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Venous thromboembolism and chronic venous disease among people who inject drugs: A systematic review and meta-analysis

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ABSTRACT

Introduction: Intravenous drug use continues to pose a substantial burden worldwide and little is known about the risk of venous thromboembolism (VTE) and its sequelae in people who inject drugs (PWID).
Methods: A systematic literature search was conducted on the prevalence of VTE and chronic venous disease in intravenous drug users, as well as on the prevalence of intravenous drug use among selected VTE patients. Two reviewers independently selected the articles and appraised their quality. A random-effect meta-analysis was performed to pool risks across studies.
Results: We included 18 studies with a total of 7691 patients. The overall prevalence of VTE among PWID was 29% (95%CI: 19–40%). Among patients diagnosed with VTE, 15% (95%CI: 10–20%) were PWID. Similar rates were confirmed in more recent studies published in the past decade, although these studies are often based on the general population from higher-risk areas. Reported rates of chronic venous disease ranged between 58% and 61%. The majority of the included studies had a low to moderate quality of evidence. We could not exclude a selection bias in the studies in geographical regions with high intravenous drug use prevalence.
Conclusion: VTE and chronic venous disease appear to be common and understudied complications of injective drug use. National programs for PWID patients should also focus on early and late VTE-associated complications.

1. Introduction

Almost forty years after the heroin epidemic in the 1980s and 1990s, intravenous drug use still poses a substantial economic, social, and medical burden, with an estimated number of up to 24 million people who inject drugs (PWID) worldwide with marked geographical differences: east and southeast Asia, eastern Europe and North America have the highest rate of injective drugs use [1,2]. According to the European Monitoring Centre for Drugs and Drug Addiction, the three most commonly injected drugs are cocaine, amphetamines, and heroin [1]. Together with the harmful effects of the narcotic itself and the high rate of blood-borne virus transmission, venous thromboembolism (VTE), the third most common cardiovascular disease [3–5], represents a further, under-discussed factor that significantly contributes to the morbidity and mortality affecting PWID [6,7].

Several mechanisms, such as direct endothelial damage, bloodstream infections, immobilization induced by opioid intoxication and dehydration caused by nausea and vomiting, lead to the development of deep vein thrombosis (DVT) and pulmonary embolism in PWID, when the drug is injected into the proximal veins, such as the common femoral, iliac or axillary veins [8–10]. Injecting drugs is also linked to a higher risk of developing septic pulmonary emboli, with a mortality rate around 20% [11], and chronic complications, such as chronic venous insufficiency, and post-thrombotic syndrome. Furthermore, two studies conducted by Stein et al. and Cooke et al., in 2001 and 2006 showed that DVT among PWID leads to longer hospitalizations and higher healthcare costs [12,13].

However, scarce data is available on the prevalence, optimal management, and risk of long-term VTE complications in PWID. This contrasts sharply with the accumulating evidence on the epidemiology of acute VTE, its management, and its sequelae in other patient populations [14–17]. This systematic review and meta-analysis aims to summarize

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the available evidence on the risk of VTE and its complications among intravenous drug users.

2. Methods

2.1. Literature search and study selection

We conducted a systematic literature review of the risk of VTE and chronic venous disease among current or former PWID and vice versa, of the prevalence of intravenous drug users among VTE and chronic venous disease patients. Our electronic bibliography search of PubMed included randomized controlled trials, cohort studies, case-control studies, and patient surveys. No language restrictions were applied. Appendix I contains the complete list of the used search terms. The literature search was performed between October 2021 and January 2022. Initially, titles and abstracts were identified through a search query and screened independently by two reviewers (G.F. and M.S.); disagreements were solved by a third reviewer (S·B.). Then, three reviewers (G.F., M.S. and S·B.) independently assessed the full text of the selected articles in order to apply the inclusion and exclusion criteria. Selected reviews were screened for cross-references. Finally, the JBI manual for evidence synthesis critical appraisal tools were applied to assess the quality of research evidence of included observational studies [18].

2.2. Eligibility criteria

Studies were considered eligible if they fulfilled at least one of the following criteria: (i) reporting the prevalence of current or former intravenous drug users among patients with VTE or chronic venous disease; (ii) reporting the prevalence of VTE or chronic venous disease among current or former intravenous drug users. Case reports and small case series ($n < 10$) were excluded.

2.3. Study outcomes

The primary outcomes encompassed VTE events, defined as acute DVT of the lower or upper limb or the jugular vein, or pulmonary embolism. VTE diagnosis was established if documented in the patient's medical charts or confirmed by appropriate imaging methods: for DVT, we accepted diagnosis made by venography, sonography, and autopsy; for pulmonary embolism accepted diagnosis was by CT pulmonary angiogram, ventilation-perfusion scan, and autopsy. Considering the design of the study, information on the primary outcome was collected as reported prevalence among PWID. The secondary outcomes were (i) chronic venous disease prevalence among PWID; (ii) Intravenous drug users prevalence among patients presenting with VTE or chronic venous disease. Chronic venous disease was defined as any morphological and functional abnormalities of the venous system of long duration manifested either by symptoms or signs indicating the need for investigation or care; it included chronic venous insufficiency and post-thrombotic syndrome.

2.4. Statistical analysis

We calculated weighted and unweighted rates of the primary and secondary outcomes by applying a random-effect model [95% confidence interval (CI)]. We assessed (statistical) heterogeneity of exposure effects by calculating the I^2 statistic, which summarizes the amount of variance among studies beyond chance. Heterogeneity was defined as low ($I^2 < 25\%$), moderate ($I^2 = 25$–75%), or high ($I^2 > 75\%$). The presence of publication bias was evaluated by visually inspecting funnel plots (Figs. 1 and 2). Extracted data (including first author, year of publication, study design, number of study participants, sex, characteristics of the study population, screening method, and prevalence of the outcomes) are presented descriptively in the table charts.

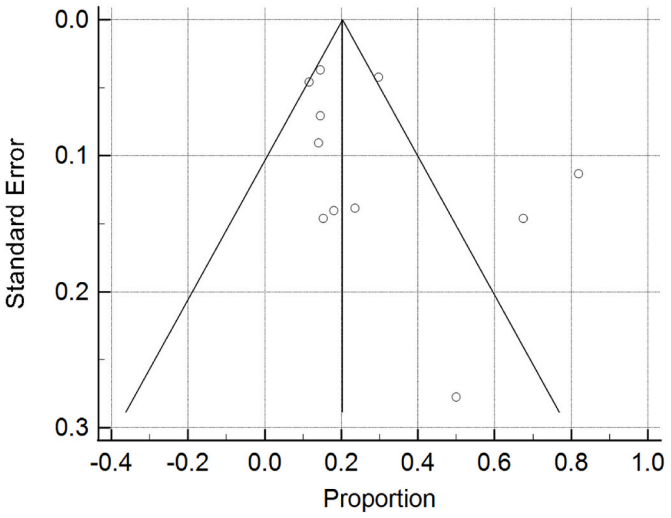

Fig. 1. Proportion of patients with venous thromboembolism among intravenous drug users: funnel plot.

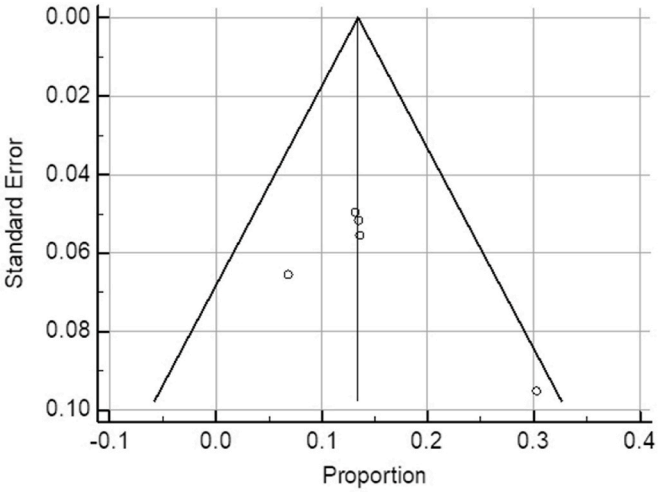

Fig. 2. Proportion of intravenous drug users among patients with venous thromboembolism: funnel plot.

3. Results

We identified 1074 records from the database and 10 through screening the cross-references. Title and abstract screening eliminated 1050 articles, leaving 34 for full-text evaluation. The PRISMA flowchart of study selection process is displayed in Fig. 3. Ultimately, 18 articles with a total of 7691 patients were included: 12 studies were retrospective, 4 were cross-sectional, and 2 were prospective. Study size ranged from 12 to 4333 patients. Sixteen studies including 7520 patients reported the sex of participants. Of these, 5069 patients (67%) were males. Patient age ranged from 19 to 68 years. Size, setting, and general characteristics of the studies are summarized in Table 1. Two authors independently appraised all 18 studies using the JBI checklist. Differences in the assessment were discussed and a consensus was made for each paper. Only four papers out of 18 met all the criteria of good quality research, as can be seen in the quality assessment table in Appendix II.

3.1. Prevalence of VTE among current or former intravenous drug users

The overall prevalence of VTE among intravenous drug users was 29% (95%CI: 19–40%, I^2 96%, n = 11 studies, n = 2377 patients, Fig. 4).

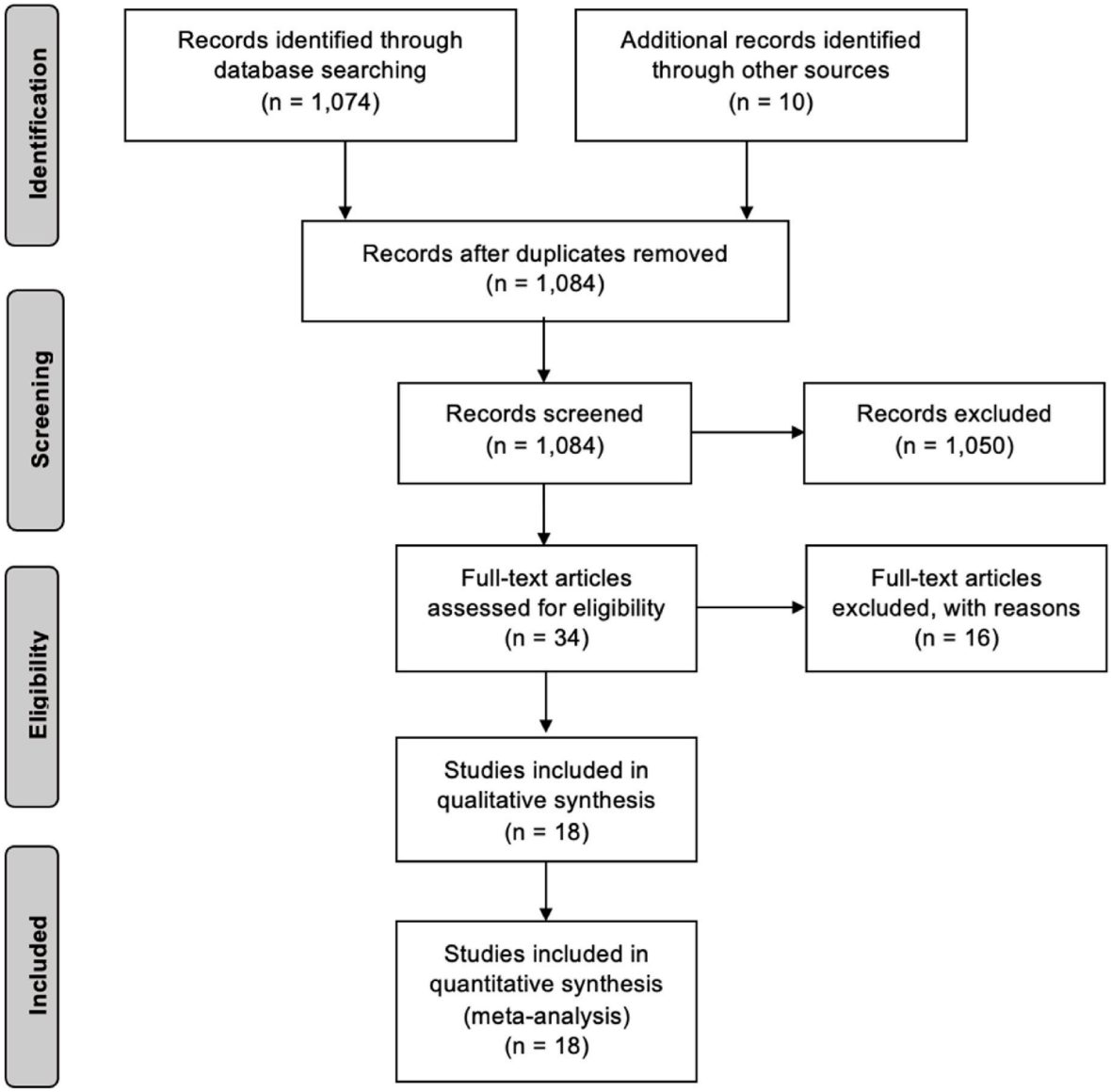

Fig. 3. Flowchart with included and excluded studies.

Nine studies reported rates of DVT, three studies reported rates of pulmonary embolism, and one study reported a prevalence of VTE, not discerning between DVT and pulmonary embolism. The diagnosis of DVT was established by compression and/or doppler ultrasound as a main diagnostic tool for DVT in five out of nine studies. Diagnosis of pulmonary embolism was based on clinical and CT scan findings as well as ventilation-perfusion scans in two out of four studies. In a total of six studies the VTE diagnosis was documented as reported in patient records, registry data, or ad hoc questionnaires. The overall duration of addiction among the patients ranged from 8 to 17 years (n = 8 studies, n = 1384 patients; Table 2). Six studies described the total duration of injective drug abuse; two studies duration of a drug abuse, not discerning between the routes of administration. Fig. 1 indicate that a publication bias cannot be excluded, as studies exhibiting lower VTE prevalence may have been underrepresented.

3.2. Prevalence of intravenous drug users among selected patients with VTE

The observed overall prevalence of intravenous drug users among selected VTE patients was 15% (95%CI: 10–20%, I^2 87%, n = 5 studies, n = 1442 patients, Fig. 5). Five studies reported rates of DVT and two studies reported rates of pulmonary embolism. Diagnosis of DVT was established with Doppler ultrasound in four out of five studies and discharge codes. In one study the diagnosis of VTE was based solely on the patients' medical records. Diagnosis of pulmonary embolism was made through ventilation-perfusion scan or CT pulmonary angiogram only in two studies, while one used additional data from the autopsy (Table 3) (see Fig. 6).

3.3. Chronic venous disease and intravenous drug use

Two studies, both conducted by Pieper et al., reported the prevalence of chronic venous disease among PWID: this ranged from 58% to 61% (n = 250 patients). Due to the limited number of studies, we did not perform any pooled analysis. No studies reporting the prevalence of intravenous drug users among patients diagnosed with chronic venous disease were identified.

4. Discussion

In this systematic review and meta-analysis of studies published

Table 1
Size, setting, and general characteristics of the included studies.

First author, Year	Study design	Age (median or range)	Men (%)	Study period	Country	Number of patients	Cohort
Rasmussen LD, 2010 [22]	retrospective	36.6	76	1995–2008	Denmark	4333	Danish HIV-infected patients with VTE diagnosis
Cornford CS, 2011 [6]	retrospective	34	73	2004–2009	United Kingdom	734	Patients receiving treatment for illicit opioid addiction
Abdar Esfahani M, 2014 [26]	cross sectional	18.8	59	2003–2013	Iran	403	Patients admitted to St. Alzahra Hospital in Isfahan
Liu HS, 2002 [40]	retrospective	68	46	1997–2000	Hong Kong	376	Chinese patients with VTE followed over four consecutive years
MacLeod CS, 2021 [41]	retrospective	37	59	2011–2018	United Kingdom	330	Patients admitted with limb related pathology attributable to intravenous drug use.
McColl MD,2000 [32]	retrospective	16–70	0	1993–1997	United Kingdom	322	Women with DVT or pulmonary embolism during admission
Syed FF, 2004 [39]	retrospective	62.8	58	1996	United Kingdom	223 (232 DVT episodes)	Patients with a lower-limb DVT during admission
Pieper B, 2001 [42]	cross sectional	45.8	51	2000	USA	204	PWID recruited from three methadone clinics
Coull AF, 2020 [23]	cross sectional	34.6	76	2008–2009	United Kingdom	200	PWID recruited from Drug Services
Cooke VA, 2006 [12]	retrospective	29 (IVDU) 51 (non-IVDU)	NA	2001–2002	United Kingdom	109	Patients self-presenting to the emergency department
Williams PG, 1997 [43]	retrospective	24	53	1991–1992	South Africa	86	Patients admitted for one or more of the following diagnostic categories: drug overdose or abuse, drug withdrawal, bacteremia, endocarditis, pyrexial illness, deep venous thrombosis, pulmonary embolism and pneumothorax.
Schulz S, 2002 [44]	prospective	31	63	1995–2000	Germany	77	PWID admitted with conspicuous clinical findings or symptoms in the inguinal region
Pieper B, 2006 [45]	cross sectional	45.8	49	2002–2003	USA	73	HIV positive patients recruited from an infectious disease clinic
Yegane RA, 2006 [46]	prospective	NA	NA	2002–2005	Iran	62	Patients admitted with symptoms related to injection sites and/or lower limbs edema
O'Donnel AE, 1988 [47]	retrospective	35	76	1985–1987	USA	51	51 PWID inpatients followed by pneumologist
Mohammadzadeh MA, 2007 [25]	retrospective	15–74	88	1996–2006	Iran	50	Patients consecutively admitted to an Iranian hospital with conspicuous clinical findings in the groin or cubital fossa
Behera A, 2003 [48]	retrospective	32.8	100	1996–2001	India	46	Male PWID with injection-related vascular complications
Kaiser M, 1997 [49]	retrospective	30.5	75	1994–1997	Germany	12	12 patients with 15 drug-related abscesses of the groin

DVT – deep venous thrombosis, IVDU – intravenous drug users, NA - not applicable, PE – pulmonary embolism, VTE – venous thromboembolism.

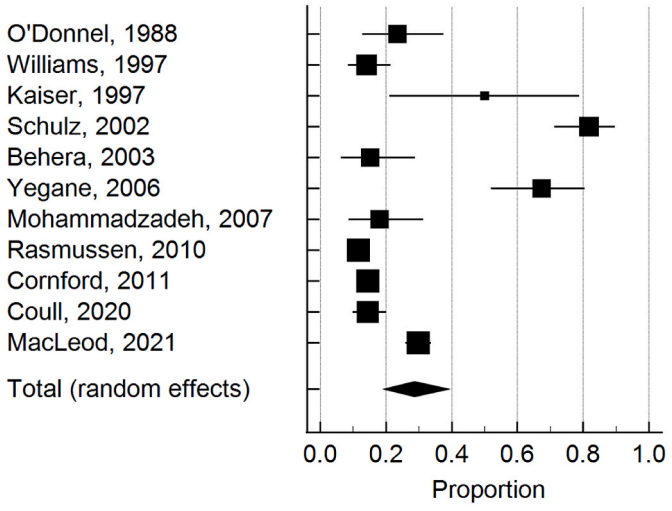

Fig. 4. Proportion of patients with venous thromboembolism among people who inject drugs.

between 1988 and 2021, we provided possibly the first comprehensive risk estimates of acute and late venous thromboembolic complications in PWID. These results, while preliminary, are of clinical relevance as they may serve to quantify the burden of VTE and post-thrombotic syndrome related to intravenous drug use, an addiction that currently affects up to 24 million users worldwide [1,2]. At the same time, they highlight the need for tailored therapeutic strategies for PWID, in whom a systematic screening for vein diseases and evaluation of therapeutic strategies should be considered on a routine basis. For instance, endovascular reconstruction with balloon angioplasty and stent placement represents a novel approach that has been showed to improve symptoms and functional capacity in patients with post-thrombotic syndrome [19].

The significantly high prevalence of VTE events among PWID, approximately 29%, indicates that intravenous drug exposure represents a strong risk factor for VTE. Of note, the median age of the subjects in most of the included studies did not exceed 40 years. These figures contrast with the expected prevalence of VTE in the general population, which has been estimated to be lower than 8% when no age limitations are applied and to be around 1.5% if one limits the observation age to 50 [20,21]. Even though some studies dated back to the heroin epidemic in the 1980s and 1990s, the more recent cohort from the past 15 years had a similarly high prevalence of DVT, pulmonary embolism, and chronic venous insufficiency among PWID [6,22–26]. Further supporting this data, we showed that the prevalence of intravenous drug use among VTE patients could be as high as 13% in some geographical regions with a high prevalence of drug use, such as the areas of Glasgow, Sheffield, or Liverpool [27–30]. The funnel plot displayed in Fig. 2 may indicate some degree of bias of the result, with a tendency not to report studies with a lower prevalence of PWID among patients presenting with VTE. Although the rates were high, they were similar for most of the considered studies with only one outlier (the study with the smallest sample).

Table 2
Study outcomes and measures among patients who inject drugs.

First author, year	Number of patients	Injective drugs exposure, n. (%)	Diagnostic Tool	Outcome	Outcome n (%)	Time of drug use in years, Mean (±SD) or range
Rasmussen LD, 2010 [22]	4333	482 (9)	VTE, defined as the first date an individual was registered with a diagnosis of DVT and/or PE in DNHR	VTE (DVT and/or PE)	56 (12)	NA
Cornford CS, 2011 [6]	734	342 (47)	Doppler US (82.4%); not specified (17.6%) Not specified (patient records) Not specified (patient records)	DVT PE CVD	102 (14) 4 16	8 (in average, before the DVT)
MacLeod CS, 2021 [41]	330 (558 Admissions)	558 (100)	Not specified (patient records)	DVT	166 (30)	NA
Pieper B, 2001 [42]	204	204 (100)	Clinical leg specialist assessment (CVD)	CVD	179 (88)	17 (±10)[a]
Coull AF, 2021 [23]	200	200 (100)	Interviewer-administered questionnaire in a private setting	DVT CVD	29 (15) 30 (15)	10 (±8)[a]
Williams PG, 1997 [43]	86 (121 admissions)	121 (100)	Doppler US or venography Isotope perfusion scan	DVT PE	15 (12) 2 (2)	NA
Schulz S, 2002 [44]	77	77 (100)	Doppler US	DVT	63 (81)	11 (average)[a]
Pieper B, 2006 [45]	73	46 (63)	Clinical leg assessment	CVD	28 (61)	17 (±10)[a]
O'Donnel AE, 1988 [47]	51	51 (100)	CT/clinical diagnosis	septic PE	12 (24)	NA
Yegane RA, 2006 [46]	46	46 (100)	Doppler US	DVT	31 (67)	6 (2–20)
Behera A, 2003 [48]	46	46 (100)	Not specified (probably Doppler US)	DVT	7 (15)	45 (2–11)[a]
Mohammadzadeh MA, 2007 [25]	50	50 (100)	Not specified (patient records)	DVT	9 (18)	76% of patients injected for 10 years or less[a]
Kaiser M, 1997 [49]	12	12 (100)	US or Doppler US, Phlebography	DVT	6 (50)	NA

CVD – chronic venous disease, DNHR – Danish National Hospital Registry, DVT – deep venous thrombosis, IVDU – intravenous drug use, NA - not applicable, PE – pulmonary embolism, SD – standard deviation, US – ultrasound, VTE – venous thromboembolism.
[a] Intravenous drug use only.

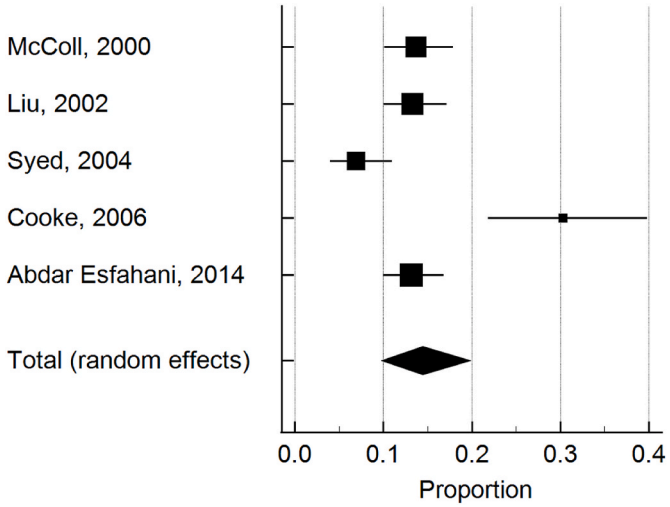

Fig. 5. Proportion of injecting drug exposure among patients with venous thromboembolism.

Intravenous drug use (although not considered a traditional risk factor for VTE) possibly promotes DVT through interference with all the three dimensions described in Virchow's triad: endothelial damage, hypercoagulability, and venous stasis. This condition reflects the vascular trauma caused by repeated injections, the possible prothrombotic role of the impurities in the substance itself, and physical inactivity during the induced stuporous state [31–33]. Other mechanisms might be involved, possibly similar to the procoagulant effect exerted by cocaine in the arterial system, such as vasoconstriction [34,35]. Moreover, the clinical presentation and course of DVT usually differ from that of the general population, being often accompanied by soft tissue infections, bacteremia, or septic embolism [9,36], and characterized by a higher prevalence of potentially prothrombotic viral diseases, such as hepatitis and HIV. As a result, PWID are hospitalized more frequently than patients who do not inject drugs and have a longer inpatient stay [12].

Such a high prevalence is even more remarkable when considering difficulties in screening, counseling, and managing intravenous drug users due to their low engagement in treatment and the stigmatization they suffer [12,37,38].

Besides reporting the higher prevalence of DVT in PWID compared to non-PWID, this work reveals the scarce evidence on the therapy and risk of DVT and its complications in people who inject drugs. Namely, no guidelines for the management and no standard anticoagulant therapy have been established, with most clinicians choosing either low-molecular-weight heparin or oral anticoagulation. Also, it may be difficult to distinguish between acute and chronic events in this patient group as their symptoms often overlap and present with other local complications. Consequently, we are still not able to precisely quantify the burden of post-thrombotic syndrome secondary to injecting drug use and correspondingly offer the optimal treatment.

The generalizability of these results is subject to certain limitations: first of all, a number of the analyzed studies were conducted in areas with a high prevalence of drug use and included patient samples presenting clinically conspicuous findings or analyzed only selected patients with vascular complications, potentially overestimating the prevalence of the disease. Some presented studies considered intravenous drug exposure as the only risk factor for VTE or investigated selected PWID patients with concomitant HIV infection. Another weakness is that all the included studies are observational and mostly retrospective.

The aforementioned limitations, however substantial, owe to the scant evidence concerning this disadvantaged group of patients that are often excluded from the studies [39]. Clinical history taking may be culturally sensitive and injective drug use may be omitted in the medical documentation available to retrospective researchers and thus could be easily missed and overall number underestimated if the study design does not specifically ask to heed the PWID. Our review included most of the existing research on the argument by minimizing the number of exclusion criteria. Taken together these factors may This have affected the results, possibly overestimating the intravenous drug use and/or VTE prevalence. Furthermore, the reported prevalence must be interpreted with caution in light of possible confounders and high heterogeneity of risk estimates across studies. Along with collecting and summarizing the current data about VTE prevalence, this review aims to

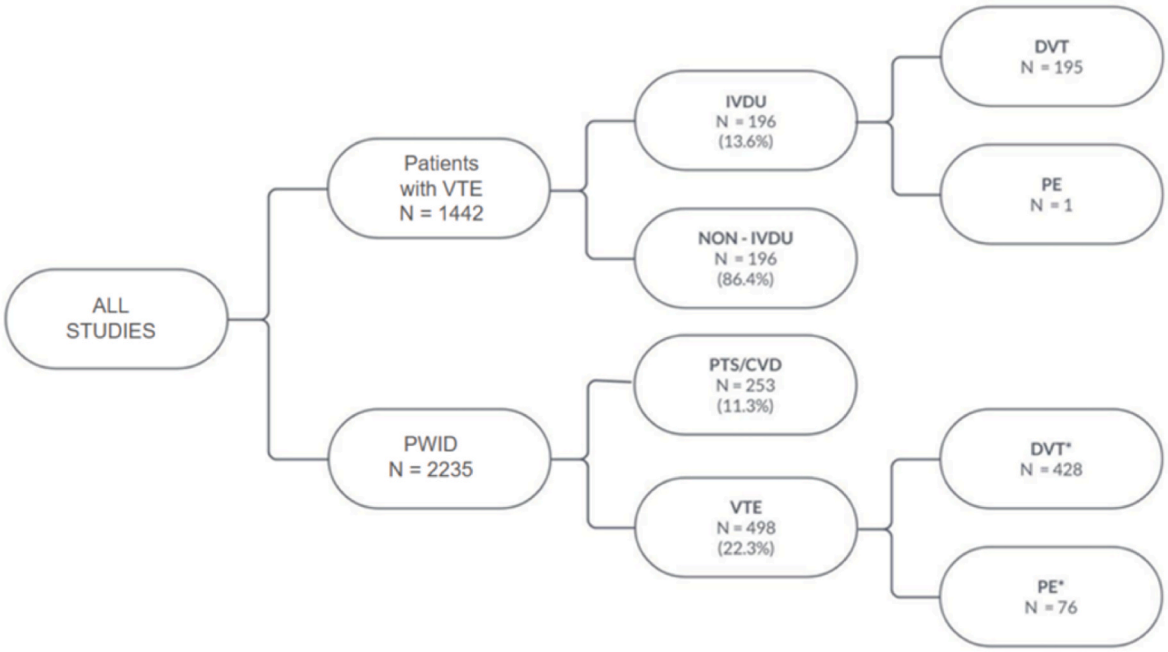

Fig. 6. Analysis stratification schema
Legend:
N: number of patients
VTE: venous thromboembolism
PWID: people who inject drugs
IVDU: intravenous drug use
CVD: chronic venous disease
DVT: deep venous thrombosis
PE: pulmonary embolism
PTS: post-thrombotic syndrome
*: events reported in Rasmussen et al., [2010] study are not included.

Table 3
Study outcomes and measures among patients with venous thromboembolism.

First author, year	Total patients	Diagnostic Tool	VTE	Injecting drug exposure, n (%)	PWID with DVT n.	PWID with PE n.
Abdar Esfahani M, 2014 [26]	403	Not specified (records of patients discharged with a DVT diagnosis)	DVT	53 (13)	53	NA
Liu HS, 2002 [40]	371	Doppler US (DVT); ventilation-perfusion scanning or CT or autopsy (PE)	DVT, PE	50 (13)	49	1
McColl MD,2001 [32]	322	US or Doppler US or contrast venography (DVT); ventilation-perfusion scan (PE)	DVT, PE	44 (13)	44	0
Syed FF, 2004 [39]	223 (232 DVT episodes)	Doppler US or venography or autopsy (7 cases with clinical criteria alone)	DVT	16 (11)	16	NA
Cooke VA, 2006 [12]	109	Doppler US	DVT	33 (30)	33	NA

CT – computed tomography, CVD – chronic venous disease, DVT – deep venous thrombosis, IVDU – intravenous drug users, NA - not applicable, PE – pulmonary embolism, US – ultrasound, VTE – venous thromboembolism.

raise awareness of the paucity of good-quality studies and consequently the importance of further research that would include this fragile group of patients.

5. Conclusions

In conclusion, VTE appears to be at least ten times more frequent in intravenous drug users compared to the general population of similar age. The vast majority of intravenous drug users presented with chronic venous insufficiency, irrespective of their initial DVT status. National programs for PWID should also focus on early and late VTE-associated complications.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix I

Literature Search

"Venous Thromb*" OR "Vein Thromb*" OR "Pulmonary Embolism" OR "Postthrombotic Syndrome" OR "Post-thrombotic Syndrome" OR "Chronic thromboembolic pulmonary hypertension" OR "CTEPH" OR "VTE" OR "PTS" OR "DVT" OR "deep vein thrombosis" OR "deep venous thrombosis" OR "anticoagulation" OR "anticoagulation" OR "anticoagul*" OR "vein occlusion" OR "venous occlusion"

AND

"Substance Abuse, Intravenous" OR "Substance-Related Disorders" OR "intravenous drug" OR "drug abuse*" OR "drug user" OR "Heroin" OR "Heroin Dependence" OR "illicit drug" OR "street drug" OR "injecting drug user" OR "injection drug user" OR "drug addiction" OR "drug depend" OR "injecting opioids"

Appendix II

Quality assessment

Author, list	ITEM ASSESSED									
	Cohort studies									
Rasmussen, 2010	Cohort critical appraisal tool could not be applied as two cohorts are HIV + and HIV- and PWID are just a substrata of patients									
	Analytical cross - sectional studies									
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**		
Pieper B, 2006	1	1	1	1	1	1	1	1		
Pieper B, 2001	1	1	1	1	1	1	1	1		
Coull AF, 2020	1	1	1	0	1	1	0	1		
	Prevalence studies									
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	
Abdar Esfahani M, 2014	1	1	1	1	1	0	0	1	NA	
Liu HS, 2002	1	1	1	1	1	1	1	1	NA	
MacLeod CS, 2021	1	1	1	1	1	0	0	1	NA	
McColl MD,2000	1	1	1	1	1	1	1	1	NA	
Syed FF, 2004	1	1	1	1	1	1	1	1	NA	
Cooke VA, 2006	1	1	0	0	0	1	1	0	NA	
Williams PG, 1997	1	1	0	1	1	1	1	0	NA	
Schulz S, 2002	1	1	0	1	1	1	1	0	NA	
Yegane RA, 2006	1	1	0	0	1	1	1	0	NA	
O'Donnel AE, 1988	0	1	0	1	1	0	0	0	NA	
Behera A, 2003	1	1	0	1	1	0	0	0	NA	
Mohammadzadeh MA, 2007	1	1	0	1	1	0	0	0	NA	
Cornford, 2011	Prevalence studies appraisal tool could not be applied as intravenous drug use is only described as a risk factor in terms of incidence rate ratio, no prevalence is reported									
	Case series									
	Q1	**Q2**	**Q3**	**Q4**	**Q5**	**Q6**	**Q7**	**Q8**	**Q9**	**Q10**
Kaiser M, 1997	0	1	1	1	1	1	0	1	0	1

Q – question, PWID – people who inject drugs. NA – not applicable.

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