



# A Systematic Review and Meta-Analysis of Studies of Defibrotide Prophylaxis for Veno-Occlusive Disease/Sinusoidal Obstruction Syndrome

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## Abstract

**Background and Objectives** Defibrotide is approved to treat severe veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) after haematopoietic cell transplantation in patients aged > 1 month in the European Union and for VOD/SOS with renal/pulmonary dysfunction post-haematopoietic cell transplantation in the United States. This meta-analysis estimated the incidence and risk of VOD/SOS after intravenous defibrotide prophylaxis using the published literature.

**Methods** PubMed, Embase and Web of Science were searched through 30 November 2021 for defibrotide studies in VOD/SOS “prevention” or “prophylaxis,” excluding phase I studies, case reports, studies with fewer than ten patients and reviews.

**Results** The search identified 733 records; 24 met inclusion criteria, of which 20 ( $N = 3005$ ) evaluated intravenous defibrotide for VOD/SOS prophylaxis. Overall VOD/SOS incidence with intravenous defibrotide was 5%, with incidences of 5% in adults and 8% in paediatric patients. In eight studies with data on intravenous defibrotide prophylaxis vs controls (e.g. heparin, no prophylaxis), VOD/SOS incidence in controls was 16%. The risk ratio for developing VOD/SOS with defibrotide prophylaxis vs controls was 0.30 (95% confidence interval 0.12–0.71;  $p = 0.006$ ).

**Conclusions** This analysis suggests a low incidence of VOD/SOS following intravenous defibrotide prophylaxis, regardless of age group, and a lower relative risk for VOD/SOS with defibrotide prophylaxis vs controls in patient populations at high risk of VOD/SOS.

## Key Points

This meta-analysis estimated the risk of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) after intravenous defibrotide prophylaxis.

Twenty identified studies evaluated intravenous defibrotide for VOD/SOS prophylaxis.

VOD/SOS incidence was 16% in controls and 5% with intravenous defibrotide prophylaxis.

The risk ratio for developing VOD/SOS with defibrotide prophylaxis vs controls was 0.30.

## 1 Introduction

Hepatic veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) is a rare, potentially life-threatening complication of haematopoietic cell transplantation (HCT) conditioning that may also occur after chemotherapy alone [1, 2]. Sustained exposure to chemotherapy and HCT conditioning regimens results in sinusoidal endothelial cell (EC) activation and damage, leading to a procoagulant and proinflammatory state [3, 4]. This EC dysfunction is hypothesised to contribute to hepatic VOD/SOS [1]. The incidence of VOD/SOS following HCT ranges from <5% with autologous HCT to approximately 10–15% with allogeneic HCT based on the presence of risk factors and use of a myeloablative conditioning regimen [5, 6]. Patient-related and transplantation-related risk factors for developing VOD/SOS include older and very young age, lower performance status, pre-existing liver disease, type of conditioning regimen, and type and number of transplants [5, 7, 8].

Defibrotide is a polydisperse mixture of predominantly single-stranded polydeoxyribonucleotide sodium salts [9]. In vitro, defibrotide has been shown to reduce EC activation,

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promote EC-mediated fibrinolysis and protect ECs from damage caused by chemotherapy [4, 10]. Defibrotide is approved for the treatment of severe hepatic VOD/SOS after HCT in patients older than 1 month of age in the European Union and for the treatment of adult and paediatric patients with hepatic VOD/SOS with renal or pulmonary dysfunction after HCT in the United States [9, 11]. The recommended dose for the treatment of VOD/SOS is 6.25 mg/kg every 6 hours (25 mg/kg/day), given as a 2-hour intravenous (IV) infusion [9, 11].

Several studies have found that defibrotide prophylaxis can reduce the incidence of VOD/SOS in high-risk patients [12–14]. Among these, a previous systematic review from Zhang et al. examining 13 studies from 2002 to 2010 showed an overall mean incidence of VOD/SOS after HCT of 4.7% (95% confidence interval [CI] 3.3–6.1) in patients receiving defibrotide prophylaxis vs 13.7% (95% CI 13.3–14.1;  $p < 0.005$ ) in patients without defibrotide prophylaxis [14]. Among controlled trials, the relative risk of VOD/SOS was lower with defibrotide prophylaxis (risk ratio [RR] 0.47, 95% CI 0.31–0.73) [14].

In contrast, a 2015 Cochrane systematic review concluded that there was insufficient evidence to indicate a reduction in the incidence of VOD/SOS or mortality with defibrotide prophylaxis; however, only one randomised controlled defibrotide trial was analysed and the authors acknowledged further evaluation was needed through high-quality, randomised controlled trials [15]. An ongoing phase III, prospective study (ClinicalTrials.gov Identifier: NCT02851407) of defibrotide for VOD/SOS prophylaxis recently stopped enrolment after meeting the protocol-defined criteria for futility, suggesting a low probability of meeting the primary endpoint of demonstrating a significant 30-day VOD/SOS-free survival difference with the sample size estimates used; analyses are ongoing and results are not yet reported [16].

In addition to patient-related and transplantation-related risk factors of VOD/SOS, some approved antitumour therapies, such as gemtuzumab ozogamicin and inotuzumab ozogamicin, have been shown to contribute to an increased risk of VOD/SOS [17]. Given the variety of factors that may place a patient at high risk of VOD/SOS, there is a need to better understand the utility of IV defibrotide prophylaxis for VOD/SOS post-HCT. The goal of this systematic literature review and meta-analysis was to provide a current estimate of the overall incidence and risk of developing VOD/SOS after IV defibrotide prophylaxis using the published literature, as an update to the Zhang et al. analysis [14].

## 2 Methods

### 2.1 Search Strategy and Selection Criteria

A systematic search of PubMed (MEDLINE), ClinicalTrials.gov, Google Scholar, Web of Science and Embase,

which was used to search for abstracts (e.g. EBMT, Blood and Marrow Transplantation, American Society for Hematology and European Hematology Association) from database inception through 30 November 2021, was performed per a prespecified and clearly defined protocol based on Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines. The search terms for all databases were “prevention” or “prophylaxis” of defibrotide in VOD/SOS; search fields were limited to the title or abstract and to articles published in the English language. Duplicate results from these searches were removed.

Defibrotide studies of adult or paediatric patients, including controlled trials, observational or retrospective studies, retrospective or post hoc analyses, and case reports with ten or more patients were eligible for inclusion in the meta-analysis. Phase I studies, case reports, studies with fewer than ten patients and review articles were excluded.

### 2.2 Data Analysis

The full text of the selected studies and conference abstracts were assessed for study design, sample size, dose, route of administration, treatment duration and control comparators. Publications were evaluated for the presence of data on endpoints of interest, which included incidence of VOD/SOS, incidence of severe/very severe VOD/SOS, overall adverse events, bleeding and/or haemorrhagic events and site of bleeding (if reported).

All studies with relevant data were included in the meta-analysis. Pooled VOD/SOS incidence estimates with 95% CIs were calculated using a random-effects model after Freeman–Tukey double arcsine transformation. The Mantel–Haenszel method and random-effects modelling (Stata 14.2 software) were used for overall incidence rates and RRs, respectively. Interstudy heterogeneity was assessed with Cochrane  $Q$  and  $I^2$  tests (with significant heterogeneity indicated by  $p < 0.10$  or  $I^2 \geq 50\%$ ). For analyses by patient age, only studies specifying adult or paediatric data were included. All reported  $p$ -values were nominal. Safety results were not pooled because of differences in adverse event reporting among studies. The quality of the data was assessed based on study design parameters, such as retrospective vs prospective design, number of sites and size of the study population.

## 3 Results

### 3.1 Literature Search Results

A total of 733 records were identified in the search (Fig. 1), and 24 met inclusion criteria for the analysis. Of

these 24 studies, 20 ( $N = 3005$ ) reported on IV defibrotide for VOD/SOS prophylaxis, including eight adult studies, six paediatric studies and six studies with both age groups or in which age was not specified. Of these 20 studies, 14 reported on VOD/SOS severity based on the investigator’s assessment. Four of the studies did not specify the mode by which defibrotide was administered; therefore, these studies were not included in the subanalysis by dose. This analysis included prospective cohort studies and case series; retrospective case series, studies and chart reviews; and phase II and III open-label, randomised controlled studies. Details pertaining to data quality are included in Table 1, which summarises key features of each study’s design.

### 3.2 Incidence of VOD/SOS

With IV defibrotide prophylaxis, the overall incidence of VOD/SOS among the 20 studies was 5% (95% CI 3–8;  $I^2 = 75.85\%$ ;  $p < 0.01$ ; Fig. 2A). In studies reporting results in either adult or paediatric patients, the incidences of VOD/SOS were 5% (95% CI 3–8;  $I^2 = 36.16\%$ ;  $p = 0.13$ ) and 8% (95% CI 6–11;  $I^2 = 25.25\%$ ;  $p = 0.24$ ), respectively (Fig. 3). Among eight studies using IV defibrotide prophylaxis that also included data from control groups (e.g. heparin or no prophylaxis), the incidence of VOD/SOS with control treatment was 16% (95% CI 7–28). The RR for developing VOD/SOS with defibrotide prophylaxis vs control was 0.30 (95% CI 0.12–0.71;  $p = 0.006$ ;  $I^2 = 75\%$ ; Fig. 4).

The overall incidence of severe/very severe VOD/SOS with IV defibrotide prophylaxis was 2% (95% CI 0–4;  $I^2 = 69.46\%$ ;  $p < 0.01$ ; Fig. 2B) in the 14 studies reporting disease severity based on the investigator’s assessment. In the four studies that reported data from control groups, the incidence of severe/very severe VOD/SOS with control treatment was 8% (95% CI 2–15); the RR for developing severe/very severe VOD/SOS with

defibrotide prophylaxis vs control was 0.59 (95% CI 0.31–1.14;  $p = 0.12$ ).

### 3.3 Safety

While safety data were not pooled because of differences in reporting, defibrotide safety results in individual studies were generally consistent with the known safety profile of defibrotide in the prophylactic setting (Table 2). Among studies that reported bleeding, the largest study in adults ( $N = 63$ ) described grade 2 or 3 bleeding events in 22% of those receiving IV defibrotide prophylaxis [18]. Similarly, the largest paediatric study ( $N = 356$ ) reported a cumulative haemorrhage incidence of 22% for those receiving IV defibrotide prophylaxis (and 21% for controls) [12].

## 4 Discussion

VOD/SOS is a life-threatening complication of HCT. A number of factors may place a patient at high risk of developing VOD/SOS, including age, primary disease, type of conditioning regimen, and type and number of HCTs [5, 8, 17]. In addition, exposure to some antitumor agents, such as gemtuzumab ozogamicin and inotuzumab ozogamicin, has also been shown to increase the risk of VOD/SOS [17]. Thus, there is a medical need for therapies that could reduce the risk of VOD/SOS. In this meta-analysis of defibrotide use for the prevention of VOD/SOS, the overall incidence of VOD/SOS following prophylaxis with IV defibrotide was low (at 5%) and was comparable in adults (5%) and in paediatric patients (8%). There was a lower relative risk of developing VOD/SOS with defibrotide vs controls such as heparin or no prophylaxis. Similarly, the incidence of severe/very severe VOD/SOS with IV defibrotide prophylaxis was low (at 2%), and the relative risk of VOD/SOS was lower with defibrotide vs control treatment.

**Fig. 1** Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram of studies included and excluded. PK/PD pharmacokinetic/pharmacodynamic, VOD/SOS veno-occlusive disease/sinusoidal obstruction syndrome

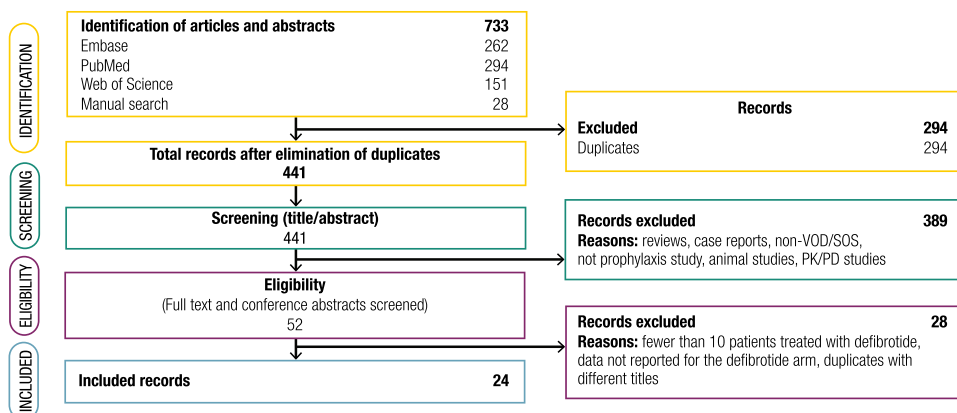


Table 1 Summary of studies included in the meta-analysis

Authors, year	Study design	Control	N	Patient population	VOD/SOS diagnostic criteria used	Route of administration	Total dose per day
Antmen et al., 2019 [24]	Prospective cohort study	NA	214	Paediatric patients undergoing HCT	Seattle criteria	IV	25 mg/kg
Bonini et al., 2010 [25]	Case series	NA	46	Adults undergoing allo-HCT	Baltimore criteria	IV	10 mg/kg
Bonnin et al., 2016 [26]	Retrospective case series	NA	44	Adults at high risk of developing VOD/SOS	Modified Baltimore criteria	IV	25 mg/kg
Calore et al., 2015 [27]	Prospective cohort study	NA <sup>a</sup>	58	Paediatric patients undergoing HCT	Seattle/Baltimore criteria	IV	NR
Cappelli et al., 2009 [28]	Case series	NA	57	Paediatric patients undergoing HCT for beta thalassaemia	Seattle criteria	Oral	10–40 mg/kg
Chalandon et al., 2017 [13]	Retrospective study	No prophylaxis	237	Patients undergoing HCT for haematologic disease	Baltimore criteria	IV	800–2400 mg
Corbacioglu et al., 2006 [29]	Retrospective study	No prophylaxis	20	Paediatric patients with infantile osteopetrosis	Seattle criteria	IV	Median of 40 mg/kg
Corbacioglu et al., 2012 [12]	Phase III, open-label, randomised, controlled study	No prophylaxis	356	Patients < 18 years of age undergoing MAC before HCT with $\geq 1$ risk factor for VOD/SOS based on modified Seattle criteria	Presence of $\geq 2$ of the following: bilirubin > 34 $\mu\text{mol/L}$ , hepatomegaly, ascites, unexplained weight gain >5% from baseline	IV	25 mg/kg
Dignan et al., 2007 [30]	Retrospective study	NA	58	Adults undergoing HCT	Baltimore criteria	IV	10 mg/kg
Giglio et al., 2019 [31]	Case series	NA	11	Adults undergoing HCT	2016 EBMT criteria	IV	25 mg/kg
Gray et al., 2008 [32]	Retrospective case series	NA	92	Paediatric patients who received high-dose chemotherapy and HCT	Baltimore criteria	IV	20 mg/kg
Hasenkamp et al., 2004 [33]	Case series	Heparin	60	High-risk patients <sup>b</sup> undergoing an HCT with busulfan-containing conditioning regimens	NR	IV	800 mg
Joshi et al., 2002 [34]	Prospective case series	NA	57	Adult and paediatric patients with $\geq 2$ risk factors for VOD/SOS	Baltimore criteria	Oral	20 mg/kg
Kikuta et al., 2018 [35]	Phase II, multicentre, open-label, randomised, controlled study	No prophylaxis	50	Paediatric and adult patients undergoing MAC before allo-HCT with $\geq 1$ risk factor for VOD/SOS	Modified Seattle criteria plus > 5% weight gain	IV	25 mg/kg
Milone et al., 2008 [36]	Case series	NA <sup>c</sup>	120	Patients <sup>b</sup> undergoing HCT for haematologic disease	Seattle criteria plus bilirubin > 2.5 mg/dL	IV	600 mg
Milone et al., 2014 [37]	Case series	No prophylaxis	107	Adults with ALL undergoing MAC before allo-HCT	Baltimore criteria	Oral	600–800 mg

**Table 1** (continued)

Authors, year	Study design	Control	N	Patient population	VOD/SOS diagnostic criteria used	Route of administration	Total dose per day
Mohy et al., 2021 [38]	Prospective registry	NA	76	Patients at high risk of VOD/SOS after primarily allo-HCT	Investigator's discretion using classical/standard criteria	IV	NR (median dose was 25 mg/kg)
Pasqualini et al., 2016 [39]	Retrospective chart review	NA	56	Paediatric patients with high-risk neuroblastoma treated with busulfan-melphalan	Modified Seattle criteria	NR	NR
Picod et al., 2018 [18]	Retrospective chart review	NA	63	Adults at high risk of developing VOD/SOS undergoing allo-HCT	2016 EBMT criteria	IV	25 mg/kg
Qureshi et al., 2008 [40]	Prospective case series with historic case control	No prophylaxis	103	Paediatric patients undergoing HCT	Modified Seattle criteria	IV	20 mg/kg
Roh et al., 2020 [41]	Retrospective chart review	No prophylaxis	147	Paediatric patients undergoing HCT	2018 EBMT criteria	IV	12.5 mg/kg
Soyer et al., 2020 [6]	Retrospective chart review	No defibrotide	1153	Patients undergoing allo-HCT	Baltimore criteria	IV	17.5 mg/kg
Tekgunduz et al., 2012 [42]	Retrospective chart review	Standard prophylaxis	87	Adults undergoing HCT for haematologic disease	Seattle criteria	IV	10 mg/kg
Wass et al., 2018 [43]	Retrospective chart review	NA	10	Paediatric patients undergoing HCT	Seattle criteria	IV	25 mg/kg

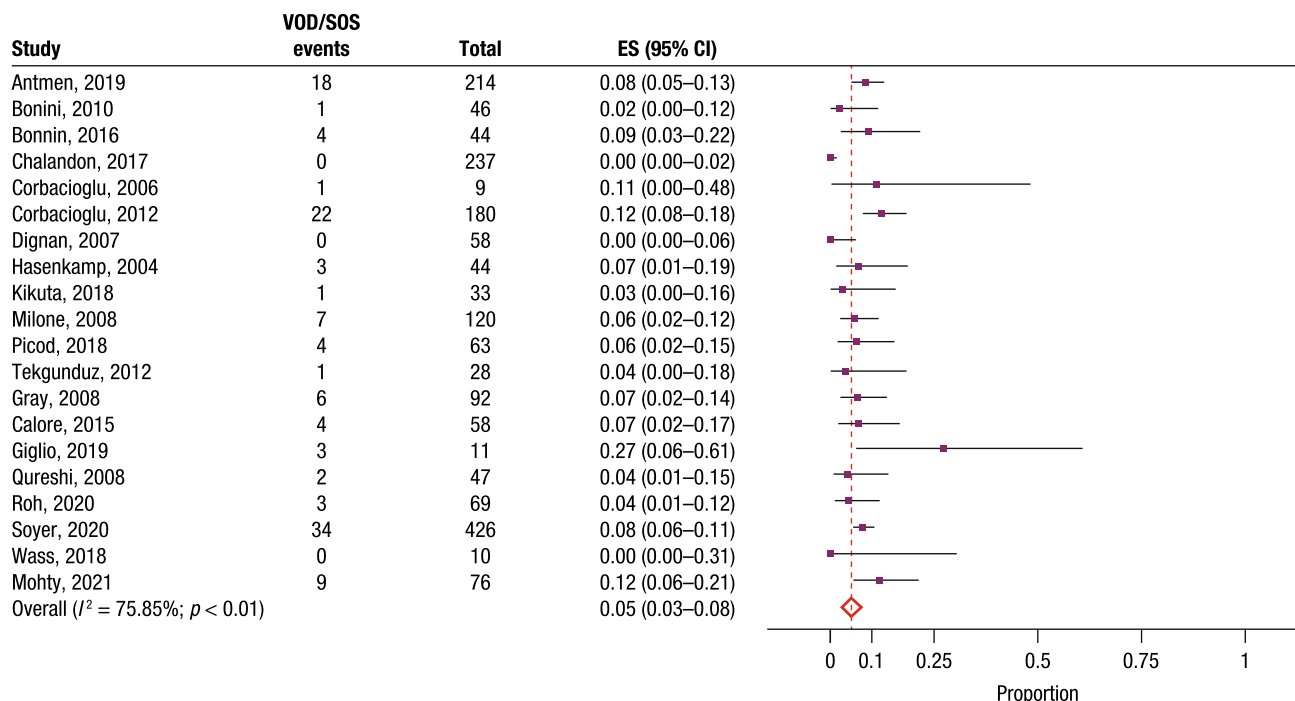
ALL acute lymphocytic leukaemia, *allo* allogeneic, *HCT* haematopoietic cell transplantation, *IV* intravenous, *MAC* myeloablative conditioning, *NA* not applicable, *NR* not reported, *VOD/SOS* veno-occlusive disease/sinusoidal obstruction syndrome

<sup>a</sup>This study included a heparin-treated group that was not considered in this analysis because the patients in the group had a low risk of VOD/SOS

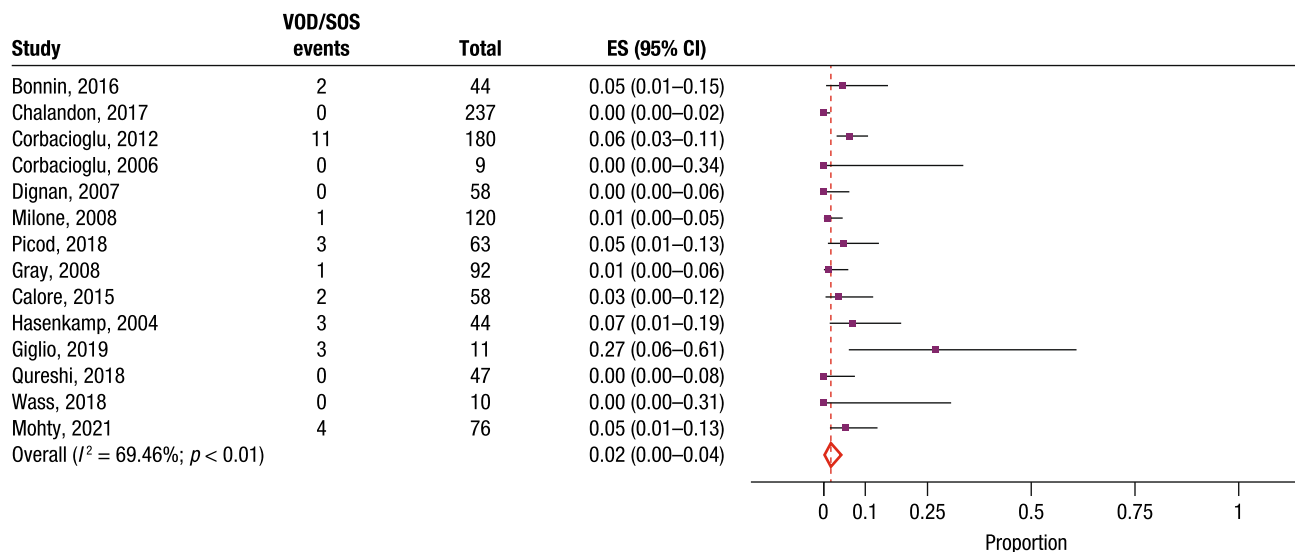
<sup>b</sup>Age was not specified

<sup>c</sup>The text of this abstract mentions comparison to a heparin group (*N* = 78), but data are not reported for that group

## A. All VOD/SOS



## B. Severe/very severe VOD/SOS

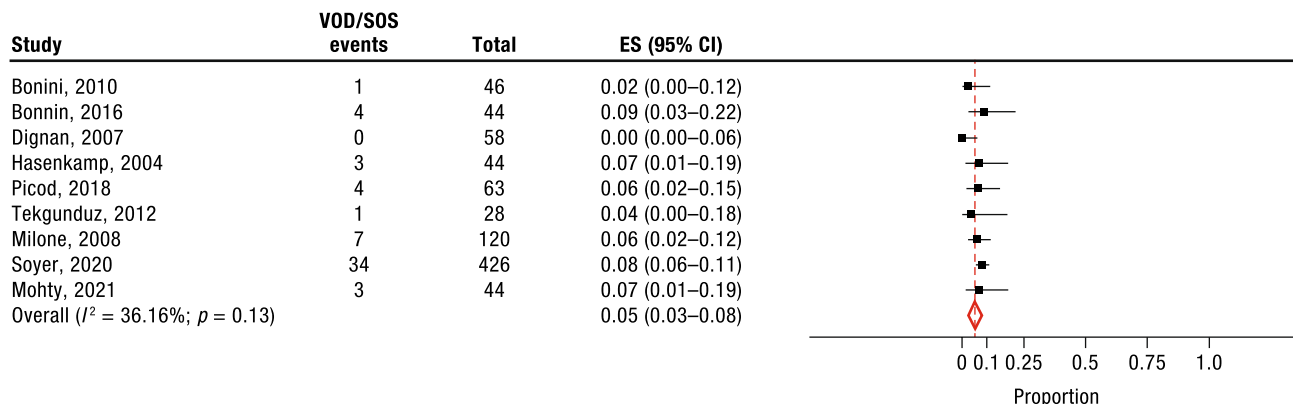


**Fig. 2** Incidence of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) with intravenous (IV) defibrotide prophylaxis [6, 12, 13, 18, 24–27, 29–33, 35, 36, 38, 40–43]. *CI* confidence interval, *ES* effect size

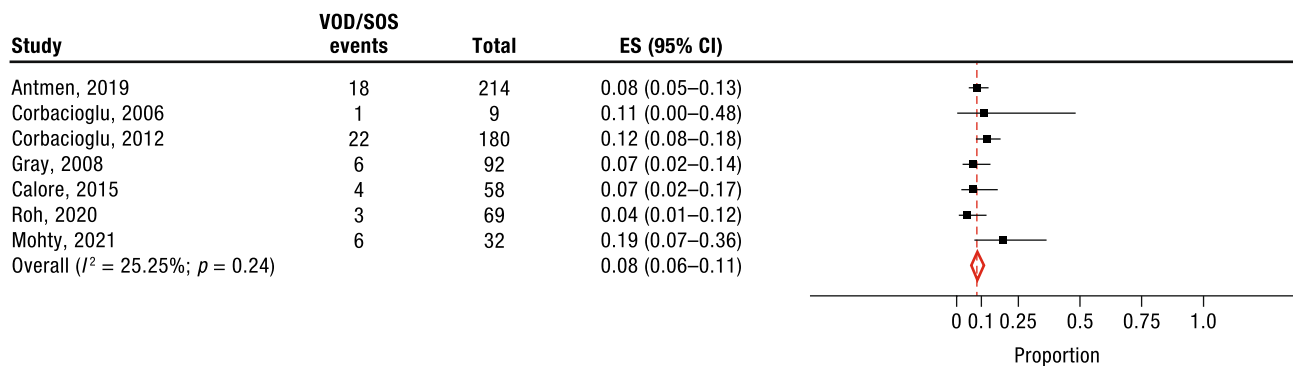
Many of the studies included in this meta-analysis specified the inclusion of patients at high risk for developing VOD/SOS and, thus, with a potential need for VOD/SOS prophylaxis. High risk of VOD/SOS was defined in a variety of ways across the publications but was generally based upon patient-related factors (e.g. primary disease) or HCT-related factors (e.g. conditioning regimen or transplant type). For example, the randomised controlled phase III study by Corbacioglu et al. included patients with one or more of

the following risk factors for VOD/SOS: pre-existing liver disease; second myeloablative HCT; allogeneic HCT for leukaemia beyond the second relapse; conditioning with busulfan and melphalan; previous treatment with gemtuzumab or zoledronic acid; and diagnoses of inherited haemophagocytic lymphohistiocytosis, adrenoleukodystrophy or osteopetrosis [12]. VOD/SOS was generally diagnosed and graded using Baltimore or modified Seattle criteria. These criteria utilise the presence of hyperbilirubinaemia, ascites, hepatomegaly

**A. Adult patients**

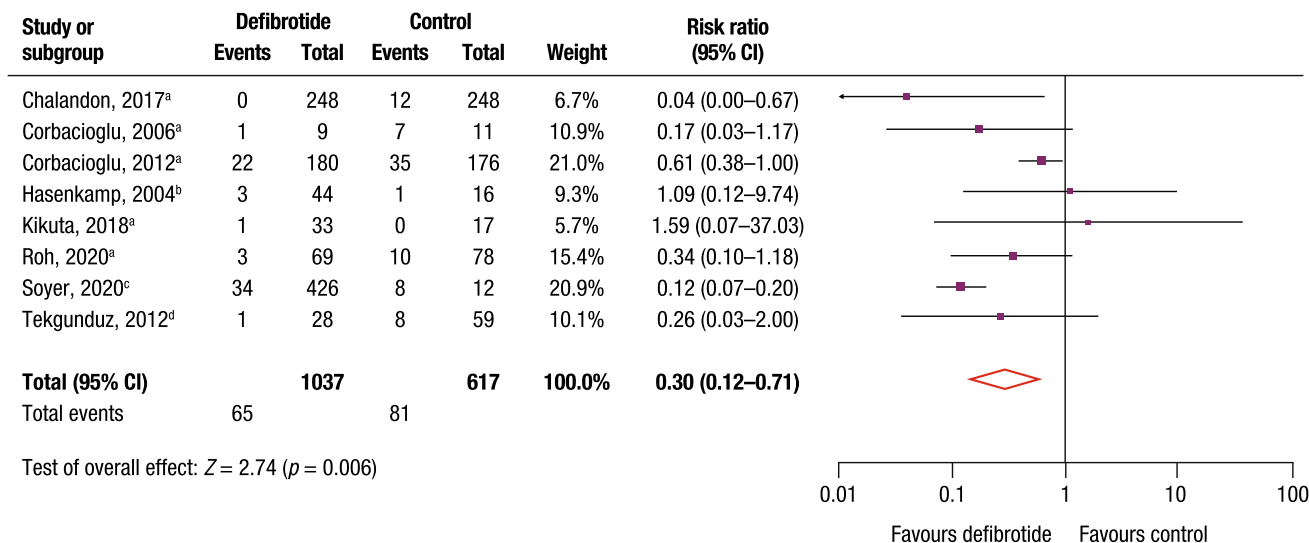


**B. Paediatric patients**



**Fig. 3** Incidence of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) with intravenous (IV) defibrotide prophylaxis in adult (A) and paediatric (B) patients [6, 12, 18, 24–27, 29, 30, 32,

33, 36, 38, 41, 42]. *CI* confidence interval, *ES* effect size. Five studies with IV defibrotide prophylaxis included patients of both age groups or did not specify age



**Fig. 4** Risk ratio of veno-occlusive disease/sinusoidal obstruction syndrome (VOD/SOS) vs controls in intravenous (IV) defibrotide prophylaxis studies that included a control arm [6, 12, 13, 29, 33, 35,

41, 42] *CI* confidence interval. Note: Weights are from the random-effects analysis. <sup>a</sup>Control was no prophylaxis. <sup>b</sup>Control was heparin. <sup>c</sup>Control was without defibrotide. <sup>d</sup>Control was standard of care

Table 2 Summary of reported adverse events in the studies included in the analysis

Authors, year	Control	Bleeding	Haemorrhage	Other AEs
Antmen et al., 2019 [24]	NA	NR	NR	No serious AEs were observed
Bonini et al., 2010 [25]	NA	NR	None	NR
Bonnin et al., 2016 [26]	NA	8 patients had bleeding events <sup>a</sup>	2 patients <sup>a</sup>	NR
Calore et al., 2015 [27]	None	None	None	Defibrotide arm had a lower incidence of hepatotoxicity than controls; no deaths due to VOD/SOS were reported <sup>b</sup>
Cappelli et al., 2009 [28]	NA	No defibrotide-related events	None	No AEs considered probably related to defibrotide were observed
Corbacioglu et al., 2006 [29]	No prophylaxis	NR	NR	No AEs were observed; defibrotide did not influence incidence of infectious complications or GvHD
Corbacioglu et al., 2012 [12]	No prophylaxis	NR	Cumulative incidence of haemorrhage was similar between arms (22% with defibrotide and 21% with control; $p = 0.8176$ )	207 serious AEs were reported in 108 patients in the defibrotide group (and 231 in 103 control patients) Grade 5 infections and infestations occurred in 3% of the defibrotide arm and 6% of the control arm
Dignan et al., 2007 [30]	NA	NR	No defibrotide-related events	No discontinuations were reported
Giglio et al., 2019 [31]	NA	2 non-severe GI bleeding events <sup>a</sup> requiring temporary discontinuation	NR	4 patients developed grade 2–4 acute GvHD; no TA-TMA was reported
Gray et al., 2008 [32]	NA	NR	No defibrotide-related events	NR
Hasenkamp et al., 2004 [33]	Heparin prophylaxis	No defibrotide-related events	No defibrotide-related events	No serious AEs were attributed to defibrotide
Joshi et al., 2002 [34]	NA	No bleeding or other AEs	No bleeding or other AEs	No other AEs
Kikuta et al., 2018 [35]	No prophylaxis	NR	Cumulative incidence of haemorrhage was not significantly different between groups (39% with defibrotide and 53% with control)	Overall AE profiles were similar between groups
Mohy et al., 2021 [38]	NA	Bleeding in 4 out of 76 patients	NR	Serious AEs occurred in 24% of the defibrotide arm and 12% of controls
Pasqualini et al., 2016 [39]	NA	NR	2 intra-alveolar haemorrhages <sup>a</sup>	NR; safety of defibrotide in real-world setting was consistent with the known safety profile
Picod et al., 2018 [18]	NA	Bleeding occurred in 22% of patients; defibrotide prophylaxis was discontinued in 11% of patients; 6% because of bleeding and 5% because of a need for antithrombotic therapy <sup>a</sup>	None	NR
Roh et al., 2020 [41]	No prophylaxis	5 bleeding events occurred in the defibrotide group; 15 bleeding events occurred in the control group Upper GI bleeding occurred in 16% of the defibrotide group and 26% of the control group	2 haemorrhagic events occurred in the control group	Epistaxis was the most common event (30% in the defibrotide group and 39% in the control group)



Table 2 (continued)

Authors, year	Control	Bleeding	Haemorrhage	Other AEs
Wass et al., 2018 [43]	NA	No defibrotide-related events	1 bleeding event was reported: a nose bleed likely related to nasogastric tube placement	None

Note: Chalandon 2017 [13], Milone 2008 [36], Milone 2014 [37], Qureshi 2008 [40], Soyer 2020 [6] and Tekgunduz 2012 [42] were not included in the table because they did not report specific AE data

AE adverse event, GI gastrointestinal, GVHD graft-vs-host disease, NA not applicable, NR not reported, TA-TMA transplant-associated thrombotic microangiopathy, VOD/SOS veno-occlusive disease/sinusoidal obstruction syndrome

<sup>a</sup>It is unclear from the publication if these events were deemed to be defibrotide related

<sup>b</sup>Data from the heparin arm were not included in the analysis

and weight gain as the primary basis for diagnosis [7, 19]. Use of VOD/SOS diagnostic and severity grading criteria in the studies in this meta-analysis is reasonable, given the time at which the studies were conducted. As diagnostic and grading criteria have evolved to include more sensitive measures of disease, the observed incidence of VOD/SOS has increased; for instance, an up to four-fold increase in the incidence of VOD/SOS was seen with the transition from Baltimore to modified Seattle criteria [20]. In the more recent adult and paediatric EBMT criteria, additional factors are considered and the severity of VOD/SOS is based on multiple elements, including liver enzyme and bilirubin levels, international normalised ratio for coagulation, ascites, weight gain, renal function, encephalopathy, persistent refractory thrombocytopenia and pulmonary function [5, 21]. As use of these more recent, sensitive VOD/SOS diagnostic criteria becomes more widespread, leading to a greater recognition of conditions such as anicteric or late-onset VOD/SOS, it is possible that the incidence of VOD/SOS post-HCT will increase [22, 23].

Our findings are consistent with previous studies that have demonstrated a benefit of defibrotide prophylaxis in patients with VOD/SOS [12–14]. In a randomised phase III trial of defibrotide prophylaxis in paediatric patients, VOD/SOS occurred by 30 days post-HCT in 22 (12%) of 180 patients treated with defibrotide vs 35 (20%) of 176 control patients (risk difference  $-7.7\%$ , 95% CI  $-15.3$  to  $-0.1$ ; Z test for competing risk analysis  $p = 0.0488$ ; log-rank test  $p = 0.0507$ ) [12]. In a large retrospective study ( $N = 237$ ), a multivariate analysis demonstrated that defibrotide prophylaxis had a beneficial impact on the day 100 cumulative incidence of VOD/SOS post-HCT (hazard ratio  $7.5 \times 10^{-7}$ ; 95% CI  $1.8 \times 10^{-7}$ – $3.2 \times 10^{-6}$ );  $p < 0.00001$ ) [13]. The previous systematic review from Zhang et al. reported an overall mean incidence of VOD/SOS after HCT of 4.7% (95% CI 3.3–6.1) in patients receiving defibrotide prophylaxis vs 13.7% (95% CI 13.3–14.1;  $p < 0.005$ ) in patients without defibrotide prophylaxis [14]. The relative risk of VOD/SOS was also lower with defibrotide prophylaxis among controlled trials (RR 0.47, 95% CI 0.31–0.73) [14].

Compared with the Zhang et al. analysis [14], this meta-analysis was able to include 11 more studies evaluating IV defibrotide in 1775 more patients, bringing the total number of patients included in this meta-analysis to 3005. This number is impactful when considering that VOD/SOS is a rare condition. In addition, the inclusion of more recent studies (conducted from 2012 through 2021) captures more current clinical practice. Despite these differences, the overall incidences of VOD/SOS in the defibrotide and control groups were similar between our analysis and the Zhang et al. analysis. Also similar to our analysis, the Zhang et al. study concluded that there was a lower relative risk of VOD/SOS with defibrotide prophylaxis than with controls (RR 0.47, 95% CI 0.31–0.73). This is in contrast to a 2015 Cochrane Report on prophylaxis

for VOD/SOS post-HCT, in which the authors stated that there was insufficient evidence to support prophylactic defibrotide use; however, only one trial was included and the quality of evidence for those statements was low [15].

This analysis is limited by the small number of controlled peer-reviewed studies. Some of the studies included in the analysis were congress abstracts with limited detail; however, we made efforts to contact the authors and gather additional details, with variable results. Variations in the diagnosis and classification of VOD/SOS and its severity, along with different defibrotide doses and durations of treatment, may complicate the comparison of results across studies. Importantly, data from large, prospective, randomised controlled trials were included in the current analysis; however, there were a number of small analyses that were only reported as congress abstracts. Because of the rare nature of VOD/SOS and the reality that few researchers study this disease, there is a limited number of studies to assess, and many of those summarised in this report are small retrospective studies. Therefore, we did not analyse the effect of the quality of data on the meta-analysis results, and a formal bias assessment was not conducted.

## 5 Conclusions

This meta-analysis suggests a low incidence of VOD/SOS following IV defibrotide prophylaxis at 5%, regardless of age group (5% in adults; 8% in paediatric patients), and a lower relative risk of 0.30 for VOD/SOS with defibrotide prophylaxis vs controls in studies that included a control arm. These results support a potential benefit of defibrotide prophylaxis for the prevention of VOD/SOS in both adult and paediatric patients. An ongoing phase III study of defibrotide prophylaxis (NCT02851407) recently stopped enrolment after meeting the protocol-defined futility criteria; when the final results are available, this study will provide additional context for understanding the role of defibrotide in VOD/SOS prophylaxis. In addition, use of the most recent diagnostic and grading criteria to better identify and understand high-risk patient populations will provide more context on the utility of prophylactic therapy in these patients.

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## Declarations

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**Ethics approval** This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

**Availability of Data and Material** All of the data in this systematic review were taken from the published literature.

**Code Availability** Not applicable.

**Authors' Contributions** SC, OT and SA designed the meta-analysis. OT and SA performed the meta-analysis and analysed and verified the data. SC, OT and SA were involved in the interpretation of the data, and provided critical input, review and approval to submit the manuscript.

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