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Comparison of intravascular ultrasound and multidimensional contrast imaging modalities for characterization of chronic occlusive iliofemoral venous disease: A systematic review

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ABSTRACT

Background: Techniques to diagnose and treat chronic iliofemoral venous obstruction (CIVO) have continued to evolve. Intravascular ultrasound (IVUS) displays real-time cross-sectional venous anatomy and can be used to guide venous interventions. However, being invasive, it is not a suitable initial screening tool. The comparison of IVUS with other three-dimensional contrast imaging modalities is less well documented. We have provided a systematic analysis of the performance of IVUS and other three-dimensional contrast imaging modalities for the evaluation of CIVO.

Methods: A search of various databases, including MEDLINE, Embase, EBSCOhost, Cochrane Library, CINAHL PLUS, and Web of Science, was conducted to identify studies that had compared IVUS and at least one other multidimensional contrast imaging modality, including multiplanar venography, computed tomography venography (CTV), computed tomography angiography, or magnetic resonance venography in the evaluation of CIVO.

Results: A total of 2117 articles were screened. Of these, eight met the inclusion criteria. Additionally, 12 other studies were identified that had compared IVUS and single plane venography. A meaningful meta-analysis could not be conducted owing to data heterogeneity. The quality of evidence varied from very low to low. IVUS identified stenotic lesions in 0% to 30% more patients compared with multiplanar venography. The CTV and IVUS measurements correlated well with each other. The sensitivity of the two-segment CTV technique approached 97%. The specificity of CTV was 57% to 86% and varied with the venous segment. The sensitivity and specificity of magnetic resonance venography compared with IVUS was 100% and 22.7%, respectively.

Conclusions: Given that IVUS is considered the reference standard used to guide venous interventions in patients with CIVO, the use of venography, despite using multiple projection views, underestimates the severity and presence of venous stenosis and should not be used as the only diagnostic modality. Three-dimensional CTV is noninvasive with a high sensitivity. It can be used to screen patients who might benefit from a more invasive investigation with IVUS. CTV can also be considered for the preoperative planning of venous interventions in patients with CIVO. (J Vasc Surg Venous Lymphat Disord 2021;9:1545-56.)

Keywords: Chronic venous occlusive disease; Computed tomography venography; Iliac vein stent; Intravascular ultrasound; IVUS; Magnetic resonance venography; Multiplanar venography

The diagnosis of chronic iliofemoral venous obstruction (CIVO) remains challenging. Veins are elliptical and dynamic structures that behave anisotropically and are affected by factors such as the intravascular volume and respiratory movement.[1-3] Intravascular ultrasound (IVUS) displays the real-time cross-sectional venous anatomy and can be used as a guide during interventions for CIVO.[4] It can delineate detailed features of venous lesions.[1] The use of IVUS has been well-documented in coronary and peripheral arterial studies.[5,6] The use of IVUS during peripheral venous interventions has increased in popularity in the past decade. In some specialized venous centers, IVUS has been most frequently used in conjunction with another diagnostic modality, most often venography. At other centers, IVUS has not yet been fully incorporated into the diagnostic and treatment algorithm for CIVO and, thus, is not used.

Overall, the comparison of IVUS and other three-dimensional (3D) contrast imaging modalities has not been well documented. Owing to its invasive nature, IVUS is not suitable as the initial screening tool for patients with suspected CIVO.[7] To the best of our knowledge, only one study to date has evaluated patients using IVUS without any preprocedural or intraoperative contrast

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imaging study and noted a 100% diagnostic yield in the investigation of venous stenosis in at least one of the three segments evaluated (common femoral vein [CFV], external iliac vein [EIV], and common iliac vein [CIV]).[4]

We performed a systematic analysis of the performance of IVUS and other 3D contrast imaging modalities for the evaluation of CIVO.

METHODS

A thorough literature review was performed in accordance with the PRISMA (preferred reporting items for systematic review and meta-analysis) recommendations.[8] The eligibility and inclusion criteria were predefined. A comprehensive search was conducted to identify studies that had compared IVUS and other multidimensional contrast imaging modalities in the characterization of CIVO. These multidimensional contrast imaging modalities included multiplanar venography (MPV), contrast-enhanced (CE) computed tomography (CT), and CE-magnetic resonance imaging (MRI). MPV refers to any venographic study used to evaluate the iliofemoral venous vasculature in more than one view.

Study eligibility

Type of studies. Observational studies and randomized controlled trials (RCTs) in the English language that had compared IVUS and at least one multidimensional contrast imaging modality for the evaluation of CIVO were included. Reports focusing on the use of IVUS and other diagnostic modalities for acute deep vein thrombosis (DVT) were excluded. Case reports, animal experiments, and review articles were not included; however, the references of these reports were searched for additional studies. Conference abstracts for which full-length articles had not yet been published were also excluded. No limitation was set for the date of publication.

Imaging modality. The multidimensional contrast imaging modalities were MPV, CT venography (CTV), CT angiography (CTA), and CE-MRI (magnetic resonance venography [MRV]). Single plane venography (SPV) studies were also evaluated. However, their data have been presented separately and in brief but excluded from the final systematic review because the primary purpose of the present systematic review was multidimensional CE imaging modalities.

Type of patients. Participants aged ≥15 years were included. For a study to be included, a minimum of 15 study patients was required.

Outcomes. Any comparison (qualitative or quantitative) of the performance of IVUS with at least one other multidimensional CE imaging modality to evaluate CIVO was considered a primary outcome.

Search strategy

A literature search was conducted in August 2020 of the following databases: MEDLINE, Embase, EBSCOhost, Cochrane Library, CINAHL PLUS, and Web of Science. Only English language reports were included. No date limitations were set. The references of the included studies and review studies were searched for additional reports. The search terms included "intravascular ultrasound" and one of the following terms: "vein," "venous," "iliac," "femoral," "computed tomography," "magnetic resonance imaging," and "venography."

Data extraction and analysis. The studies identified from the search were screened by one of us (T.S). The full length text was then reviewed and discussed with S.R. before the final selection for inclusion by consensus of both of us. The following data points were collected: study type, inclusion and exclusion criteria, number of patients, other diagnostic modalities used, follow-up details, management, results, and key findings.

Risk bias. The Cochrane Collaboration instrument was used in the assessment of risk of bias,[9] and the GRADE (grading of recommendations assessment, development, and evaluation) tool was used to assess for bias in the outcomes.[10]

RESULTS

Study selection

A total of 4494 reports in MEDLINE, 3376 in Embase, 2160 in EBSCOhost, 143 in the Cochrane Library, 225 in CINAHL PLUS, and 1647 in Web of Science were identified. Once the duplicates had been excluded, the title and abstract of 2117 studies were reviewed. The full-length text of 58 articles was eventually reviewed (Fig). Of the 58 studies, 8 met the inclusion criteria (Table I).[1,7,11-13,15-17] Twelve studies had compared IVUS and SPV.[18-29] Additionally, one study had used IVUS and MPV in a sample of 16 patients but had not provided any comparison of the two modalities.[30] Therefore, the study was not included. The study had also included two patients with DVT (one with acute on chronic DVT and one with presumed acute DVT based on the patient's response to thrombolytic therapy).[30]

Study characteristics

IVUS vs MPV. The VIDIO (venogram vs IVUS for diagnosing iliac vein obstruction) trial compared the diagnostic efficacy of IVUS and MPV for CIVO. The trial was a prospective, multicenter, international cohort study.[1] One additional report related to the VIDIO trial was identified but was not counted as an additional study.[2] Another retrospective study had evaluated IVUS and MPV for patients with iliac venous compression syndrome.[11]

IVUS vs CTV. Three studies were identified that had compared IVUS and CTV.[7,12,13] Two of these studies were retrospective cohort studies[7,12] and one study[13] had included patients who had been recruited as part of a previously reported study in which iliac vein stenting had been compared with medical treatment in the treatment of chronic venous disease.[14]

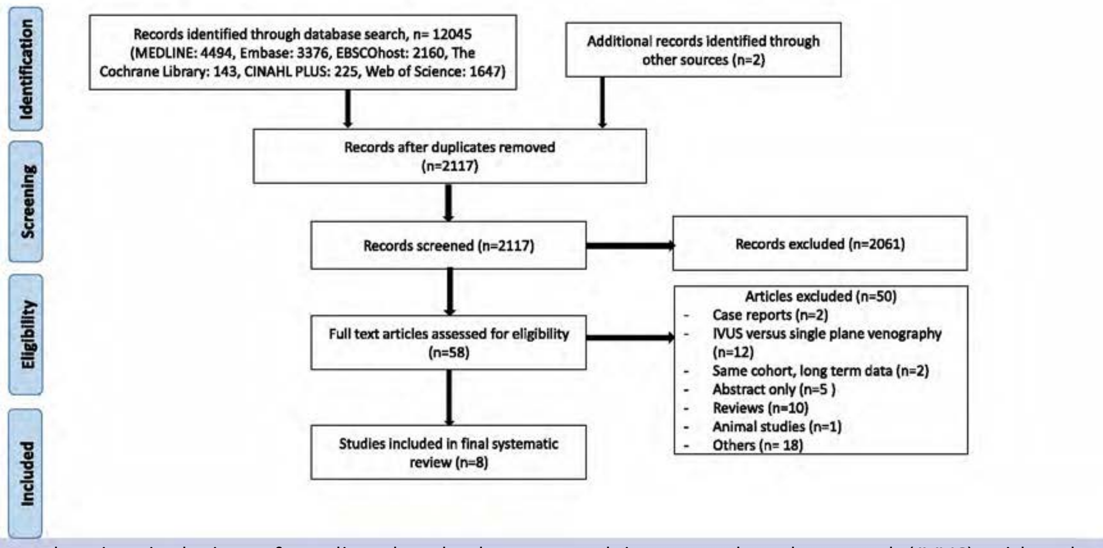

Fig. Flowchart showing inclusion of studies that had compared intravascular ultrasound (*IVUS*) with other multidimensional contrast-enhanced (CE) imaging modalities.

IVUS vs MRI. One study was identified that had compared CE-MRI, non—CE-MRI, and IVUS in the evaluation of patients with post-thrombotic syndrome.[15]

IVUS vs more than one modality. In two studies, IVUS had been compared with more than one multidimensional CE imaging modality. Shammas et al[16] compared the performance of IVUS against MPV and CTA. An additional study compared IVUS, MPV, and MRV.[17]

IVUS vs anteroposterior venography. During the literature search, 12 studies were identified in which IVUS had been compared with anteroposterior venography or SPV (Table II). These were all retrospective studies.[18-29]

Study quality assessment

The general quality was weak because most of the studies were retrospective reviews of data; this inherently introduces a selection bias. Additional bias assessments are summarized in Table III. The GRADE method was used to rate the quality of evidence, which was very low to low (Table IV).

Comparison of IVUS with multidimensional CE imaging modalities

IVUS vs MPV. IVUS identified stenotic lesions in 0% to 30% more patients compared with MPV.[1,11,17] Collateral vessels were not seen on all venograms, even when IVUS had identified a stenosis.[11] This was especially true for right iliac vein compression, for which stenosis >50% found using IVUS showed no collateral vessels on venography. On the left side, stenosis >50% found using IVUS was associated with collateral vessels on venography in 85% of patients.[11]

The diameter reduction using MPV was 11% less than that using IVUS,[1] and the percentage of stenosis calculated by venography was underestimated by 15% compared with that using IVUS.[16] The diameter reduction had probably been used such that a comparison between the two modalities could be provided across the same parameter in that study.[1] The interclass correlation coefficient between IVUS and venography was 0.505 (95% confidence interval, 0.296-0.658) for vein diameter stenosis.[1] In another study, the Spearman correlation coefficient between the percentage of stenosis by venography vs IVUS was 0.471 ($P < .001$).[16] Venography underestimated the residual stenosis after the procedure compared with IVUS (14% vs 25%-28%).[2]

A revision in the treatment plan because of the IVUS findings was made in 57 of 100 patients in one study. Most often, this was because venography had failed to detect a significant lesion compared with IVUS (41 of 57; 72%). The change in the treatment plan included an increased number of stents in 13 patients (23%) and the avoidance of stenting in 3 (5%).[1] IVUS compared with MPV had better characterized spurs (82.3% vs 3.1%; $P < .001$) and venous scars (36.2% vs 3.1%; $P < .001$).[1] Compared with venography, the baseline stenosis measurements using IVUS better predicted for clinical improvement after venous stenting.[2]

IVUS vs CTV or CTA. The differences in the CTV measurements compared with the IVUS measurements for CIV and EIV was +2.5% and +7.3%, respectively.[12] For IVUS, the area was measured using the machine planimetry software. For CTV, the smallest diameter was used for the conversion to the area.[12] The Pearson statistic for the CIV, EIV, CFV, and stent inflow channel areas for CTV and IVUS was 0.89 ($P < .01$), 0.77 ($P < .01$), 0.69 ($P < .01$), and 0.90 ($P < .01$), respectively.[7] For the minimal luminal area calculated by CTV vs IVUS, the Spearman correlation coefficient was 0.27 ($P = .01$).[16] CE-CT

Table I. Summary of included studies: *IVUS* vs multidimensional imaging modalities

Investigator	Study design	Inclusion criteria	Exclusion criteria	Sample size, No.	Age, years	Comparison modality with IVUS	Mean follow-up, months	Intervention	Findings
Gagne et al,[1] 2017	Prospective multicenter international cohort study	Age, 18-85 years; CEAP, C4-C6; patency of CFV and profunda femoral or femoral veins of index extremity by duplex ultrasound; intent to treat obstructive lesions of iliofemoral veins, if identified	Previous venous stenting or surgical bypass in index leg or IVC; severe untreated superficial reflux; acute DVT in either leg; history of hypercoagulable syndrome; elevated creatinine; vein obstruction from malignant disease	100 Patients	62.3 ± 12 (30-85)	MPV	6	Stenting	IVUS identified significant lesions not detected by venography in 26% of patients; diameter reduction by venography was 11% less than that with IVUS ($P < .001$); IVUS changed the treatment plan for 57% of patients; ICC between IVUS and venography, 0.505 (95% CI, 0.296-0.658) for vein diameter stenosis
Sang et al,[11] 2019	Retrospective case series of prospectively recorded data	Suspicion for iliac vein compression at presentation: varicose veins, chronic nonthrombotic limb swelling, hyperpigmentation, ulceration, venous claudication	Clinical or radiographic history of DVT; cardiac failure; pelvic tumors; life expectancy <5 years	85 Patients	55 (21-72)	MPV	12.1 (range, 1-24)	PTA, stenting, venous stripping	RIVC: IVUS stenosis >50% not associated with collateral vessels on venography; LIVC: IVUS stenosis >50% associated with collateral vessels on venography in 85% of patients
Jayaraj et al,[7] 2020	Retrospective case series of prospectively recorded data	Patients with CIVO in whom conservative therapy failed	CTOs; acute DVT	22 Patients	60 ± 12.3	CTV	12	Stenting	Pearson correlation coefficient for luminal areas between 3D-CTV and IVUS: CIV, 0.89 ($P < .01$); EIV, 0.77 ($P < .01$); CFV, 0.69 ($P < .01$); inflow channel luminal area, 0.90 ($P < .01$); 3D-CTV sensitivity for CIVO diagnosis: CIV, 100%; EIV,100%; CFV, 80%
Raju et al,[12] 2020	Retrospective case series of prospectively recorded data	Patients with CTV before IVUS during 5-year period	Technically unsatisfactory IVUS or CTV examination	91 Limbs	62 (17-86)	CTV	NR	Stenting	Single-segment diagnostic sensitivity of CTV compared with IVUS: CIV, 83%; EIV, 73%; sensitivity increased to 97% for iliac vein stenosis in ≥1 of 2 segments (CIV and EIV); ROC AUC for accuracy: 0.89 ($P < .001$) for 2-segment method
Rossi et al,[13] 2020	Previous randomized prospective study[14]	CEAP C3-C6 and VAS for pain score >5 and/or VCSS >8	Allergy to iodinated contrast agent; PAD; renal failure; age >80 years	70 Patients	47 ± 6 (26-77)	CTV	6	NR	Compared with IVUS, CTV sensitivity and specificity was 94.0% and 79.2%, respectively, in detection of IVO of ≥50%; interobserver agreement, 92.1% (95% CI, 87.1-97.7; kappa, 0.899)
Kusiak et al,[15] 2019	Case series, not clearly reported	Diagnosis of PTS qualifying for venous intervention	NR	18 Patients	27-55	CE and NCE-MRI	NR	Stenting	No significant relationships found between section areas measured using MRI and IVUS; differences in measurements, 27%-60%; CE-MRI and NCE-MRI section areas correlated significantly with each other ($R = 0.87$-0.97; $P < .001$)

Table I. Continued.

Investigator	Study design	Inclusion criteria	Exclusion criteria	Sample size, No.	Age, years	Comparison modality with IVUS	Mean follow-up, months	Intervention	Findings
Shammas et al,[16] 2018	Retrospective case series	Patients who had undergone iliofemoral vein compression treatment	Incomplete or uninterpretable imaging study	96 Patients	62.3 ± 14.8	CTA and MPV	NR	Stenting	Percentage of stenosis on venography correlated with IVUS (Spearman's rho, 0.471; $P < .001$) but underestimated it by 15.2% (95% CI, 10.4-20.1; $P < .001$); similar measurements were not significantly different statistically between IVUS and CT (median difference, 5.6 mm^2; 95% CI, −12.2 to 0.7)
Massenburg et al,[17] 2015	Retrospective case series	Patients with signs and symptoms of PVOO who had undergone IVUS, MRV, and venography	NR	46 Patients	NR	MPV and MRV	NR	Stenting	Compared with IVUS and MPV, MRV had a sensitivity of 100% and specificity of 22.7%; PPV for diagnosing proximal venous outflow obstruction with suspicious or abnormal MRV was 58.5%

3D, Three-dimensional; *AUC,* area under curve; *CE,* contrast-enhanced; *CEAP,* clinical, etiologic, anatomic, pathophysiologic; *CFV,* common femoral vein; *CI,* confidence interval; *CIV,* common iliac vein; *CIVO,* chronic iliofemoral venous obstruction; *CTA,* computed tomography angiography; *CTO,* chronic total occlusion; *CTV,* computed tomography venography; *DVT,* deep vein thrombosis; *EIV,* external iliac vein; *ICC,* intraclass coefficient; *IVC,* inferior vena cava; *IVO,* iliac vein obstruction; *IVUS,* intravascular ultrasound; *LIVC,* left iliac vein compression; *MPV,* multiplanar venography; *MRI,* magnetic resonance imaging; *MRV,* magnetic resonance venography; *NCE,* non–contrast-enhanced; *NR,* not reported; *PAD,* peripheral arterial disease; *PPV,* positive predictive value; *PTS,* post-thrombotic syndrome; *PVOO,* proximal venous outflow obstruction; *PTA,* percutaneous transluminal angioplasty; *RIVC,* right iliac vein compression; *ROC,* receiver operating characteristic.

overestimated the minimal luminal area compared with IVUS by +41 mm^2. However, for the percentage of stenosis, the difference between CTA and IVUS was much smaller (−5.6 mm^2).[16]

The sensitivity of CTV, compared with IVUS, was 83% and was 73% for the CIV and EIV.[12] In another study, the sensitivity of CTV was high (94%) when detecting stenosis >50% in the iliac veins.[13]

The diagnostic CTV stenosis threshold used for comparison with IVUS in one study was a CIV area <200 mm^2 (diameter <16 mm) and an EIV area <150 mm^2 (diameter <14 mm).[12] The Spearman correlation coefficient between CTV and IVUS was poor if a 50% stenosis threshold had been used instead to define obstruction (<100 mm^2 for CIV and <75 mm^2 for EIV), indicative of the limited ability of CTV to discriminate various degrees of stenosis.[12] The use of a two-segment CTV technique increased the sensitivity of CTV to 97%.[12] This method refers to the consideration of a stenosis in at least one of the two veins (CIV and EIV) as diagnostic of iliac vein stenosis, rather than considering each segment in isolation.[12]

The specificity of 3D-CTV in identifying CIVO for the CIV, EIV, and CFV was 67%, 57%, and 86%, respectively. The positive predictive value (PPV) was 89%, 83%, and 92% and the negative predictive value (NPV) was 100%, 100%, and 67% for the CIV, EIV, and CFV, respectively.[7]

In another study, the specificity, PPV, NPV and accuracy of CTV was 79%, 94%, 79%, and 87%, respectively.[13]

For >90% patients, 3D-CTV predicted the actual stent diameter used at intervention within 2 mm. Clinical improvement, determined by a decrease in the mean venous clinical severity score (from 6 ± 0.9 to 3.6 ± 0.6; $P = .04$) and mean pain score (from 6.6 ± 0.8 to 2.7 ±0.9; $P = .08$), was noted in patients who had undergone CTV followed by IVUS-guided stenting.[7]

IVUS vs MRI or MRV. Kusiak and Budzyński[15] evaluated CE-MRI, non–CE MRI (NCE-MRI) and IVUS.[15] A significant correlation was found for the target vein section areas between CE-MRI and NCE-MRI (Spearman correlation coefficient, 0.87-0.97; $P < .001$) but not with IVUS (Spearman correlation coefficient, −0.28 to 0.47; $P > .05$). The percentage of the difference in the vein section areas between CE-MRI or NCE-MRI and IVUS ranged from 27% to 60%.[15] Compared with IVUS, MRV had a sensitivity, specificity, PPV, and NPV of 100%, 22.7%, 58.5%, and 100%, respectively.[17]

Comparison of IVUS and SPV

Rokitansky stenosis, a characteristically long and diffuse venous lesion, was reported to be seen more readily on IVUS than with SPV. However, quantification of this comparison was not provided.[18]

Table II. Summary of studies of *IVUS* vs anteroposterior venography

Investigator	Study design	Inclusion criteria	Exclusion criteria	Sample size	Age, years (range)	Comparison modality with IVUS	Mean follow-up, months	Intervention	Findings
Raju et al,[18] 2014	Retrospective case series	Consecutive treated patients with CVD	NR	2534 Iliac vein stent procedures	Group 1, 66 (28-97); group 2, 59.5 (22-86)	APV	NR	Stenting, reintervention	Rokitansky stenosis not frequently apparent on venography compared with IVUS; however, no quantification provided
Ascher et al,[19] 2017	Retrospective case series	Patients with CVD randomly selected from larger cohort with venography and IVUS	NR	92 Patients	71.1 ± 15.4	APV, few patients had MPV but details unclear	NR	Stenting	More severe venographic abnormalities (types II, III, IV) had positive IVUS findings (100%)
Raju et al,[20] 2012	Retrospective case series	Patients with IVUS, venography, and lymphangiography	Preclusion of venography by clinical or technical factors	819 Limbs	Group 1, 48 (18-86); group 2, 57 (17-91)	APV	Group 1, 27 ± 33; group 2, 18 ± 21	Stenting, reintervention	Diagnostic sensitivity of venography vs IVUS, 61% vs 88%
Raju et al,[21] 2013	Retrospective case series	Patients with venous leg ulcers in whom conservative therapy failed	NR	192 Limbs	Group 1, 59 (15-92); group 2, 62.5 (33-91)	APV	NR	Stenting, saphenous vein ablation	Direct or indirect venographic evidence for obstructive lesion present in 52% of stented limbs; IVUS-measured area stenosis ≥50% in 85% of limbs and stenosis <50% in 15% of limbs (n = 23); of 23 limbs, 14 had significant stenosis according to balloon sizing; IVUS correctly diagnosed stenosis in 91% of patients
Neglen et al,[22] 2002	Retrospective case series of prospectively recorded data	Patients with CVD with venography and IVUS	NR	345 Limbs	NR	APV	NR	Stenting	Compared with IVUS, venography had poor sensitivity (45%) and NPV (49%) for detection of obstruction >70%
Montminy et al,[23] 2019	Retrospective cohort	Patients with new iliac vein stents	Patients without venography with IVUS	155 Limbs	59 ± 13	APV	NR	Stenting	Compared with IVUS, venography failed to identify lesions in 19% of limbs; median maximal stenosis lower with venography than with IVUS (52% vs 69%; $P < .001$); venography missed maximal stenosis location in 68% of limbs; venography correlated with IVUS for iliocaval confluence location in 15% of patients; correlation 26% between both modalities for distal landing zone location

Table II. Continued.

Investigator	Study design	Inclusion criteria	Exclusion criteria	Sample size	Age, years (range)	Comparison modality with IVUS	Mean follow-up, months	Intervention	Findings
Gagne et al,[24] 2019	Retrospective cohort	Consecutive patients with new iliac vein stents	NR	67 Patients	63 (47-83)	APV	50 (range, 0.25-100)	Stenting	Stenting correlated with both IVUS and venography in 48% of limbs; in ≤42% of limbs, IVUS estimated a longer lesion length than did venography
Raju et al,[25] 2006	Retrospective cohort	Patients with NIVL	PTS lesions	319 Patients	54 (18-90)	APV	10 (range, 1-85)	Stenting, saphenous vein ablation	Diagnostic sensitivity of venography vs IVUS: 66% vs >90%
Raju et al,[26] 2011	Retrospective cohort	Postmenopausal women (≥55 years) with leg swelling in whom conservative therapy failed	Proximate history of DVT (≤5 years) preceding symptom onset	150 Patients	68 (55-92)	APV	22 ± 26 (range, 1-113)	Stenting	Sensitivity of venography compared with IVUS, 69%; sensitivity of collateral vessels in venous obstruction, 28%; in 5% of patients, IVUS failed to detect a significant lesion noted on ballooning
Raju et al,[27] 2010	Retrospective cohort	Iliac vein stenting	Use of other concurrent procedures, absence of deep reflux	504 Patients	55 (15-87)	APV	17 (range, 1-145)	Stenting	Compared with IVUS, venography diagnostic rate, 63%; collateral vessels were seen on 43% of venograms
Lau et al,[28] 2019	Retrospective cohort	CVD patients with iliofemoral stenting	Reoperation, acute pre operative DVT, incomplete records	86 Patients	60.8 ± 1.4	APV	NR	Stenting	Sensitivity of combined venography findings for stenosis: LCIV, 97%; LEIV, 58%; LCFV, 48%; RCIV, 66%; REIV, 55%; RCFV, 48%; IVUS resulted in treatment plan change for 2%, 32%, and 48% of patients in LCIV, LEIV, and LCFV and 26%, 35%, and 48% in RCIV, REIV, and RCFV, respectively
Rollo et al,[29] 2017	Retrospective cohort	May-Thurner syndrome compression of LCIV	Other causes of non thrombotic iliac venous disease	63 Patients	46	APV	20.3	Stenting	Venography overestimated minimum LCIV diameter by 61% (7 vs 4.2 mm) and cross-sectional area by twofold (104 vs 53 mm^2) compared with IVUS

APV, Anteroposterior venography; *CFV,* common femoral vein; *CIV,* common iliac vein; *CVD,* chronic venous disease; *DVT,* deep vein thrombosis; *EIV,* external iliac vein; *IVUS,* intravascular ultrasound; *LCFV,* left common femoral vein; *LCIV,* left common iliac vein; *LEIV,* left external iliac vein; *MPV,* multiplanar venography; *NIVL,* nonthrombotic iliac vein lesion; *PTS,* post-thrombotic syndrome; *RCFV,* right common femoral vein; *RCIV,* common iliac vein; *REIV,* right external iliac vein.

Table III. Bias assessment

Bias	Relevant comments regarding presence of bias or how it was addressed
Random sequence generation (selection bias)	In VIDIO trial, stenosis treated at investigator's discretion[1]; of 100 patients, ≥50 were required to be C6 in VIDIO trial[1]; one study did not provide enough details about randomization[13,14]; only highly symptomatic patients were preselected to undergo randomization in one study[13,14]
Allocation concealment (selection bias)	One study did not provide details about allocation concealment[13,14]
Blinding of participants and personnel (performance bias)	Core laboratory assessment of IVUS and venography blinded to assessment by investigators; images were random and not sequential[1]; blinding of patients and staff used in one study[13,14]; MRI studies reviewed in blinded fashion by single physician who performed IVUS and venography for all patients in one study[17]
Blinding of outcome assessment (detection bias)	Blinding of both patient and physician at follow-up visits[13,14]
Incomplete outcomes data (attrition bias)	Follow-up reported in a few studies only[2,7,11,13]; in one study, 17/85 patients (20%) were lost to follow-up[11]
Selective reporting (reporting bias)	Most studies mentioned predefined outcomes or objectives[1,7,12,13,15-17]
Other bias	Venography and IVUS assessed by both investigators and core laboratory to minimize image interpretation bias[1]; CT scans interpreted by vascular radiologist on rotation (5 total), which can introduce interpretation bias[12]; MRV performed at different radiology facilities using different MRI machines and protocols[17]; images presented in a random sequence to avoid recognition bias[17]; one study used CTA[16] and others used CTV

CT, Computed tomography; *CTA,* computed tomography angiography; *IVUS,* intravascular ultrasound; *MRI,* magnetic resonance imaging; *MRV,* magnetic resonance venography; *VIDIO,* venogram vs IVUS for diagnosing iliac vein obstruction.

SPV appears to underestimate the degree of stenosis from 17% to >30%.[22,23] The diagnostic sensitivity of SPV varied from 45% to 88%.[19-23,25-27] The specificity, NPV, and PPV of SPV was 95%, 49%, and 94%, respectively.[22] In contrast, the sensitivity of IVUS compared with SPV was reported to be >90% in several studies.[21,25-27]

Compared with IVUS, SPV discordantly identified the location of maximal stenosis, the iliocaval venous junction, and the caudal stent landing zone in more than two thirds of the limbs.[23] Stenting corresponded with both IVUS and venography in only 48% of the sample in another study.[24]

Table IV. Grading of recommendations assessment, development, and evaluation assessment of evidence

Outcome	Relative effect (95% CI)	Events, No.	Quality of evidence (GRADE)	Comment
IVUS vs MPV	NE	281 Patients	Low	Small sample size; only one study was prospective, multicenter but nonrandomized[1]; two studies were retrospective case series[11,16]; mean follow-up, 6-12 months[1,2,11]; one study did not mention follow-up[16]; 20% loss to follow-up in one study[11]; treatment at investigator's discretion in one study[1]
IVUS vs CTV	NE	279 Patients or limbs	Low	Small sample size; three were retrospective case series[7,12,16]; one was part of previously reported randomized prospective trial comparing iliac vein stenting and medical treatment of CVD[13,14]; details on random sequence generation and allocation concealment not clear in one study[14]; blinding of patient and doctor used at follow-up in one study[14]; mean follow-up, 6-12 months[7,13]; two studies did not mention follow-up[12,16]
IVUS vs MRV	NE	64 Patients	Very low	Very small sample size; both studies were retrospective case series[15,17]; follow-up not reported for either study[15,17]

CI, Confidence interval; *CTV,* computed tomography venography; *IVUS,* intravascular ultrasound; *MRV,* magnetic resonance venography; *NE,* not estimable.

When the severity of the venographic findings increased, the probability of positive IVUS findings was reported to be greater.[19,22] With ≥70% stenosis found on venography, IVUS stenosis was also noted to ≥70% in almost 80% of the limbs.[22] In one study, the more severe venographic abnormalities were defined as a ≥21% caliber reduction or distention of the vein compared with the neighboring vein segment and the bull's eye sign ("central circle with minimal or no dye within a dilated vein and forking of the dye around the circle").[19] However, ≥21% narrowing has not been traditionally considered as a hemodynamically significant venographic finding.

The combination of multiple venographic findings (eg, pancaking, contrast thinning, and collateral vessels) can lead to increased sensitivity.[28] The sensitivity of combined venography findings for stenosis was 97% left CIV, 58% left EIV, 48% left CFV, 66% right CIV, 55% right EIV, and 48% right CFV. As seen with MPV, IVUS resulted in a revision of the treatment plan in ≤48% of patients in the left and right limbs (depending on the specific venous segment) when used with SPV.[28]

DISCUSSION

Iliofemoral outflow obstruction is a significant component of chronic venous pathology. CIVO can exist in combination with reflux disease.[31] During the past two decades, the number of minimally invasive venous interventions for CIVO has increased tremendously.[32] Imaging modalities to guide such interventions have also continued to evolve. Since its discovery, IVUS has continued to be increasingly used in a number of medical disciplines to guide therapy and has several benefits in the treatment of venous disease (Supplementary Table, online only).[33-41] IVUS will be typically be used in the same setting as an intervention and is not prohibitive for use in patients with kidney disease or a contrast allergy.[4]

IVUS and venography. Several retrospective cohort studies in the past two decades have reported higher sensitivity for IVUS compared with SPV and regarded it as the diagnostic reference standard for venous interventions. It was then suggested that MPV might perform better than SPV compared with IVUS because veins are elliptical and follow a multiplanar pelvic course that can be better captured by MPV.[1] The VIDIO trial was designed to answer this question and is the only prospective trial that has compared IVUS and MPV.[1] The superiority of IVUS vs MPV in the diagnosis of CIVO was noted in the VIDIO trial as IVUS detected ≤30% more significant iliofemoral lesions than MPV.[1] It also showed a significant rate in the change in the treatment plan when IVUS was used.[1] A subsequent report of the VIDIO trial also noted that using IVUS predicted the clinical outcomes better than did MPV at follow-up after the intervention.[2]

Threshold stenosis. Most of the reviewed studies, including the VIDIO trial,[1] used a 50% stenosis threshold for IVUS as indicating clinical relevance. Studies involving venography have used a similar stenosis criterion. However, a morphologic stenosis of this degree might not always be pathologic. Therefore, the presence of a venous stenosis of ≥50% is thought to be important by many investigators for the development of symptoms although not sufficient in all cases to result in problems. Asymptomatic individuals, ≥20% of the population, might have iliac venous stenosis found on imaging.[42,43] In several series, the mean and median stenosis noted in patients who had undergone IVUS-guided venous stenting was actually approximately ≥70%.[20-22,26,27,44] Some investigators believe that the criterion of 50% stenosis on IVUS requires further clinical correlation.[29,45] Analysis of the VIDIO trial showed that, per IVUS, a >54% stenosis was estimated to be the optimal threshold for interventional treatment; this threshold was even greater (>61%) for patients with post-thrombotic syndrome.[2] A stenosis threshold of 50% on MPV did not correlate well with clinical improvement.[2] The pathology in symptomatic individuals is believed to be "permissive."[25] Permissive conditions can be viewed as pathologies that are silent until an additional insult is superimposed on them.[25] Additional factors could play a role in creating a decompensated state leading to overt clinical manifestations of chronic venous disease.[46] These factors can include trauma, weight gain, infection, thrombosis, and the development of reflux.[12] Therefore, the identification of stenosis in the appropriate clinical context is important, and IVUS can help in the accurate morphologic diagnosis of CIVO.[42]

The recommendation for the following stent sizes in the CIV, EIV, and CFV as 16 mm (area, 200 mm^2), 14 mm (area, 150 mm^2), and 12 mm (area, 125 mm^2), respectively, merits consideration.[47,48] These are the minimal stent sizes required to establish ideal venous flow and have been derived from Poiseuille's equation and Young's scaling ratios in healthy individuals.[4,48]

Significance of collateral vessels. It has been suggested that venography might provide physiologic information, in addition to morphologic data, such as pelvic and retroperitoneal collateralization and contrast stagnation.[29,49] Rollo et al[29] described contemporary outcomes after treatment using venography, rather than IVUS, of May-Thurner syndrome.

Although collateral vessels found on venography might have some hemodynamic significance,[22] a significant proportion of patients with significant obstruction that will require intervention in routine practice will not actually have collateral vessels on venography.[22] In one study, the rate of significant venous stenosis was not affected by presence of collateral vessels.[50] The mean area of stenosis on IVUS planimetry has been noted to be

~70% ± 20%,[20,26,27] and the median area of stenosis was 70% to 80%.[21,22,51] In a few studies, collateral vessels were noted in 26% to 70% of the venograms, and obstructive lesions that were stented were noted by IVUS in 88% to 95% of these patients.[20,21,26,27,31] In a study by Nelgen et al,[22] when collateral vessels were present, the stenosis was usually noted to be more severe (median, 85%; range, 25%-100%).[22] A hyperemia-induced pressure gradient (≥2 mm Hg) occurred more frequently with collateral vessels (34% vs 11%).[22] Collateral vessels on venography were also associated with higher mean stenosis on both IVUS and venography in the VIDIO trial.[1]

Another observation in one study was that after intervention, collateral vessels had disappeared completely in most (60%), but not all, patients who had collateral vessels before intervention.[31] It remains less clear whether patients with collateral vessels have more severe symptoms or a higher CEAP (clinical, etiologic, anatomic, pathophysiologic) class at presentation than patients without collateral vessels. Although venography might provide some additional information, the clinical utility or universal presence of various findings, including collateral vessels, has remained unclear. One might expect collateral vessels to be present in patients with lowered venous pressure gradients, because it is considered a compensatory mechanism of the body to achieve a more homeostatic venous state. However, that does not appear to be the case, and collateral vessels might actually represent a more severe and uncompensated state of venous disease.[52] The combination of multiple findings on MPV might lead to increased sensitivity; however, it is unclear which combination of findings would have the greatest diagnostic yield or discriminatory power. Also, unclear is whether each specific venographic finding reflects the same hemodynamic or morphologic significance. Further research aimed at elucidating the clinical and hemodynamic significance of various venographic findings might be highlighted as an area of future research. More research is also needed regarding IVUS and venous pressure gradients because the data on this particular subject are sparse. At least one study has examined the relationship between IVUS and venous pressure gradients in CIVO. That study found low sensitivity, NPV, and accuracy associated with various venous pressure gradients.[52]

Complications of IVUS. In the arterial and coronary systems, the potential complications associated with the use of IVUS catheterization include dissection, perforation, bleeding, thrombosis, and vasospasm. The reviewed studies for the comparison of IVUS and other modalities in the venous system did not report any IVUS-specific complications. The potential access-related complications can include access site hematomas, arteriovenous fistulas, nerve damage, access site venous thrombosis, and arterial pseudoaneurysms.

IVUS, CTV, and MRV. CTV and MRV are emerging CE imaging modalities that can provide cross-sectional information about the venous anatomy. Studies of acute DVT have shown high sensitivity and high specificity (>90%) with both CTV and MRV. However, only limited reports are available that have compared the two techniques with IVUS in CIVO.

Overall, the CTV findings appear to have excellent correlation with the IVUS findings and has high sensitivity and can be used to screen patients before IVUS. CTV can be direct or indirect. Indirect CTV involves injection of contrast via the cubital vein in the arm and direct CTV involves injection of contrast via the dorsal vein of the foot.[53] The two techniques could even be combined to achieve the best imaging but at the expense of a higher contrast dose.[54] The use of single-segment caliber measurements on CT could have limitations, including (1) the possibility of exaggeration of compression severity owing to pre- and post-stenotic dilation; and (2) the possibility of underestimation of compression if the whole anatomic venous segment is involved.[16] The use of the two-segment caliber method appears to improve the sensitivity and accuracy of CTV.[12] Also, the findings from the present studies suggest that the sensitivity, specificity, PPV, NPV, overall accuracy, and correlation coefficient statistic will vary according to the venous segment being measured (ie, CIV, EIV, CFV).[7] Because of the ability to reasonably predict the length and diameter of the stents used, 3D-CTV appears to have potential utility in operative planning for CIVO interventions.[7] This is especially important because, for a small subset of patients, IVUS measurements could have missing borders, leading to incomplete measurement of the venous caliber owing to a lack of centering mechanism or bias from the tilt of the catheter near confluences. In these patients, CTV measurements can reliably provide this missing data point.[12] Areas highlighted for future investigation include the optimum phase (use of venous vs arterial contrast phase), morphometric parameter (use of diameter vs area in venous segment measurements), and technique (use of direct vs indirect CT technique). CTA is believed to more optimally display the compression of venous structures by crossing arterial structures.

In contrast, the correlation between MRV and IVUS measurements was weaker. Although the sensitivity of MRV has been reported to be high, the specificity was poor, with a high rate of false-positive findings.[55] The noninferiority of NCE-MRI compared with CE-MRI also requires further research. In one study, NCE, balanced steady-state, free precession MRI was compared with intravenous digital subtraction angiography. Although the former performed well in most cases compared with intravenous digital subtraction angiography, it overdiagnosed chronic intraluminal webs and underdiagnosed stenosis in smaller veins.[54,56]

Potential exists for improved clinical outcomes with CTV- or MRV-guided interventions; however, follow-up data and long-term outcomes were neither provided nor well-documented in most of the studies reviewed. Longer term follow-up is available for studies in which SPV and IVUS were used. The outcomes included significant relief from swelling and pain, healing of venous ulcers, and resolution of recurrent cellulitis after IVUS-guided intervention.[20,21,25-27,31,32] However, some of these studies were limited to specific patient populations, such as venous lymphedema,[20] venous ulcers,[21] postmenopausal women,[26] and octogenarians and nonagenarians.[51]

Algorithmic diagnostic approach. A potential algorithmic testing approach to the preoperative assessment of patients with CIVO has been provided in the Supplementary Fig (online only).

Study limitations. A systematic review can help provide a useful synthesis of existing data when incongruity is present in the trends seen in various studies.[57] In the present systematic review, although certain trends were noted regarding various diagnostic modalities, considerable heterogeneity was present in the study populations and diagnostic methods. Also, the proportion of thrombotic and nonthrombotic iliac lesions in each study was highly variable. The statistical analysis and metrics used were not standardized. More recently reported studies used more robust statistical techniques. A few studies evaluated the segment-specific performance of the diagnostic modalities and others did not. With IVUS, it is now accepted that the area rather than the diameter should be used for measurements because of the unique elliptical structure of veins. With CT and MRI, some studies used the diameter instead of the area for calculations. This limited the comparability of the studies owing to the lack of a standardized measuring parameter.[58] A meta-analysis was not performed because of the paucity of the data points available, the heterogeneous study populations, and heterogeneous statistical methods used. The GRADE system was used to estimate study quality, and most studies were of low quality. We found a lack of robust and rigorously designed RCTs. However, the conduct of such RCTs in this patient population could be difficult. A strong recommendation can be made from consistent evidence from various observational studies.[59,60]

CONCLUSIONS

IVUS demonstrated high sensitivity and specificity in guiding venous interventions for CIVO and results in few, if any, adverse events. It should be used for all patients because of its diagnostic superiority compared with all other modalities. The available data have shown that venography, despite using multiple projection views, will underestimate the severity and presence of venous stenosis and should not be used as the only imaging study to guide venous interventions. 3D-CTV is noninvasive with a high sensitivity. It can be used to screen and select patients for a more invasive investigation with IVUS. Its use can also be considered in the preoperative planning of venous interventions for patients with CIVO. Experience with MRV and its comparison with IVUS for the evaluation of CIVO is currently very limited.

AUTHOR CONTRIBUTIONS

Conception and design: TS, SR
Analysis and interpretation: TS, SR
Data collection: TS, SR
Writing the article: TS, SR
Critical revision of the article: TS, SR
Final approval of the article: TS, SR
Statistical analysis: TS
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Overall responsibility: TS

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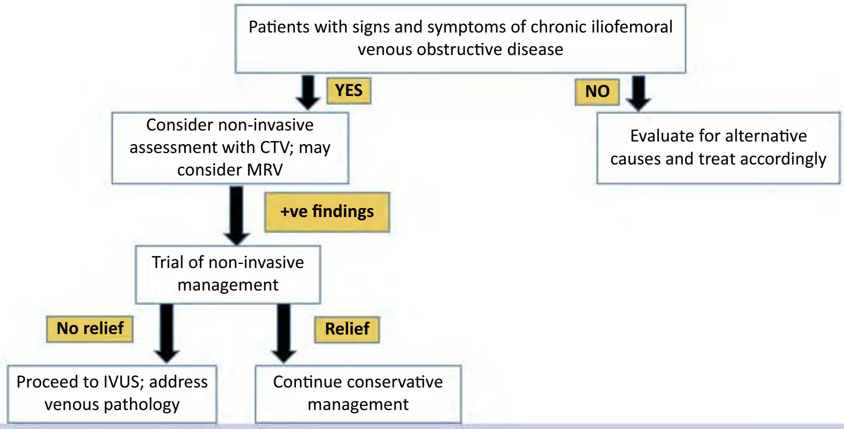

Supplementary Fig (online only). Diagnostic algorithm for patients with suspected chronic iliofemoral obstructive venous disease. *CTV,* Computed tomographic venography; *IVUS,* intravascular ultrasound; *MRV,* magnetic resonance venography.

Supplementary Table (online only). Comparison of IVUS with other multidimensional CE imaging modalities

IVUS		MPV		CTV/CTA		MRV	
Advantages	Disadvantages	Advantages	Disadvantages	Advantages	Disadvantages	Advantages	Disadvantages
No contrast	Invasive	Provides roadmap for stenting procedure	Stenosis underestimated	Noninvasive	Contrast required	Noninvasive	Uses contrast
Can be used for pregnant women with minimal radiation exposure	Not always possible to clearly differentiate spurs from venous wall in severe compression	Helpful in chronic total venous occlusion	Contrast required	Has internal scale of reference	Cannot be used for intervention concurrent with diagnosis of lesion	Postprocessing provides 3D rendering	Cannot be used for intervention concurrent with diagnosis of lesion
Better intraluminal characterization of lesions (frozen valves, trabeculation, spurs)	Incomplete measurements due to missing borders; lack of centering mechanism	Can provide some hemodynamic information with presence of collateral vessels	Invasive	Measurements possible at multiple points, with provision of multiple data points	Relative contraindication for patients with renal insufficiency or contrast allergy	Measurements possible at multiple points, with provision of multiple data points	Relative contraindication for patients with renal insufficiency or contrast allergy
Can be used to diagnose lesions missed by venography	Can miss lesions near confluences	Can be used for intervention concurrent with diagnosis of lesion	Radiation exposure, especially with multiple projections	Postprocessing provides 3D rendering	3D reconstruction requires dedicated software	Has internal scale of reference	3D reconstruction requires dedicated software
Real-time continuous image	Less widely available than venography	Helpful in delineating pelvic anatomy and anatomic variants	Can miss highly eccentric lesions	All venous borders visible	Radiation exposure	All venous borders visible	Study can be degraded by motion or flow artifacts
Can be used for intervention concurrent with diagnosis of lesion	Can miss very discrete lesions (eg, membranous lesions)	Can be used to assess immediate technical outcome of intervention	Lacks internal scale	Can be helpful with operative planning	Can be affected by factors (eg, CO, degree of hydration)	Can be helpful with operative planning	Can be limited by contrast injection timing
Safe for patients with renal insufficiency or contrast allergy	Must pass through obstruction to provide visualization	More readily available and accessible than IVUS	Misses stenotic lesions compared with IVUS	Can provide information on other abdominopelvic pathology	Can be difficult to discern intraluminal details (eg membranes, synechiae)	Can provide information on other abdominopelvic pathology	Severely tortuous vein anatomy can degrade signal quality
Can be used to assess complete or incomplete stent apposition to vessel wall	Acoustic shadowing can be caused by calcification, stent struts, IVC filters	More experience than with IVUS ("a legacy technique")	Should be avoided for pregnant women	Appears to correlate well with IVUS measurements	Should be avoided for pregnant women	Can be considered for pregnant women	Generalizability could be limited by variation in study protocols
Can be used to assess immediate technical outcome of intervention	Less experience than with venography	Some quantification of in-stent restenosis possible	Relative contraindication for patients with renal insufficiency or contrast allergy	High sensitivity with 2-segment caliber method	Can be limited by contrast injection timing	High sensitivity	Low specificity
Can be used to estimate degree of in-stent restenosis	Specific access sheath sizes required for delivery depending on catheter type	Not restricted by sheath size	Hyperconcentrated contrast can mask lesions	Lack of operator dependence	Generalizability could be limited by variation in study protocols	Lack of operator dependence	Cannot be used to assess immediate technical outcome of intervention
More accurately defines iliocaval confluence than venography	Limitations with assessment of ipsilateral infrainguinal segments	Detects presence of collateral vessels	Less accurate delineation of iliocaval confluence, distal landing zone for stent than IVUS	Provides indirect evidence of stenosis (eg, collateral vessels)	Cannot be used to assess immediate technical outcome of intervention	Provides indirect evidence of stenosis (eg, collateral vessels)	Implants could be safe, unsafe, or conditional for MRI

3D, Three-dimensional; *CE,* contrast-enhanced; *CO,* cardiac output; *CTA,* computed tomography angiography; *CTV,* computed tomography venography; *IVC,* inferior vena cava; IVUS, intravascular ultrasound; *MPV,* multiplanar venography; *MRI,* magnetic resonance imaging; *MRV,* magnetic resonance venography.