and without T2D (p=0.303).

Patient-Reported Outcomes: MPFF versus Diosmin

Patients with concomitant T2D receiving MPFF-based treatment (n=471) experienced a greater reduction in global symptom severity than those receiving diosmin-based treatment (n=159), based on VAS (Figure 4A). After adjustment for CEAP clinical class and main baseline characteristics, mean changes from baseline to V2 were −2.7±1.8 for MPFF-based treatment and −2.0±1.8 for diosmin-based treatment (p=0.004).

Individual analysis of symptoms revealed reductions in intensity that were significantly greater for MPFF-based vs diosmin-based treatment for pain (p=0.011), leg heaviness (p=0.006), and sensation of swelling (p=0.014). Both MPFF-based and diosmin-based treatment showed a significant reduction in cramp intensity at V2 versus V0 (p<0.001); however, the difference between them was not significant (mean changes: −2.4±2.0 vs −1.8±1.8, respectively; p=0.270).

Regarding QoL, a significant improvement for patients receiving either MPFF-based or diosmin-based treatment was observed at V2 (p<0.001), with no difference between the two groups (−21.3±15.8 vs −15.5±14.6, p=0.204) (Figure 4B).

Among patients with concomitant T2D, VCSS showed significant improvement for those receiving MPFF-based treatment (n=336) and those receiving diosmin-based treatment (n=144) (−3.0±3.3 and −2.4±3.8, respectively; both p<0.001 vs V0). The difference between groups did not reach statistical significance (p=0.236) (Figure 4C).

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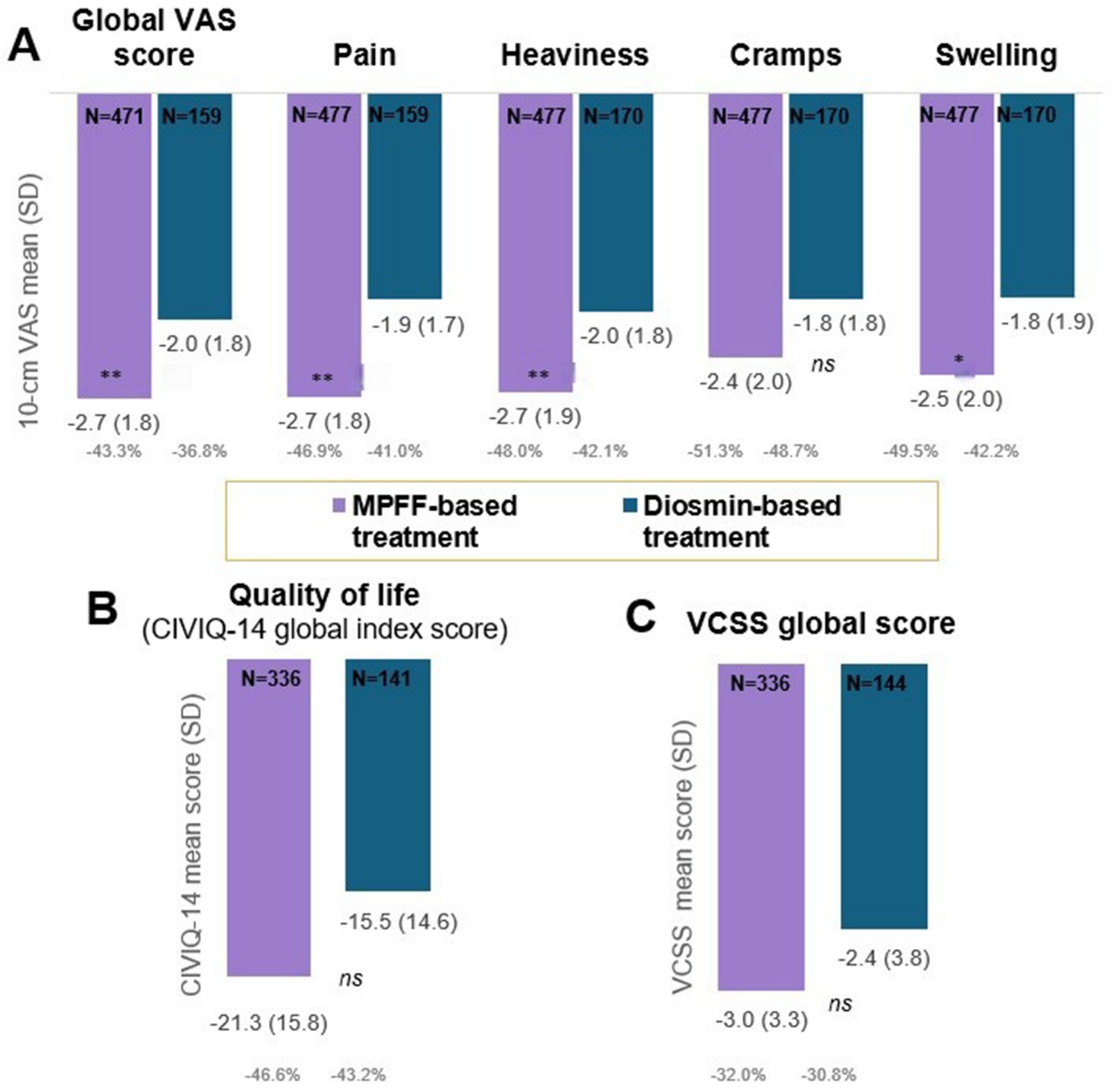

Figure 4 Mean changes from baseline to week 4 in (**A**) VAS, (**B**) CIVIQ-14 and (**C**) VCSS scores in patients with CVD and concomitant T2D receiving MPFF-based treatment compared with patients receiving diosmin-based treatment. CIVIQ-14, Chronlc Venous Insufficiency quality of life Questionnaire. * p≤0.05, ** p≤0.01.
Abbreviations: ns, non significant. VAD, venoactive drug; VAS, visual analog scale; VCSS, venous clinical severity score; MPFF, micronized purified flavonoid fraction.

Discussion

The global age-standardized total prevalence of diabetes is currently at 11.1%.[8] In the VEIN STEP study, 11.5% of patients who consulted spontaneously or who had been referred for treatment of symptomatic CVD had T2D. In some VEIN STEP regions this prevalence was similar to the local diabetes prevalence, whereas in others, including Europe, it was much higher.[23] In general, the literature shows up to twice the frequency of concomitant T2D in patients with CVD compared with the general population.[12,24] In our subanalysis, patients presenting with both conditions had a higher cardiovascular risk profile, and were more likely to be older (mean age 58.8 vs 49.6 years), obese (49.6% vs 27.9% had a BMI ≥30 kg/m^2), have a sedentary lifestyle (58.0% vs 37.6%), and concomitant hypertension (43.9% vs 17.1%) than those with CVD alone. These risk factors, typically found in modern-day society, are common to both CVD and T2D. Alongside genetic influences, the main drivers of T2D, such as increased obesity levels, sedentary lifestyles, high-calorie

diets and population ageing, have quadrupled the incidence and prevalence of T2D over the past half-century.[25,26] The fact that CVD and T2D frequently coexist,[13–15] suggests venous disease may be part of a possible cardiometabolic continuum.

The frequency of comorbid CVD and T2D is likely the result of a shared pathophysiology. It is hypothesized that when both conditions are present, they may have a combined negative effect on the vascular endothelium leading to endothelial dysfunction, vascular wall remodeling, increased vascular permeability and impaired blood flow.[12,15,27–29] Inflammation is widely accepted to be a driver of CVD. It primarily affects the microcirculation, with changes in capillary permeability, vein wall and valve remodeling, and increased oxidative stress.[30] Likewise, hyperglycemia, hypertension, and obesity stimulate oxidative stress and inflammation, two major factors in the development and progression of T2D.[31] Oxidative stress predisposes tissues to a pathological state that can lead to direct cellular damage and trigger an inflammatory cascade that further perpetuates tissue injury. It has been suggested that an inflammatory diabetic environment may make it more likely for CVD to develop. Data in support of this have been provided by a small study of 80 patients, 40 with T2D and 40 without, with chronic venous insufficiency (CVI) of the lower limbs.[28] In both sets of patients, ultrasound scans of the lower extremities were performed, and the microvasculature was analyzed by Doppler flowmetry. Among those with T2D and CVI, there was a greater incidence of saphenofemoral junction and perforating vein failure in the lower extremities, in addition to severe leg edema and trophic changes. These complications were more frequent in T2D patients with uncontrolled blood sugar and earlier disease onset. This led the authors of the paper to suggest that T2D may exacerbate the course of CVI by disrupting the microcirculation of the lower extremities. Results of a study in 782 Chinese subjects with cardiometabolic risk factors further support the hypothesis that T2D may be a risk factor for early-onset CVD of the lower limbs.[32] Other studies have provided evidence that diabetes often precedes the development of CVD. An international survey of 900 patients with CVD, 53% of whom had comorbid T2D, found that diabetes was more likely to be diagnosed before CVD, with a mean difference of 5.3 years.[33]

The intersection between CVD and T2D is frequently overlooked, but the presence of T2D may predispose individuals to the development and progression of CVD. Results from the current VEIN STEP subanalysis indicate that patients with CVD who had concomitant T2D were more likely to present with a more advanced (C4-C6) CEAP class than those without T2D (24.1% vs 11.3%, respectively). Physician-assessed VCSS also confirmed a significant difference in clinical severity between those with and without T2D. These findings are in agreement with an Italian observational study which included over 10,000 patients with CVD and reported that the presence of T2D was associated with more severe signs of the disease in 50% of the population.[34] A number of other studies have also reported more severe forms of CVD in patients with T2D than patients without.[27,32,33,35] Delayed wound healing is a further common complication of T2D[36] that may have a negative impact in higher CEAP classes, particularly for patients with venous ulcers.

Among patients with T2D, patient-reported CVD symptoms were typically more frequent and severe. There were statistically significant differences between those with and without T2D for VAS-assessed global symptoms as well as individual symptoms of pain, leg heaviness, cramps, and sensation of swelling. The correlation of symptom intensity with the severity of the disease has been debated.[37,38] However, it is hypothesized that ischemia and elevated pro-inflammatory states associated with both CVD and T2D may exacerbate symptom severity.

CVD can impair health-related QoL at all stages of the disease, affecting physical, psychological and social functioning.[39,40] T2D also has a major impact on health-related QoL, which progressively worsens as glycemic control deteriorates and with increasing number of disease complications.[41] As expected given the progressive nature of both diseases, this subanalysis revealed a significantly worse QoL rating for individuals with CVD and T2D than for those with CVD only.

In the current study, patients with T2D were less likely to receive monotherapy and more likely to be prescribed multiple conservative therapies compared to those without T2D. For example, the combination of four conservative treatments (oral VAD, compression, pain killer, topical therapy) was prescribed to 22.9% of patients with T2D vs 8.7% of those without T2D, which is suggestive of greater CVD severity in patients with concomitant T2D. MPFF was the most widely prescribed VAD, followed by diosmin. Given that the majority of patients received these medications, it was of interest to conduct a comparison of the two treatments in patients with T2D. Compared to diosmin, MPFF was associated

with a greater improvement in VAS-assessed symptom severity, global symptom severity, and individual symptoms of pain, leg heaviness, and sensation of swelling. A non-significant trend for greater improvement with MPFF was also observed for cramps. Improvements in QoL reflected the reduction in symptom severity, as well as reduction in VCSS score for both MPFF and diosmin treatment.

Venoactive drugs such as MPFF and diosmin have anti-inflammatory, antioxidant, and free-radical scavenging properties.[30,42,43] They target several inflammatory pathways involved in the microvascular damage associated with CVD[30] and T2D.[44] Due to its unique combination of active flavonoids, MPFF has shown greater effectiveness than diosmin on microvascular variables in an experimental model of venous hypertension.[45] In addition, data from randomized, placebo-controlled trials and subsequent meta-analyses have confirmed its efficacy for improving leg symptoms, edema, and QoL in patients with CVD,[46,47] and resulted in high levels of recommendation in international guidelines.[42] The current subanalysis, provides support for considering the use of VADs as part of the treatment strategy in patients with CVD including patients who have T2D.

When treating patients with T2D, it is essential to perform a comprehensive screening for CVD, and vice versa. Edema and trophic changes in the lower limbs, which are common to both CVD and T2D, must be carefully assessed in patients with T2D in order to rule out other conditions, such as heart failure. The co-existence of T2D with CVI can also impact wound healing outcomes, and the presence of diabetic neuropathy can mask symptoms of CVI due to reductions in pain.[28] Despite the burden of CVD and T2D among the general population, CVD signs and symptoms are often overlooked, particularly in the presence of additional comorbidities.[33] However, as this subanalysis has shown, CVD severity and QoL are significantly worsened in patients with T2D. This highlights the need for early diagnosis and treatment with agents such as VADs, which have been proven to reduce the microvascular damage common to both conditions.[12,16]

Strengths and Limitations

The strength of the VEIN STEP study lies in the collection of large-scale data during the course of usual care. The data therefore reflect the characteristics and patterns of patients with CVD and T2D and their treatment in routine clinical practice. To the best of our knowledge, there are no published large-scale studies describing real-world conservative treatment approaches of patients with concomitant CVD and T2D. Other strengths include the prospective recruitment of participants from general practitioner practices, and the use of the CEAP classification, an internationally accepted standard for describing patients with CVD and for reporting clinical research findings. Additionally, participants were recruited from nine different countries in five continents, so findings are more likely to be generalizable to wider populations. Limitations of the VEIN STEP study have been fully described in the study's original publication.[17] However, this analysis failed to record HbA1c levels and disease onset for T2D, thus their impact on CVD severity could not be assessed. Observational real-world studies can only evaluate association and not causality. Due to these limitations, real-world data analyses cannot be used as stand-alone evidence to validate the efficacy and/or safety of a given treatment. Consequently, while comparisons have been made between MPFF and diosmin, this was not a randomized comparison and the data should be interpreted with caution, particularly as the proportion of patients receiving the two treatments differed.

Conclusions

CVD and T2D frequently coexist, share similar risk factors, and may have a common microvascular pathophysiology. Results from this VEIN STEP subanalysis indicate that CVD patients with T2D are more likely to present with a higher CEAP class, have a greater number and severity of CVD signs and symptoms, and a worse QoL than CVD patients without T2D. Conservative therapy with VAD, most commonly MPFF, was observed to be associated with significant symptomatic improvements in patients with CVD and T2D. Wider recognition of the frequency and impact of comorbid CVD and T2D and earlier specialist intervention are also required to improve care in this population.

Data Sharing Statement

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Ethical Approval

The study was conducted in accordance with the principles of the Declaration of Helsinki. All patients provided written informed consent to participate in the study. The study was registered (NCT04574375) and approved by local institutional ethics committees. The ethics committees are listed in the supplementary material.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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References

1. Davies AH. The seriousness of chronic venous disease: a review of real-world evidence. *Adv Ther*. 2019;36(Suppl S1):5–12. doi:10.1007/s12325-019-0881-7
2. Lurie F, Passman M, Meisner M, et al. The 2020 update of the CEAP classification system and reporting standards. *J Vasc Surg Venous Lymphat Disord*. 2020;8(3):342–52.2. doi:10.1016/j.jvsv.2019.12.075
3. Salim S, Machin M, Patterson BO, Onida S, Davies AH. Global epidemiology of chronic venous disease: a systematic review with pooled prevalence analysis. *Ann Surg*. 2021;274(6):971–976. doi:10.1097/SLA.0000000000004631
4. Brand FN, Dannenberg AL, Abbott RD, Kannel WB. The epidemiology of varicose veins: the Framingham study. *Am J Prev Med*. 1988;4(2):96–101. doi:10.1016/S0749-3797(18)31203-0
5. Criqui MH, Denenberg JO, Bergan J, Langer RD, Fronek A. Risk factors for chronic venous disease: the San Diego population study. *J Vasc Surg*. 2007;46(2):331–337. doi:10.1016/j.jvs.2007.03.052
6. He J, Ma F, Yao J, et al. Dietary effects on chronic venous disease. *Ann Vasc Surg*. 2023;88:257–267. doi:10.1016/j.avsg.2022.06.015
7. Hariharan R, Odjidja EN, Scott D, et al. The dietary inflammatory index, obesity, type 2 diabetes, and cardiovascular risk factors and diseases. *Obes Rev*. 2022;23(1):e13349. doi:10.1111/obr.13349
8. International Diabetes Federation. Diabetes Atlas. Available from: https://diabetesatlas.org/resources/idf-diabetes-atlas-2025/. Accessed July 10, 2025.
9. Kovács N, Shahin B, Andrade CAS, Mahrouseh N, Varga O. Lifestyle and metabolic risk factors, and diabetes mellitus prevalence in European countries from three waves of the European health interview survey. *Sci Rep*. 2024;14(1):11623. doi:10.1038/s41598-024-62122-y
10. Bergan JJ, Pascarella L, Schmid-Schönbein GW. Pathogenesis of primary chronic venous disease: insights from animal models of venous hypertension. *J Vasc Surg*. 2008;47(1):183–192. doi:10.1016/j.jvs.2007.09.028
11. Stumvoll M, Goldstein BJ, van Haeften TW. Type 2 diabetes: principles of pathogenesis and therapy. *Lancet*. 2005;365(9467):1333–1346. doi:10.1016/S0140-6736(05)61032-X
12. Gastaldi G, Pannier F, Roztočil K, et al. Chronic venous disease and diabetic microangiopathy: pathophysiology and commonalities. *Int Angiol*. 2021;40(6):457–469. doi:10.23736/S0392-9590.21.04664-2
13. Marston WA, Carlin RE, Passman MA, Farber MA, Keagy BA. Healing rates and cost efficacy of outpatient compression treatment for leg ulcers associated with venous insufficiency. *J Vasc Surg*. *J Vascu Surg*. 1999;30(3):491. doi:10.1016/s0741-5214(99)70076-5
14. Lionis C, Erevnidou K, Antonakis N, Argyriadou S, Vlachonikolis I, Katsamouris A. Chronic venous insufficiency. A common health problem in general practice in Greece. *Int Angiol*. 2002;21(1):86–92.
15. Mani R, Yarde S, Edmonds M. Prevalence of deep venous incompetence and microvascular abnormalities in patients with diabetes mellitus. *Int J Low Extrem Wounds*. 2011;10(2):75–79. doi:10.1177/1534734611409372
16. Jarošíková R, Roztočil K, Husáková J, et al. Chronic venous disease and its intersections with diabetes mellitus. *Physiol Res*. 2023;72(3):280–286. doi:10.33549/physiolres.935033

17. Mezalek ZT, Feodor T, Chernukha L, et al. VEIN STEP: a prospective, observational, international study to assess effectiveness of conservative treatments in chronic venous disease. *Adv Ther*. 2023;40(11):5016–5036. doi:10.1007/s12325-023-02643-6
18. Launois R, Le Moine JG, Lozano FS, Mansilha A. Construction and international validation of CIVIQ-14 (a short form of CIVIQ-20), a new questionnaire with a stable factorial structure. *Qual Life Res*. 2012;21(6):1051–1058. doi:10.1007/s11136-011-0008-3
19. Le Moine J-G, Fiestas-Navarrete L, Katumba K, Launois R. Psychometric validation of the 14 items chronic venous insufficiency quality of life questionnaire (CIVIQ-14): confirmatory factor analysis. *Eur J Vasc Endovasc Surg*. 2016;51(2):268–274. doi:10.1016/j.ejvs.2015.08.020
20. Radak DJ, Vlajinac HD, Marinković JM, Maksimović MŽ, Maksimović ŽV. Quality of life in chronic venous disease patients measured by short chronic venous disease quality of life questionnaire (CIVIQ–14) in Serbia. *J Vasc Surg*. 2013;58(4):1006–1013. doi:10.1016/j.jvs.2011.08.003
21. Rutherford RB, Padberg FT Jr, Comerota AJ, Kistner RL, Meissner MH, Moneta GL. Venous severity scoring: an adjunct to venous outcome assessment. *J Vasc Surg*. 2000;31(6):1307–1312. doi:10.1067/mva.2000.107094
22. American Venous Forum Ad Hoc Outcomes Working Group, Vasquez MA, Rabe E, McLafferty RB, et al. Revision of the venous clinical severity score: venous outcomes consensus statement: special communication of the American venous forum ad hoc outcomes working group. *J Vasc Surg*. 2010;52(5):1387–1396. doi:10.1016/j.jvs.2010.06.161
23. Saeedi P, Petersohn I, Salpea P, et al. IDF diabetes atlas committee. Global and Regional Diabetes Prevalence Estimates for 2019 and Projections for 2030 and 2045: Results From the International Diabetes Federation Diabetes Atlas, 9th Edition. *Diabetes Res Clin Pract*. 2019;157:107843.
24. Bozkurt AK, VAN Rijn MJ, Bouskela E, et al. Enhancing identification and treatment of patients with concomitant chronic venous insufficiency and diabetes mellitus. A modified Delphi study from the CODAC (ChrOnic venous disease and diabetes advisory council) group. *Int Angiol*. 2023;42(5):427–435. doi:10.23736/S0392-9590.23.05061-7
25. NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. *Lancet*. 2016;387(10027):1513–1530. doi:10.1016/S0140-6736(16)00618-8
26. Galicia-Garcia U, Benito-Vicente A, Jebari S, et al. Pathophysiology of type 2 diabetes mellitus. *Int J Mol Sci*. 2020;21(17):6275. doi:10.3390/ijms21176275
27. Fejfarová V, Roztočil K, Svědínková A, et al. The relationship between chronic venous insufficiency and diabetes mellitus. *Int Angiol*. 2017;36(1):90–91. doi:10.23736/S0392-9590.16.03736-6
28. Shlyakova AA, Strongin LG, Kudykin MN, K.g K. Clinical and pathogenetic features of lesions of the lower extremities in patients with type 2 diabetes mellitus and chronic venous insufficiency. *Diabetes mellitus*. 2016;19(3):212–220.
29. Rajendran P, Rengarajan T, Thangavel J, et al. The vascular endothelium and human diseases. *Int J Biol Sci*. 2013;9(10):1057–1069. doi:10.7150/ijbs.7502
30. Mansilha A, Sousa J. Pathophysiological mechanisms of chronic venous disease and implications for venoactive drug therapy. *Int J Mol Sci*. 2018;19(6):1669. doi:10.3390/ijms19061669
31. Charlton A, Garzarella J, Jandeleit-Dahm KAM, Jha JC. Oxidative stress and inflammation in renal and cardiovascular complications of diabetes. *Biology*. 2020;10(1):18. doi:10.3390/biology10010018
32. Zhong J, Chen J, Zhao Z-G, et al. Diabetes mellitus is associated with early chronic venous disorder of the lower extremities in Chinese patients with cardiometabolic risk factors. *Diabetes Metab Res Rev*. 2014;30(6):505–512. doi:10.1002/dmrr.2551
33. Rosas-Saucedo J, Lukanova D, Glauser F, et al. Treatment patterns for chronic venous disease and diabetes mellitus: lessons from an international market-research survey. *Diabetes Manag*. 2021;S1:1–10.
34. Agus GB, Mattana P, Monitor CF. 2010: italian epidemiological survey on chronic venous diseases. *Acta Phlebologica*. 2012;13(1):9–17.
35. Singh TP, Velu RB, Quigley F, Golledge J. Association of chronic venous disease with major adverse cardiovascular events. *J Vasc Surg Venous Lymphat Disord*. 2022;10(3):683–688. doi:10.1016/j.jvsv.2021.08.021
36. Deng L, Du C, Song P, et al. The role of oxidative stress and antioxidants in diabetic wound healing. *Oxid Med Cell Longev*. 2021;2021(1):8852759. doi:10.1155/2021/8852759
37. Perrin M, Eklof B, VAN Rij A, et al. Venous symptoms: the sym vein consensus statement developed under the auspices of the european venous forum. *Int Angiol*. 2016;35(4):374–398.
38. Blättler W, Mendoza E, Zollmann C, Bendix J, Amsler F. Homeostatic feelings – a novel explanation of vein symptoms derived from an experimental patient study. *Vasa*. 2019;48(6):492–501. doi:10.1024/0301-1526/a000807
39. Ulloa JH, Lurie F, Santiago FR, et al. Systematic literature review and expert meeting report on health-related quality of life in chronic venous disease. *Int Angiol*. 2023;42(6):465–476. doi:10.23736/S0392-9590.23.05108-8
40. Santiago F. Quality of life in chronic venous disease: bridging the gap between patients and physicians. *Clin Drug Investig*. 2023;43(Suppl S1):3–8. doi:10.1007/s40261-023-01264-9
41. Rodríguez-Almagro J, García-Manzanares Á, Lucendo AJ, Hernández-Martínez A. Health-related quality of life in diabetes mellitus and its social, demographic and clinical determinants: a nationwide cross-sectional survey. *J Clin Nurs*. 2018;27(21–22):4212–4223. doi:10.1111/jocn.14624
42. Nicolaides A, Kakkos S, Baekgaard N, et al. Management of chronic venous disorders of the lower limbs. Guidelines according to scientific evidence. Part I. *Int Angiol*. 2018;37(3):181–254. doi:10.23736/S0392-9590.18.03999-8
43. Huwait E, Mobashir M. Potential and therapeutic roles of diosmin in human diseases. *Biomedicines*. 2022;10(5):1076. doi:10.3390/biomedicines10051076
44. Testa R, Bonfigli AR, Genovese S, de Nigris V, Ceriello A. The possible role of flavonoids in the prevention of diabetic complications. *Nutrients*. 2016;8(5):310.
45. Das Graças C de Souza M, Cyrino FZ, de Carvalho JJ, Blanc-Guillemaud V, Bouskela E. Protective effects of micronized purified flavonoid fraction (MPFF) on a novel experimental model of chronic venous hypertension. *Eur J Vasc Endovasc Surg*. 2018;55(5):694–702. doi:10.1016/j.ejvs.2018.02.009
46. Ulloa JH. Micronized purified flavonoid fraction (MPFF) for patients suffering from chronic venous disease: a review of new evidence. *Adv Ther*. 2019;36(Suppl S1):20–25. doi:10.1007/s12325-019-0884-4
47. Kakkos SK, Nicolaides AN. Efficacy of micronized purified flavonoid fraction (Daflon®) on improving individual symptoms, signs and quality of life in patients with chronic venous disease: a systematic review and meta-analysis of randomized double-blind placebo-controlled trials. *Int Angiol*. 2018;37(2):143–154. doi:10.23736/S0392-9590.18.03975-5