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Review Article

Anticoagulation and associated complications in veno-arterial extracorporeal membrane oxygenation in adult patients: A systematic review and meta-analysis

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ABSTRACT

Objective: To describe the incidence of bleeding and thrombotic complications in VA-ECMO according to anticoagulation strategy.

Design: This systematic review and meta-analysis included randomised controlled trials (RCTs) and observational studies reporting bleeding and thrombotic complications in VA-ECMO. The incidence of primary outcomes according to anticoagulation drug and monitoring test was described.

Data sources: CENTRAL, MEDLINE, Embase and CINAHL (2010–January 2024).

Review methods: Data was extracted using Covidence. A meta-analysis of proportions was performed using STATA MP v18.1 metaprop.

Results: We included 159 studies with 21,942 patients. No studies were at low risk of bias. The incidence of major bleeding or thrombotic events was similar among heparin-, bivalirudin- and anticoagulation-free cohorts. The pooled incidence of major bleeding and thrombotic complications were 40% (95%CI 36–44, $I^2 = 97.12$) and 17% (95%CI 14–19, $I^2 = 92.60\%$), respectively. The most common bleeding site was thoracic. The most common ischaemic complication was limb ischaemia. The incidences of major bleeding or thrombotic events, intracranial haemorrhage and ischaemic stroke were similar among all monitoring tests. Mechanical unloading was associated with a high incidence of major bleeding events (60%, 95%CI 43–77, $I^2 = 93.32$), and ischaemic strokes (13%, 95%CI 7–19, $I^2 = 81.80$).

Conclusions: Available literature assessing the association between anticoagulation strategies in VA-ECMO, and bleeding and thrombosis is of limited quality. We identified a substantially higher incidence of major bleeding events than a previous meta-analysis. Limited numbers of patients anticoagulated with alternatives to heparin were reported. Patients with additional mechanical LV unloading represent a cohort at particular risk of bleeding and thrombotic complications.

1. Introduction

Extracorporeal membrane oxygenation (ECMO) is an invasive therapy used to support patients with refractory cardiorespiratory failure. Although anticoagulation on ECMO is largely routine, the optimal anticoagulation strategy remains under debate. The coagulopathy acquired during support differs between veno-venous (VV) and veno-arterial (VA) ECMO,[1] with a higher risk of both bleeding and thrombosis in VA-ECMO.[2] Cumulative packed red cell transfusion requirement has been associated with increased mortality.[3] Conversely, thrombotic complications may be equally clinically important. These include compromise of the circuit and oxygenator which may require routine or emergent exchange, emboli to vital organs or deep vein thrombosis (DVT). The anticoagulation strategy may therefore represent a potential modifiable intervention to improve outcomes.

The components of an anticoagulation strategy include the anticoagulant drug, the monitoring test and the target range of the

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test. The most frequently used anticoagulant in ECMO is unfractionated heparin (UFH),[4] although there is increasing interest in agents such as bivalirudin.[5–9] Options for monitoring anticoagulation include activated partial prothrombin time (aPTT), anti-Xa assays and point of care tests (e.g. activated clotting time (ACT) or viscoelastic testing). Previous studies have demonstrated a poor correlation between ACT and APTT in VA-ECMO.[10] APTT has been widely adopted outside of ECMO; however, critical illness may alter the aPTT independent of the heparin effect. Anti-Xa is considered a more direct measure of heparin effect but is subject to interference by plasma-free haemoglobin and bilirubin, which are frequently elevated in ECMO.

Given the heterogeneity of VA-ECMO populations, including central cannulation, use of mechanical LV unloading necessitating additional arterial access, post-cardiotomy patients or extracorporeal cardiopulmonary resuscitation (E-CPR), it is conceivable that bleeding and thrombotic complications may vary substantially between subpopulations.

This systematic review and meta-analysis aimed to describe the incidence of bleeding and thrombotic complications in VA-ECMO according to the anticoagulation strategy employed.

2. Methods

This systematic review was reported according to the PRISMA guidelines[11] and followed a pre-published protocol.[12] The primary objective was to describe the incidence of bleeding and thrombotic complications associated with individual anticoagulation strategies in VA-ECMO described in the published literature. Due to the expected heterogeneity, this review aimed to describe the relationship between anticoagulant drug choices, and anticoagulant monitoring, as well as specific contexts such as ECPR, post-cardiotomy ECMO, central cannulation and patients requiring mechanical LV unloading.

2.1. Criteria for inclusion

All randomised controlled trials (RCTs) and observational studies describing anticoagulation and the incidence of any of the outcomes of interest in VA-ECMO were included. Case series and cohort studies with less than ten VA ECMO patients were excluded. Physiological modelling studies and cadaver studies were excluded. Abstracts and studies in press were included. Due to the evolution in ECMO technology and accumulating institutional experience, only studies published after 2010 were included.

Studies involving adults aged 16 years and older admitted to intensive care for any indication of VA-ECMO were included.

Studies that assessed any intervention in patients on VA-ECMO were included. All cannulation configurations were included, including central and peripheral cannulation. Veno-pulmonary arterial ECMO (V-PA) was not considered VA ECMO and was not included. All indications for ECMO were eligible. Studies that include both VA and VV-ECMO were only included if the VA patients' results were reported separately. Due to an anticipated low number of direct thrombin inhibitor studies, studies with combined VV and VA cohorts where VA represents greater than 85% of the cohort were included even if outcomes were not reported separately. To be included, a study had to report the following:

1. Anticoagulant drug used
   OR
2. Test for monitoring used
   AND
3. At least 1 included outcome of interest (primary or secondary)

2.2. Search methods

Electronic databases for articles using keywords, synonyms and subject headings that relate to ECMO, anticoagulation and relevant complications were searched. Further details regarding the electronic search can be found in the appendix and pre-published protocol.[12]

The following databases were searched for published trials:

1. Cochrane Central Register of Controlled Trials (CENTRAL)
2. MEDLINE Ovid
3. Elsevier Embase
4. CINAHL EBSCO

2.3. Data collection and analysis

Two review authors independently screened all titles and abstracts of each reference identified by our search and independently assessed the full text of any potentially relevant studies for

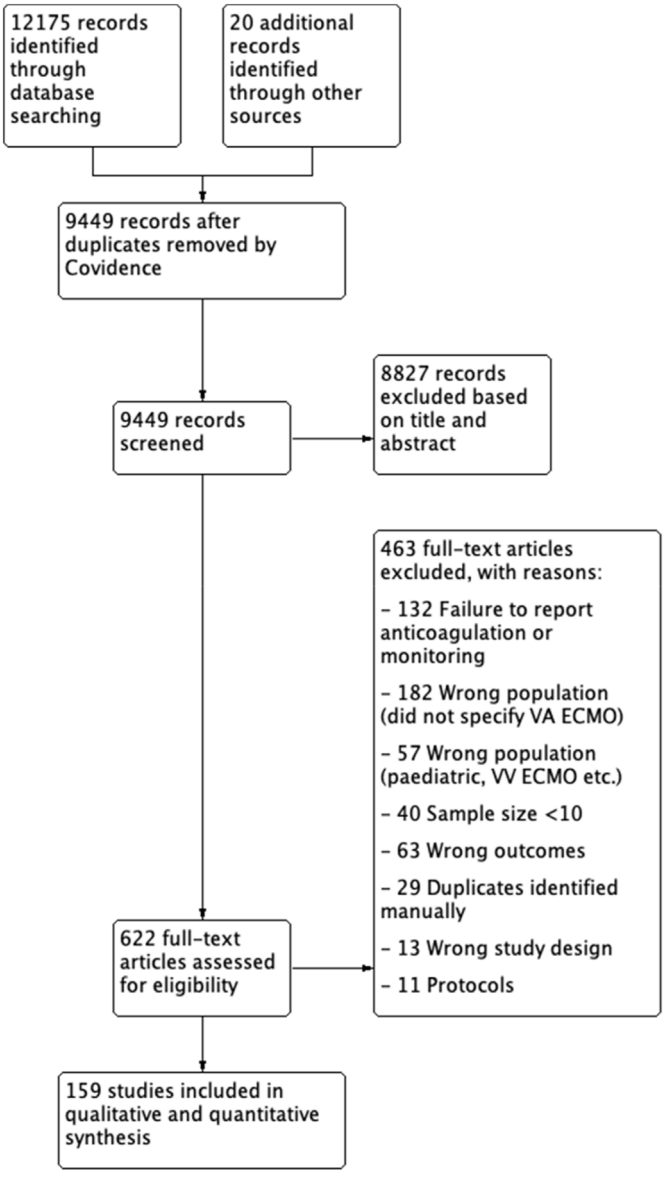

Fig. 1. Prisma diagram.

Table 1
Table of study characteristics.

Study	Country of Origin	Study Design (number of centres)	Years of Data Collection	Sample/ Male (%)	Anticoagulation Strategy	Intervention or Observation Studied	Major Bleeding Definition Used	Major Thrombosis Definition Used	Longest Follow-Up	Antiplatelets	Outcomes of Interest Included in Final Analysis	Overall Risk of Bias[a]
Aissi 2022	France	Retrospective cohort study (2)	2008–2021	10/0	Nil	ECMO for amniotic fluid embolism	Nil	Nil	ICU discharge	Were used in <50% of cases	ICH Thoracic bleeding Bleeding- need for intervention. DVT Ischaemic stroke Limb ischaemia Alive at follow-up	S
Alkazemi 2022	USA	Retrospective cohort study (1)	2016–2019	41	UFH- anti-Xa (0.3–0.7) n = 25; UFH- anti-Xa (0.2–0.5) n = 16	Conventional vs restrictive anti-Xa guided anticoagulation in ECMO	Clinically overt bleeding meeting any of the following criteria: (1) results in death, (2) results in a haemoglobin drop of >2 g/dl/day, (3) requires transfusion of >2 units of pRBC or whole blood, (4) occurs in a critical area or organ, or (5) requires surgical intervention.	Thrombotic events included arterial thrombotic events (transient ischemic attack, cerebrovascular accident, and limb ischemia), venous thromboembolism (deep vein thrombosis and pulmonary embolism) as well as clots in the ECMO circuit (cannula, pump, oxygenator) requiring intervention such a change of equipment or circuit component.	Unclear	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Bleeding- need for intervention. Circuit thrombosis DVT Ischaemic stroke Limb ischaemia Alive at follow-up	M
Alverez 2021	USA	Prospective cohort study (1)	2010–2019	156	UFH- APTT (45–55)	Peripheral cannulation in obese patients	'Required surgical interventions'	Nil	30 days after decannulation	Were not explicitly reported	Cannula site bleeding Limb ischaemia Successful weaning Alive at follow-up	S
Arachchillage 2020	United Kingdom	Retrospective cohort study (1)	2016–2018	142	UFH- anti-Xa (0.3–0.5)	Incidence of HITS in ECMO	ISTH criteria	Objectively confirmed vascular occlusion of venous or arterial circulation or visible occlusion of the ECMO circuit or sudden large rise in D dimer levels (doubling in value within 72hrs) in the absence of other explaining pathology in combination with a noisy pump indicative of pump head thrombosis requiring a change of circuit.	30	Were not explicitly reported	Major bleeding events Major thrombosis Alive at follow-up	S
Arlt 2011	Germany	Retrospective cohort study (1)	2007–2010	21	UFH- Multimodal n = 21	Hand-held ECMO circuit	Nil	Nil	30 days	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Thoracic bleeding Bleeding- need for intervention. Successful weaning Alive at follow-up	S
Arnouk 2020	USA	Retrospective cohort study (1)	2015–2017	21	UFH- anti-Xa (0.3–0.7)	Correlation between APTT and anti-Xa in ECMO	ELSO definition	Any venous or arterial systemic thromboembolic event, or clot presence in the oxygenator or circuit requiring replacement.	Hospital discharge	Were used in <50% of cases	Major bleeding events Abdominal bleeding ICH Respiratory bleeding Major thrombosis Circuit thrombosis Successful weaning Alive at follow-up	M

Aubron 2016	France, Australia	Retrospective cohort study (2)	2010–2013	111	UFH- APTT (50–70)	Predictors of bleeding in ECMO	ELSO definition	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events	M
Baldetti 2022	Italy	Retrospective cohort study (1)	2019–2021	14/13 (92.9)	Bivalirudin- APTT (50–70)	Cangrelor and bivalirudin in ECMO + PCI	BARC 3+	Any new myocardial infarction; any definite or probable stent thrombosis (ST) according to academic research consortium (ARC)-2 criteria; any peripheral arterial thrombosis, - any venous thrombosis/ venous thromboembolism; imaging-defined ischemic stroke.	Hospital discharge	Were used in >90% of cases	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Thoracic bleeding Bleeding- need for intervention. Major thrombosis DVT Ischaemic stroke Solid organ emboli Alive at follow-up	S
Berei 2018	USA	Retrospective cohort study (1)	2012–2015	44	Bivalirudin- APTT (60–80) n = 26; UFH- APTT (65–90) n = 18	Heparin vs bivalirudin in ECMO	Any bleeding event associated with a drop in haemoglobin of at least 3 mg/dL within the prior 24 h.	Clinically documented venous or arterial thromboembolism or thrombus within the ECMO circuit	30 days	Were not explicitly reported	Major bleeding events Major thrombosis Circuit thrombosis Alive at follow-up	M
Bernal 2022	USA	Retrospective cohort study (1)		159	UFH- ACT (not reported)	Thrombotic complications in ECPR	Nil	Nil		Were used in >50% of cases	Major bleeding events ICH	S
Bernal 2023	USA	Retrospective cohort study (1)	2015–2022	200	UFH- ACT (180–220)	Association between ATIII levels and complications in ECPR	Nil	Nil	Hospital discharge	Were used in >50% of cases	Major thrombosis Circuit thrombosis DVT Ischaemic stroke Solid organ emboli	M
Biocina 2014	Croatia	Retrospective cohort study (1)	2009–2014	75/47 (62.7)	UFH- Multimodal	Outcomes of ECMO	Nil	Nil	30	Were not explicitly reported	Major bleeding events Bleeding- need for intervention. Major thrombosis Limb ischaemia Alive at follow-up	S
Brunet 2015	France	Retrospective cohort study (1)	2003–2013	64/41 (64.1)	UFH- ACT (150–200)	ECPR outcomes	Massive transfusion	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding Thoracic bleeding Limb ischaemia Successful weaning Alive at follow-up	M
Cahill 2018	USA	Retrospective cohort study (1)	2013–2015	60	UFH- APTT (not reported)	Standardised transfusion protocol	Bleeding of >300 mL/h or 150 mL/h over 3 h (or by clinical team discretion).	Nil	30 days post-decannulation	Were not explicitly reported	Major bleeding events Bleeding- need for intervention. Successful weaning Alive at follow-up	M
Camporesi 2016	USA	Retrospective cohort study (1)	2007–2013	125	UFH- Multimodal	ICH in ECMO	Nil	Nil	Hospital discharge	Were not explicitly reported	ICH	M
Cartwright 2021	Australia	Prospective cohort study (1)	2017–2019	17	UFH- APTT (50–80)	Haemostatic measures in ECMO	BARC3-5	Nil	Hospital discharge	Were used in <50% of cases	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Thoracic bleeding Major thrombosis Alive at follow-up	M
Chang 2023	South Korea	Retrospective cohort study (1)	2018–2021	90	UFH- not reported n = 24; Nil n = 66	Stopping anticoagulation in ECMO	Nil	Nil	Decannulation	Were not explicitly reported	Major bleeding events Cannula site bleeding Respiratory bleeding Thoracic bleeding Limb ischaemia	S
Colombier 2019	France	Retrospective cohort study (1)	2011–2015	31/23 (74.2)	UFH- APTT (1.5-2x ULN)	ECPELLA	Nil	Nil	ICU discharge	Were not explicitly reported	Cannula site bleeding ICH Bleeding- need for intervention.	S

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Table 1 (*continued*)

Study	Country of Origin	Study Design (number of centres)	Years of Data Collection	Sample/ Male (%)	Anticoagulation Strategy	Intervention or Observation Studied	Major Bleeding Definition Used	Major Thrombosis Definition Used	Longest Follow-Up	Antiplatelets	Outcomes of Interest Included in Final Analysis	Overall Risk of Bias[a]
Czobor 2016	USA	Retrospective cohort study (1)	2012–2014	25	UFH- ACT (180–220)	Initial SOFA scores for predicting ECMO outcomes	TIMI major	Nil	30	Were not explicitly reported	Major thrombosis Ischaemic stroke Solid organ emboli Limb ischaemia Successful weaning Alive at follow-up Major bleeding events Cannula site bleeding ICH Respiratory bleeding DVT	M
Danial 2018	France	Retrospective cohort study (1)	2015–2017	532/382 (71.8)	UFH- APTT (1.5-2x ULN)	Surgical vs percutaneous cannulation	Nil	Nil	30	Were used in <50% of cases	Ischaemic stroke Limb ischaemia Alive at follow-up Cannula site bleeding	M
Danial 2023	France	Retrospective cohort study (1)	2015–2018	1253/ 879 (70.2)	UFH- APTT (1.5-2x ULN)	Shock aetiology and ECMO outcomes	Haemothorax, haemopericardium, and gastrointestinal bleeding	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events ICH Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	M
Darocha 2016	Poland	Prospective case series (1)	2013–2015	10/7 (64.1)	UFH- ACT (140–160)	ECMO for hypothermic arrest	Nil	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Abdominal bleeding Successful weaning Alive at follow-up	S
Demondion 2014	France	Retrospective cohort study (1)	2006–2009	77/58 (75.3)	UFH- ACT (150–180)	Predictors of mortality in ECMO for myocardial infarction	Nil	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events LV thrombus Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	S
Descamps 2021	France	Retrospective cohort study (3)	2017–2019	77	UFH- anti-Xa (0.2–0.7)	Anti-Xa monitoring	ELSO definition	Nil	Hospital discharge	Were used in <50% of cases	Major bleeding events Major thrombosis Successful weaning Alive at follow-up	S
Deschka 2013	Germany	Retrospective cohort study (1)	2008–2011	28/26 (92.9)	UFH- APTT 50-60	Closed chest central cannulation for limb ischaemia	Surgical re-exploration or ICH	Nil	Hospital discharge	Were used in <50% of cases	Major bleeding events ICH Thoracic bleeding Bleeding- need for intervention. Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	S
Djordjevic 2020	Germany	Prospective cohort study (1)	2006–2016	64/43 (67.2)	UFH- Multimodal	ECMO for post-cardiotomy RV failure	Nil	Nil	Hospital discharge	Were not explicitly reported	Thoracic bleeding Bleeding- need for intervention. Successful weaning Alive at follow-up	S
Duburcq 2022	France	Retrospective cohort study (1)	2014–2020	22/4 (18.2)	UFH- not reported	ECMO for toxicology	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Abdominal bleeding Respiratory bleeding Bleeding- need for intervention. DVT Successful weaning Alive at follow-up	S
Ellouze 2021	France	Retrospective cohort study (1)	2006–2016	243/170 (70)	UFH- anti-Xa (0.15–0.3)	Risk factors for ECMO bleeding	ELSO definition	Medical diagnosis of ischaemic cerebral infarction, peripheral arterial ischaemia, pulmonary embolism,	Hospital discharge	Were used in <50% of cases	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding	M

							and intracardiac or aortic thrombosis.			Thoracic bleeding Bleeding- need for intervention. Major thrombosis Alive at follow-up		
Esper 2015	USA	Retrospective cohort study (1)	2007–2013	18	UFH- APTT (50–70)	ECMO for myocardial infarction	Nil	Nil	Hospital discharge	Were used in >90% of cases	Cannula site bleeding ICH Bleeding- need for intervention. Ischaemic stroke Limb ischaemia Alive at follow-up	S
Feih 2022	USA	Retrospective cohort study (1)	2012–2018	74	UFH- ACT (160–220) n = 45; UFH- anti-Xa (0.3–0.7) n = 29	Anti-Xa vs ACT monitoring	ELSO definition	Clinically relevant thrombosis (ischaemic stroke, PE, DVT, cardiac thrombus, organ infarct or bowel ischaemia, as evidenced by imaging or replacement of any component of the tMCS device as a result of thrombus formation).	Hospital discharge	Were used in >50% of cases	Major bleeding events Bleeding- need for intervention. Alive at follow-up	M
Fisser 2022	Germany	Retrospective cohort study (1)	2010–2020	427/312 (73.1)	UFH- APTT (55–70)	Vascular complications	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding ICH DVT Solid organ emboli Limb ischaemia Alive at follow-up	S
Fong 2021	Hong Kong	Retrospective cohort study (1)	2010–2018	51	UFH- ACT (200–220)	Incidence of bleeding in ECMO	ELSO definition	Thrombotic complications included deep vein thrombosis (DVT), ischemic stroke, intracardiac thrombus, pulmonary embolism, and the presence of blood clot in the filter, the cannula or the reperfusion cannula requiring circuit change.	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Major thrombosis Circuit thrombosis DVT LV thrombus Ischaemic stroke Alive at follow-up	S
Gaisendrees 2021	Germany	Retrospective cohort study (1)	2016–2020	108/88 (81.5)	UFH- Multimodal	Manual vs mechanical CPR in ECPR	Combination of severe bleeding from several sites (e.g. pulmonary, GIT, vascular injury), which required immediate and ongoing mass transfusion to establish adequate ECMO flow	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Abdominal bleeding Respiratory bleeding Thoracic bleeding Alive at follow-up	S
Gaisendrees 2023	Germany	Retrospective cohort study (1)	2016–2020	95/76 (80)	UFH- Multimodal	Predictors of AKI in ECMO	Active bleeding with need for transfusion	Nil	Hospital discharge	Were not explicitly reported	Major thrombosis Limb ischaemia Successful weaning	S
Gami 2017	India	Retrospective case series (1)	2016–2017	19/12 (63.2)	UFH- ACT (160–180)	ECMO in toxicology	Nil	Nil	Hospital discharge	Were not explicitly reported	Abdominal bleeding Bleeding- need for intervention. Limb ischaemia Alive at follow-up	S
Grazioli 2023	USA	Retrospective cohort study (1)	2016–2019	206/129 (62.6)	UFH- APTT (60–80)	ECMO without transfusion	ELSO definition	Nil	Hospital discharge	Were used in <50% of cases	Major bleeding events Circuit thrombosis Alive at follow-up	M
Guenther 2016	Germany	Retrospective cohort study (1)	2012–2014	87/73 (83.9)	UFH- Multimodal	Description of new ECMO service	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Circuit thrombosis Limb ischaemia Successful weaning Alive at follow-up	S

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Table 1 (*continued*)

Study	Country of Origin	Study Design (number of centres)	Years of Data Collection	Sample/ Male (%)	Anticoagulation Strategy	Intervention or Observation Studied	Major Bleeding Definition Used	Major Thrombosis Definition Used	Longest Follow-Up	Antiplatelets	Outcomes of Interest Included in Final Analysis	Overall Risk of Bias[a]
Guenther 2018	Germany	Retrospective cohort study (1)	2015–2017	10/6 (60)	UFH- Multimodal	Description of long run ECMO	Nil	Nil	Decannulation	Were not explicitly reported	Major bleeding events Bleeding- need for intervention. Circuit thrombosis Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	S
Guimbretiere 2019	France	Prospective cohort study (1)	2005–2016	410/276 (67.3)	UFH- ACT (150–180)	Association of transfusion with prognosis	The need to perform at least one surgical revision for bleeding or to transfuse at least 4units of pRBC to treat anaemia resulting from bleeding	Thrombotic complications were defined by central nervous system or peripheral embolism, intravascular thrombus at any site and pulmonary embolism; lower limb ischaemia was defined by the need of re-intervention on the lower limb (including aponeurotomy).	Hospital discharge	Were not explicitly reported	Limb ischaemia Successful weaning Alive at follow-up	C
Guliani 2020	USA	Retrospective cohort study (1)	2017–2019	17/9 (52.9)	UFH- APTT[60–110]	ECMO in massive PE	Requiring transfusion	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	S
Guo 2021	China	Retrospective case series (1)	2015–2019	12/6 (50)	UFH- Multimodal	ECPR case series	Nil	Nil	Hospital discharge	Were not explicitly reported	Abdominal bleeding Thoracic bleeding Bleeding- need for intervention. Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	C
Hasde 2021	Turkey	Retrospective cohort study (1)	2015–2020	53/32 (60.4)	UFH- Multimodal	LV venting strategies	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding ICH Thoracic bleeding Ischaemic stroke Successful weaning Alive at follow-up	S
Hohlfelder 2022	USA	Retrospective cohort study (1)	2013–2015	26	UFH- not reported	APTT/ACT/Anti-Xa correlation	Bleeding complications were defined as bleeding events requiring transfusion of greater than or equal to 2 units of pRBC within a 24-h period or requiring procedural intervention.	Thrombotic complications were radiographically identified through ultrasound or computed tomography imaging.	Hospital discharge	Were not explicitly reported	Major bleeding events Major thrombosis Alive at follow-up	M
Hong 2021	South Korea	Retrospective cohort study (1)	2017–2019	31	UFH- ACT (outcomes not reported separately for strategies)	Conservative vs conventional ACT targets	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding ICH Circuit thrombosis Successful weaning Alive at follow-up	S
Hou 2021	China	Retrospective cohort study (1)	2006–2016	415/281 (67.7)	UFH- Multimodal	Neurological complications	Nil	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding ICH Thoracic bleeding Bleeding- need for intervention. Ischaemic stroke	M

										Limb ischaemia Successful weaning Alive at follow-up	
Hryniewicz 2016	USA	Retrospective cohort study (1)	2012–2013	37	Not reported-APTT	Percutaneous cannulation	Haemoglobin drop >3 g/dL	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events ICH Ischaemic stroke	C
Hu 2021	China	Retrospective cohort study (1)	2017–2020	54	UFH- APTT (60–80)	Limb ischaemia	ELSO definition	Nil	Decannulation	Were not explicitly reported	Major bleeding events	M
Hu 2022	China	Retrospective cohort study (1)	2019–2021	179/146 (85.6)	UFH- APTT (40–60)	Bilirubin's association with survival	Nil	Nil	Hospital discharge	Were not explicitly reported	Limb ischaemia Successful weaning Alive at follow-up	M
Hvas 2023	Denmark	Prospective cohort study (1)	2017–2019	69	UFH- APTT (50–65)	Haemostatic assays in bleeding	Gusto score	Nil	30 days after ECMO weaning	Were not explicitly reported	Major bleeding events Alive at follow-up	S
Iwashita 2014	Japan	Retrospective cohort study (1)	2011–2013	45	UFH- ACT (180–200)	Initial anticoagulation in ECPR	Fatal bleeding	Nil	Decannulation	Were not explicitly reported	Major bleeding events Ischaemic stroke	S
Iwashita 2015	Japan	Retrospective cohort study (1)	2011–2013	32	UFH- ACT (180–200)	Fixed dose UFH heparin bolus in ECPR	Fatal bleeding was defined as any bleeding that required surgical or trans-arterial embolization to maintain haemodynamic stability	Circuit clotting	Hospital discharge	Were not explicitly reported	Thoracic bleeding Bleeding- need for intervention. Circuit thrombosis Alive at follow-up	S
Jaamaa-Holmberg 2019	Finland	Retrospective cohort study (1)	2007–2016	133/93 (69.9)	UFH- ACT (160–180)	Quality of life outcomes	Nil	Nil	Hospital discharge	Were not explicitly reported	Ischaemic stroke Limb ischaemia Alive at follow-up	S
Jang 2023	Republic of Korea	Prospective cohort study (1)	2018–2021	17	UFH- APTT (80–90)	Association between TNF-a and haemorrhagic complications	Retroperitoneal, pulmonary, or gastrointestinal bleeding, brain or intramuscular hematoma requiring embolization, endoscopic haemostasis, or surgery, and/or a decrease in the haemoglobin level of >2 g/dL over a 24 h period	Nil	Decannulation	Were not explicitly reported	Major bleeding events	S
Jumean 2019	USA	Retrospective cohort study (1)	2015–2018	18/17 (94.4)	UFH- APTT (60–80)	Neurological complication in ECPELLA	Nil	Nil		Were not explicitly reported	ICH Ischaemic stroke	M
Keyser 2020	Germany	Retrospective cohort study (1)	2006–2016	354/260 (73.4)	UFH- APTT (50–60)	Percutaneous cannulation in obese population	Nil. Bleeding at the cannulation site was defined by the requirement of PRBC transfusion for Hb > 90.	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Limb ischaemia	S
Khazi 2018	United Arab Emirates	Prospective cohort study (1)	2015–2018	42/26 (61.9)	UFH- Multimodal	FFP for heparin resistance	"Haemorrhagic complications were defined as one or more occurrences of gastrointestinal haemorrhage, cannulation site bleeding and neurologic haemorrhage"	"Clotting complications were defined as clots found within the circuit components as well as central nervous system infarction by ultrasound or computed tomography scan"	Decannulation	Were not explicitly reported	Major bleeding events Abdominal bleeding ICH Respiratory bleeding Successful weaning Alive at follow-up	S
Kim 2016	Korea	Retrospective cohort study (1)	2005–2012	85/56 (65.9)	UFH- ACT (180–200)	ECPR survival prediction	Nil	Nil	Hospital discharge	Were not explicitly reported	Thoracic bleeding Solid organ emboli Limb ischaemia Successful weaning Alive at follow-up	S
Kim 2022	Korea	Retrospective cohort study (1)	2017–2020	32	UFH- ACT (130–160) n = 14; UFH- ACT (160–220) n = 18	High vs low ACT in ECPR	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Abdominal bleeding ICH Circuit thrombosis Ischaemic stroke Successful weaning Alive at follow-up	S

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Table 1 (*continued*)

Study	Country of Origin	Study Design (number of centres)	Years of Data Collection	Sample/ Male (%)	Anticoagulation Strategy	Intervention or Observation Studied	Major Bleeding Definition Used	Major Thrombosis Definition Used	Longest Follow-Up	Antiplatelets	Outcomes of Interest Included in Final Analysis	Overall Risk of Bias[a]
Kimmoun 2018	France	Retrospective cohort study (20)	2012–2016	39	UFH- Multimodal	HITS in ECMO	Nil	Nil	90	Were not explicitly reported	Major bleeding events Circuit thrombosis DVT Ischaemic stroke Solid organ emboli Limb ischaemia Alive at follow-up	S
Koerner 2019	USA	Retrospective cohort study (1)	2014–2018	184/131 (71.2)	UFH- APTT (50–60)	Incidence of complications in VA-ECMO	"Systemic, retroperitoneal hematoma, tamponade"	Nil	Decannulation	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Circuit thrombosis LV thrombus Ischaemic stroke Limb ischaemia Alive at follow-up	S
Kohs 2022	USA	Retrospective cohort study (1)	2016–2019	44	UFH- anti-Xa (0.35–0.7)	Association between platelet count and thrombosis	ISHT criteria	Both venous and arterial thrombosis, as well as thrombotic events within the extracorporeal circuit that mandated a circuit exchange.	Decannulation	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding Respiratory bleeding Thoracic bleeding Major thrombosis Circuit thrombosis DVT LV thrombus Ischaemic stroke Solid organ emboli	M
Kulig 2021	USA	Retrospective cohort study (1)	2010–2019	41	UFH- anti-Xa (0.3–0.7) n = 12; UFH- APTT (not reported) n = 29	APTT vs anti-Xa	Nil	Systemic clots, thrombosis enclosed within systemic vasculature.	Hospital discharge	Were not explicitly reported	Major thrombosis Circuit thrombosis DVT Ischaemic stroke Solid organ emboli	?
Laimoud 2020	Saudi Arabia	Retrospective cohort study (1)	2016–2018	67	UFH- anti-Xa (0.3–0.7)	Neurological complications in VA-ECMO	Nil	Nil	Hospital discharge	Were not explicitly reported	ICH LV thrombus Ischaemic stroke Alive at follow-up	M
Laimoud 2021	Saudi Arabia	Retrospective cohort study (1)	2015–2019	65/46 (70.8)	UFH- anti-Xa (0.3–0.7)	Vascular complications	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Abdominal bleeding Respiratory bleeding Circuit thrombosis Limb ischaemia Successful weaning	M
Lamarche 2010	Canada	Retrospective cohort study (1)	2000–2008	32	Nil	Thrombosis in anticoagulation-free ECMO	Nil	Nil	6 months	Were not explicitly reported	ICH Thoracic bleeding Bleeding- need for intervention.	M
Lansink-Hartgring 2019	Netherlands	Retrospective cohort study (1)	2010–2017	101	UFH- APTT (50–70)	Haemorrhagic complications in ECMO	ELSO defintion	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events	S
Lee 2021	Korea	Retrospective cohort study (1)	2004–2018	125/95 (76)	UFH- not reported	Multidisciplinary team protocol for ECPR	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Abdominal bleeding Ischaemic stroke Limb ischaemia Alive at follow-up	M
Lee 2022	Republic of Korea	Retrospective cohort study (1)	2017–2020	16	Nafamostat- APTT (60–90)	Nafamostat anticoagulation	Nil	Nil	Not reported	Were not explicitly reported	Major bleeding events Thoracic bleeding Major thrombosis Circuit thrombosis Alive at follow-up	S
Levy 2022	France	Prospective RCT (2)	2016–2019	374/253 (67.6)	UFH- not reported	Moderate hypothermia vs normothermia	Severe bleeding was defined as intracerebral or resulting in substantial haemodynamic compromise.	Nil	30	Were not explicitly reported	Major bleeding events Alive at follow-up	S

Liang 2021	China	Retrospective cohort study (1)	2016–2018	43/23 (53.5)	UFH- ACT (150–200)	Association between complications and prognosis	Nil	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Limb ischaemia Alive at follow-up	M
Lim 2014	Korea	Retrospective cohort study (1)	2006–2012	13/9 (69.2)	UFH- ACT (>180)	ECMO for primary graft dysfunction	Nil	Nil	30 days	Were not explicitly reported	ICH Thoracic bleeding Bleeding- need for intervention. Ischaemic stroke	S
Lim 2016	Korea	Retrospective cohort study (1)	2005–2014	320	Nafamostat- Multimodal n = 119; UFH- Multimodal n = 219	Nafamostat vs UFH	Any bleeding requiring surgical intervention, cerebral haemorrhage proved by brain CT or MRI, and gastrointestinal bleeding diagnosed by endoscopic evaluation	(1) Embolic stroke diagnosed by brain imaging such as computed tomography or magnetic resonance imaging and (2) a newly developed intracardiac thrombus confirmed by echocardiography.	Decannulation	Were not explicitly reported	Major bleeding events Major thrombosis Successful weaning Alive at follow-up	S
Lin 2021	Taiwan	Retrospective cohort study (1)	2008–2018	621	UFH- APTT (1.5-2x ULN)	Thrombolysis with ECMO for massive PE	Bleeding that required any transfusion or surgical exploration	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Bleeding- need for intervention. Successful weaning Alive at follow-up	C
Loforte 2012	Italy	Retrospective cohort study (1)	2007–2011	73/55 (75.3)	UFH- Multimodal	Outcomes for ECMO in cardiogenic shock	Nil	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding ICH Limb ischaemia Successful weaning Alive at follow-up	M
Lopez 2023	USA	Retrospective cohort study (1)	2016–2020	17/14 (82.4)	Bivalirudin- APTT (55–75)	Bivalirudin	ISTH	DVT or PE confirmed by radiographic or ultrasound imaging and device thromboses documented as thrombosis in the oxygenator, pump, or circuit, or renal replacement system.	Hospital discharge	Were used in >50% of cases	Major bleeding events Abdominal bleeding ICH Respiratory bleeding Major thrombosis Circuit thrombosis Ischaemic stroke Alive at follow-up	S
Lubnow 2022	Germany	Retrospective cohort study (1)	2006–2016	176	UFH- APTT (60) n = 166; argatroban- APTT (50) n = 4	HITS incidence and outcomes	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Respiratory bleeding LV thrombus Ischaemic stroke Limb ischaemia	S
Lusebrink 2023	Germany	Retrospective cohort study (1)	2013–2022	373/306 (82)	Nil n = 13; UFH- APTT (60–80) n = 373	HITS	BARC 3-5	Nil	Hospital discharge	Were used in <50% of cases	Major bleeding events Circuit thrombosis DVT Ischaemic stroke Limb ischaemia Alive at follow-up	M
Mansour 2022	France	Prospective cohort study (44)	2020–2022	52	UFH- anti-Xa (range not reported)	Bleeding and thrombosis in patients with COVID-19 infection on ECMO	≥1: Intracranial bleeding, upper or lower gastro-intestinal haemorrhage, peripheral cannulation site bleeding, retroperitoneal bleeding, pulmonary haemorrhage or massive haemorrhage. Peripheral cannulation site bleeding defined as a bleeding from a peripheral cannulation site requiring PRBC	One or more of the following complications: Ischemic stroke, deep vein thrombosis, pulmonary embolism or thrombosis, acute mesenteric ischemia, acute coronary syndrome, acute limb ischemia, macroscopic thrombus of circuit/ membrane without needing to change the circuit, oxygenator	Hospital discharge	Were used in <50% of cases	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Major thrombosis Circuit thrombosis DVT Ischaemic stroke Solid organ emboli Limb ischaemia	M

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Table 1 (*continued*)

Study	Country of Origin	Study Design (number of centres)	Years of Data Collection	Sample/ Male (%)	Anticoagulation Strategy	Intervention or Observation Studied	Major Bleeding Definition Used	Major Thrombosis Definition Used	Longest Follow-Up	Antiplatelets	Outcomes of Interest Included in Final Analysis	Overall Risk of Bias[a]
							transfusion and/or surgical intervention. Massive transfusion definition required >10U PRBCS/24 h.	failure requiring change due to clot formation, acute circuit thrombosis requiring change				
Mariani 2023	Netherlands	Retrospective cohort study (34)	2000–2020	2058/ 1215 (59)	UFH- not reported, n = 2058; nil n = 187; bivalirudin- not reported, n = 3; argatroban- not reported, n = 3	Post-cardiotomy ECMO	Nil	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding ICH Bleeding- need for intervention. Major thrombosis Ischaemic stroke Solid organ emboli Limb ischaemia Successful weaning Alive at follow-up	C
Mazzeffi 2015	USA	Retrospective cohort study (1)		54	UFH- Multimodal	Incidence of GI bleeding	GI bleeding only	Nil	Hospital discharge	Were not explicitly reported	Nil extracted after accounting for overlap with other studies	M
Mazzeffi 2016	USA	Retrospective cohort study (1)	2010–2013	52	UFH- Multimodal	Bleeding and transfusion in ECMO	ELSO definition or required surgical intervention	Overt thrombotic event was defined as thrombosis in the cannulas, pump, or any symptomatic event in the patient (eg, stroke, arterial thrombosis). Upper and lower extremity deep vein thromboses were not included.	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Thoracic bleeding Major thrombosis Alive at follow-up	M
Mazzeffi 2019	USA	Retrospective cohort study (1)	2010–2015	121	UFH- APTT (60–80) n = 71; UFH- ACT (180–200) n = 50	APTT vs ACT bleeding protocols	ELSO definition or required surgical intervention.	Symptomatic thromboembolic complications were recorded (eg, stroke, leg ischemia), as were circuit or oxygenator thromboses that led to a disturbance in ECMO circuit function (reduced blood flow or severely impaired gas exchange). Asymptomatic fibrin stranding on the oxygenator or circuit tubing was not considered thrombosis. Small asymptomatic venous or arterial thrombus visualized within a vessel lumen, but outside of the ECMO cannula on ultrasound, was not considered thrombosis. Deep venous thromboses after decannulation were not considered thrombosis in this study because the primary outcome of interest was arterial thromboembolic complications or circuit thrombosis.	Hospital discharge	Were not explicitly reported	Major bleeding events Bleeding- need for intervention. Major thrombosis Circuit thrombosis Ischaemic stroke Alive at follow-up	M

Mazzeffi 2021 (a)	USA	Prospective cohort study (1)		20	UFH- APTT (60–80)	PF4 concentration in ECMO	ELSO definition or required surgical intervention	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Major thrombosis Alive at follow-up	M
Mazzeffi 2021 (b)	USA	Prospective cohort study (1)		20	UFH- APTT (60–80)	TF pathway inhibitor concentrations in ECMO	ELSO definition or required surgical intervention	Nil	Hospital discharge	Were not explicitly reported	Nil extracted after accounting for overlap with other studies	C
Mazzeffi 2022	USA	Retrospective cohort study (1)	2016–2019	188/119 (63.3)	UFH- APTT (60–80)	Platelet transfusion and association with outcomes	ELSO definition or required surgical intervention	Nil	Hospital discharge	Were used in <50% of cases	Major bleeding events Major thrombosis Circuit thrombosis Solid organ emboli Alive at follow-up	M
McCloskey 2022	USA	Retrospective cohort study (1)	2000–2017	187/112 (59.9)	UFH- Multimodal	Association between transfusion and outcomes	Bleeding event (upper gastrointestinal as documented by hematemesis, melena, or endoscopy; lower gastrointestinal as documented by red blood per rectum; cannulation-site haemorrhage; surgical-site haemorrhage; pulmonary haemorrhage as documented by bronchoscopy, haemoptysis, or frank bleeding from the respiratory tract; and central nervous system haemorrhage as documented by imaging) reoperation due to bleeding (cannulation-site or surgical-site bleeding)	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Bleeding- need for intervention. Ischaemic stroke Solid organ emboli Limb ischaemia Successful weaning Alive at follow-up	S
Mehdiani 2021	Germany	Retrospective cohort study (1)	2010–2017	25/18 (72)	UFH- APTT (40–60)	Cannulation configurations	Nil	Nil	30	Were not explicitly reported	Major bleeding events Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	M
Melehy 2020	USA	Retrospective cohort study (1)	2007–2018	150	Nil n = 34; UFH- APTT (40–60) n = 116	UFH vs no anticoagulation in post-cardiotomy ECMO	Bleeding requiring transfusion or re-intervention	Circuit thrombosis, venous or arterial system thrombosis, intracardiac thrombus, and vascular catheter thrombosis	Hospital discharge	Were not explicitly reported	Major thrombosis	S
Melehy 2022	USA	Retrospective cohort study (1)	2007–2019	141	Nil n = 32; UFH- APTT (45–80) n = 112	Bleeding complications in post-cardiotomy shock	ELSO definition	Limb ischemia, intracardiac thrombosis, deep vein thrombosis, pulmonary embolism, circuit thrombosis, ischemic stroke, and other arterial system thrombosis	Hospital discharge	Were used in >90% of cases	Major bleeding events	M
Mitchell 2023	USA	Retrospective cohort study (1)	2021–2022	56	UFH- APTT (60–75) n = 41; bivalirudin- APTT (60–75) n = 15	UFH vs bivalirudin	ISTH or ELSO definition	In-circuit thrombosis, pump thrombosis, systemic thromboembolism, and haemolysis labs	7	Were not explicitly reported	Major bleeding events Major thrombosis	M
Moon 2018	South Korea	Retrospective cohort study (1)	2004–2017	14	UFH- not reported	ECMO for massive PE	Intracerebral bleeding or bleeding that caused substantial haemodynamic compromise and required treatment (GUSTO 1)	Nil	90	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding Respiratory bleeding Alive at follow-up	M

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Table 1 (*continued*)

Study	Country of Origin	Study Design (number of centres)	Years of Data Collection	Sample/ Male (%)	Anticoagulation Strategy	Intervention or Observation Studied	Major Bleeding Definition Used	Major Thrombosis Definition Used	Longest Follow-Up	Antiplatelets	Outcomes of Interest Included in Final Analysis	Overall Risk of Bias[a]
Moussa 2021	France	Retrospective cohort study (1)	2015–2019	265	UFH- anti-Xa (0.2–0.4)	Anti-Xa and APTT concordance	ELSO definition	Composite of stroke, limb ischaemia and ECMO circuit changes for thrombosis or cannulation thrombosis or any thrombosis that led to medical or surgical intervention or death	Hospital discharge	Were used in <50% of cases	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Thoracic bleeding Major thrombosis Circuit thrombosis Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	M
Murakami 2022	Japan	Retrospective cohort study (1)	2009–2021	101/83 (82.2)	UFH- Multimodal	ECMO in myocardial infarction	BARC 3–5 and TIMI criteria	Nil	Hospital discharge	Were used in >90% of cases	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding LV thrombus Ischaemic stroke Solid organ emboli Limb ischaemia Successful weaning Alive at follow-up	M
Nguyen 2022	Vietnam	Retrospective cohort study (1)	2019–2020	61	UFH- Multimodal	Major bleeding in ECMO	ELSO definition	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Ischaemic stroke Alive at follow-up	M
Ohira 2020	USA	Retrospective cohort study (1)	2010–2018	143/102 (71.3)	UFH- APTT (45–55)	Cannula associated complications	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Limb ischaemia Successful weaning Alive at follow-up	S
Ohira 2023	USA	Retrospective cohort study (1)	2009–2021	80/64 (80)	UFH- APTT (40–55)	Distal perfusion catheters	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Abdominal bleeding Bleeding- need for intervention. Limb ischaemia Successful weaning Alive at follow-up	M
Omar 2016a	USA	Retrospective cohort study (1)	2007–2014	137	UFH- Multimodal	Incidence of ischaemic stroke	Nil	Cerebral infarction was confirmed by computed tomography or magnetic resonance imaging of the brain showing features of ischemic stroke.	Hospital discharge	Were not explicitly reported	Ischaemic stroke	S
Omar 2016b	USA	Retrospective cohort study (1)	2007–2013	125	UFH- Multimodal	Incidence of ICH	Nil	Nil	Hospital discharge	Were not explicitly reported	ICH	M
Ottolina 2023	Italy	Prospective cohort study (1)	2014–2020	79/62 (78.5)	UFH- Multimodal	Mortality in ECPR	Nil	Arterial/venous thrombosis	28	Were not explicitly reported	Major bleeding events Major thrombosis Successful weaning Alive at follow-up	S
Pan 2016	Australia	Retrospective cohort study (1)	2010–2014	128	UFH- APTT (50–70)	Prevalence of haemolysis	Nil	Nil	Hospital discharge	Were not explicitly reported	Circuit thrombosis	M
Papadopoulos 2015	Germany	Prospective cohort study (1)	2001–2013	360/274 (76.1)	UFH- APTT (50–60)	Risk factors for poor outcomes in ECMO	Nil	Nil	Hospital discharge	Were not explicitly reported	Abdominal bleeding ICH Bleeding- need for intervention. Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	S

Park 2014	Korea	Retrospective cohort study (1)	2005–2011	93	UFH- ACT 180-200	Post-cardiotomy outcomes	Nil	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Abdominal bleeding ICH Thoracic bleeding Bleeding- need for intervention. Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	S
Park 2023	South Korea	Prospective RCT (2)	2018–2022	60/39 (65)	UFH- Multimodal	Early LA venting vs conventional therapy	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Abdominal bleeding ICH LV thrombus Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	S
Paulo 2022	France	Retrospective cohort study (1)	2007–2018	60/44 (73.3)	UFH- anti-Xa (0.3–0.7)	ECMO for primary graft dysfunction	Nil	Nil	Hospital discharge	Were not explicitly reported	Thoracic bleeding Bleeding- need for intervention. Successful weaning Alive at follow-up	S
Pingpoh 2022	Germany	Retrospective cohort study (1)	2008–2017	421/307 (72.9)	UFH- APTT (60–80)	Post-cardiotomy	Requiring blood transfusion of $\geq$ 6 packed red blood cells or surgical intervention	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Alive at follow-up	S
Pinto 2018	France	Retrospective cohort study (1)	2010–2015	145	UFH- APTT (2-3xULN)	Predictors of bleeding	ELSO definition	Transient ischemic attack, ischemic stroke, systemic embolism, acute myocardial infarction, intracardiac thrombosis, deep venous thrombosis, pulmonary embolism, and circuit/membrane oxygenator change due to thrombus formation	ICU discharge	Were used in <50% of cases	LV thrombus Alive at follow-up	S
Plazak 2022	USA	Retrospective cohort study (1)	2016–2019	188/69 (36.7)	UFH- APTT (60–80)	Precannulation INR	ELSO definition	Nil	Hospital discharge	Were used in >50% of cases	Major bleeding events Abdominal bleeding ICH Circuit thrombosis Ischaemic stroke Alive at follow-up	M
Pozzi 2022	France	Retrospective cohort study (1)	2007–2020	32/12 (37.5)	UFH- anti-Xa (0.3–0.7)	ECMO for toxicology	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Bleeding- need for intervention. Limb ischaemia Successful weaning Alive at follow-up	M
Radakovic 2021	Germany	Retrospective cohort study (1)	2010–2019	158/113 (71.5)	UFH- APTT (50–70)	Cannula configuration in post-cardiotomy ECMO	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Thoracic bleeding Bleeding- need for intervention. Solid organ emboli Limb ischaemia Successful weaning Alive at follow-up	M
Radakovic 2023	Germany	Retrospective cohort study (1)	2014–2021	136/99 (72.8)	UFH- ACT (160–180)	LV unloading timing	Nil	Nil	30	Were not explicitly reported	Cannula site bleeding Ischaemic stroke Limb ischaemia Alive at follow-up	C
Rajsic 2022a	Austria	Retrospective cohort study (1)	2008–2021	453/314 (69.3)	UFH- APTT (50–70) n = 320; Nil n = 47	Risk factors for mortality	ELSO definition	Stratified into peripheral thrombus (vein or artery), central venous, central arterial, embolisation, ECMO cannula, central catheter, mixed venous/arterial thrombus.	Hospital discharge	Were not explicitly reported	Major bleeding events Alive at follow-up	S

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Table 1 (*continued*)

Study	Country of Origin	Study Design (number of centres)	Years of Data Collection	Sample/ Male (%)	Anticoagulation Strategy	Intervention or Observation Studied	Major Bleeding Definition Used	Major Thrombosis Definition Used	Longest Follow-Up	Antiplatelets	Outcomes of Interest Included in Final Analysis	Overall Risk of Bias[a]
Rajsic 2022b	Austria	Retrospective cohort study (1)	2010–2019	247/170 (68.8)	UFH- APTT (50–70)	Risk factors for bleeding	ELSO definition	Nil	ICU discharge	Were not explicitly reported	Major thrombosis Successful weaning	S
Raman 2019	USA	Retrospective case series (1)	2011–2016	102	Nil n = 52; UFH-ACT (180–220) n = 50	No vs standard anticoagulation	Severe or catastrophic bleeding complications affecting the gastrointestinal tract, airway, intra-abdominal contents, intracranial structures, and thoracic cavity.	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Thoracic bleeding Major thrombosis Circuit thrombosis Ischaemic stroke Solid organ emboli Limb ischaemia Successful weaning Alive at follow-up	S
Ranucci 2011	Italy	Retrospective cohort study (1)	2008–2011	11	Bivalirudin-Multimodal, n = 8; UFH-Multimodal n = 3	Bivalirudin vs UFH	bleeding was measured as chest drain output and was standardized for body weight (ml/kg). The measurement was settled at 12 h (from T0 through T12), 24 h (from T12 through T24), 36 h (from T24 through T36), and 48 h (from T36 through T48). Total bleeding during the first 48 h on ECMO was measured and expressed as ml/kg/day.	Nil	Hospital discharge	Were not explicitly reported	Major thrombosis Ischaemic stroke Solid organ emboli Successful weaning Alive at follow-up	S
Rastan 2010	Germany	Prospective cohort study (1)	1996–2008	517/370 (71.6)	UFH- ACT (160)	Outcomes in post-cardiotomy ECMO	Nil	Nil	Hospital discharge	Were not explicitly reported	ICH Bleeding- need for intervention. Circuit thrombosis Ischaemic stroke Limb ischaemia Alive at follow-up	S
Repesse 2013	France	Retrospective cohort study (1)	2006–2011	315	UFH- APTT (1.5-2x ULN)	rFVIIa for refractory ECMO related bleeding	Bleeding requiring rFVIIa	Ischemic stroke, peripheral arterial embolism, circuit and/or oxygenator thrombosis (either a total thrombosis requiring urgent changing of the circuit or partial thrombosis responsible for haemolysis)		Were not explicitly reported	Major bleeding events	C
Roussel 2012	France	Prospective case series (1)	2009–2011	15/7 (46.7)	UFH- ACT 250-300	Femoral percutaneous cannulation	Nil	Nil	30	Were not explicitly reported	Major bleeding events Abdominal bleeding Circuit thrombosis Limb ischaemia Successful weaning Alive at follow-up	M
Sacco 2018	USA	Retrospective cohort study (1)	2011–2016	31	UFH- APTT (target not reported)	Correlation between bleeding and anti-Xa vs ACT vs APTT	Transfusion of ≥10 mL/kg of packed red blood cells (PRBCs) was categorized as severe bleeding	Thrombus in the ECMO circuit requiring circuit change, deep vein thrombosis, pulmonary embolism, or embolic stroke	NA	Were not explicitly reported	Major bleeding events Major thrombosis Circuit thrombosis DVT Ischaemic stroke Solid organ emboli	S

Saeed 2014	Germany	Retrospective cohort study (1)	2009–2011	37/21 (56.8)	UFH- multimodal	Cannula configuration	Nil	Nil	30	Were used in >90% of cases	Thoracic bleeding Bleeding- need for intervention. Limb ischaemia Alive at follow-up	S
Saeed 2019	USA	Retrospective cohort study (1)	2012–2017	150/100 (66.7)	UFH- APTT (50–70)	Ischaemic stroke	Nil	Nil	100	Were used in <50% of cases	Ischaemic stroke Alive at follow-up	M
Saeed 2022	USA	Retrospective cohort study (17)	2020–2021	18	UFH- APTT (50–70) n = 14; bivalirudin- APTT (50–70) n = 4	UFH vs direction thrombin inhibitors	Clinically significant bleeding requiring transfusion	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events ICH DVT Ischaemic stroke Alive at follow-up	M
Salas de armas 2023	USA	Retrospective cohort study (1)	2012–2019	46/27 (58.7)	UFH- APTT (60–80)	Outcomes of octogenarians on ECMO	Nil	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding Circuit thrombosis Ischaemic stroke Successful weaning Alive at follow-up	S
Sandersjoo 2017	Sweden	Retrospective cohort study (1)	2005–2016	92	UFH- Multimodal	ICH in ECMO	Nil	Nil	6 months	Were not explicitly reported	ICH	S
Santise 2014	Italy	Retrospective cohort study (1)	2006–2013	18	UFH- APTT (1.5-2x ULN)	ECMO in primary graft failure	Nil	Nil	NA	Were not explicitly reported	Thoracic bleeding Bleeding- need for intervention. LV thrombus Successful weaning Alive at follow-up	S
Schaefer 2022	Austria	Retrospective cohort study (1)	2000–2019	436/287 (65.8)	UFH- APTT (1.5-2.5x ULN)	Access site complications	Nil	Nil	Hospital discharge	Were not explicitly reported	Limb ischaemia Alive at follow-up	S
Schaefer 2023	Austria	Retrospective cohort study (1)	2000–2021	504/333 (66.1)	UFH- APTT (1.5-2.5x ULN)	Bleeding and thrombosis in post-cardiotomy	ELSO definition	Circuit or cannula thrombosis that was treated with exchange of circuit components or led to termination of ECLS; 'ischaemic stroke confirmed by cerebral computed tomography, with MRS at the time of hospital discharge $\geq$ 2; and peripheral thromboembolism other than cerebral thromboembolism (e.g. clinically apparent embolism to limb gastrointestinal or renal arteries)'	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Thoracic bleeding Bleeding- need for intervention. Major thrombosis Circuit thrombosis Ischaemic stroke Solid organ emboli	S
Scupakova 2023	Lithuania	Retrospective cohort study (1)	2008–2021	60/40 (66.7)	UFH- ACT (180–220)	Outcomes of octogenarians on ECMO	Nil	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding Thoracic bleeding Bleeding- need for intervention. Successful weaning Alive at follow-up	S
Seelhammer 2021	USA	Retrospective cohort study (1)	2014–2019	110	Bivalirudin- APTT (60–80)	UFH vs bivalirudin	Nil	Nil	Hospital discharge	Were not explicitly reported	Major thrombosis Circuit thrombosis DVT Ischaemic stroke Solid organ emboli Alive at follow-up	M
Seong 2021	Korea	Prospective cohort study (12)	2014–2018	496/343 (69.2)	UFH- ACT (180–200)	Ischaemic cardiomyopathy outcomes	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Abdominal bleeding Limb ischaemia Alive at follow-up	M

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Table 1 (*continued*)

Study	Country of Origin	Study Design (number of centres)	Years of Data Collection	Sample/ Male (%)	Anticoagulation Strategy	Intervention or Observation Studied	Major Bleeding Definition Used	Major Thrombosis Definition Used	Longest Follow-Up	Antiplatelets	Outcomes of Interest Included in Final Analysis	Overall Risk of Bias[a]
Sertic 2021	USA	Retrospective cohort study (1)	2013–2018	480	UFH- APTT (50–70)	Post-weaning predictors of inpatient mortality	Nil	Nil	Hospital discharge	Were not explicitly reported	ICH DVT Ischaemic stroke Solid organ emboli Limb ischaemia Successful weaning Alive at follow-up	M
Shibasaki 2022	Japan	Retrospective cohort study (1)	2013–2021	64/61 (95.3)	UFH- ACT (180–220)	ECPELLA in myocardial infarction	Decrease in serum haemoglobin level of 4 g/dL if the bleeding site was not identified, or 3 g/dL if the bleeding site was identified, and bleeding that required transfusion of at least 3 units of red blood cells	Nil	30 days	Were not explicitly reported	Major bleeding events Abdominal bleeding ICH Respiratory bleeding Alive at follow-up	M
Shin 2020	Korea	Retrospective case-control (1)	2017–2019	43	UFH- ACT (<150) n = 14; UFH- ACT (180–200) n = 29	Low vs conventional ACT outcomes	Nil	Nil	ICU discharge	Were not explicitly reported	Cannula site bleeding ICH Circuit thrombosis Successful weaning Alive at follow-up	S
Sim 2023	Korea	Retrospective case-control (1)	2011–2019	15/10 (66.7)	UFH- not reported	ECMO in massive PE	Nil	Nil	Hospital discharge	Were used in <50% of cases	Major bleeding events Limb ischaemia Successful weaning Alive at follow-up	S
Soltesz 2022	Hungary	Retrospective cohort study (1)	2012–2020	58/44 (75.9)	UFH- APTT (2-2.5x ULN)	Integrated hemadsorption	Nil	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Bleeding- need for intervention. Alive at follow-up	S
Staudacher 2016	Germany	Retrospective case-control (1)	2010–2013	93/68 (73.1)	UFH- APTT (40–50)	DAPT vs antiplatelets	BARC 3-5	Nil	Hospital discharge	Were used in >50% of cases	Major bleeding events Cannula site bleeding Respiratory bleeding Successful weaning Alive at follow-up	M
Sun 2018	Canada	Retrospective cohort study (1)	2009–2015	22/17 (77.3)	UFH- Multimodal	ECPR outcomes	Nil	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	?
Takahashi 2022	Japan	Retrospective cohort study (1)	2012–2020	141/102 (72.3)	UFH- ACT (180–210)	Predictors of complications	BARC 3-5	Thromboembolic events consisted of device-related thrombus, apical thrombus, distal embolism occurring in limbs, abdominal embolism, and cerebral infarctions confirmed by imaging modality	Hospital discharge	Were used in >50% of cases	Major bleeding events Cannula site bleeding Major thrombosis Ischaemic stroke Successful weaning Alive at follow-up	S
Takauji 2023	Japan	Prospective cohort study (36)	2019–2022	41/29 (70.7)	Nil n = 16; UFH- not reported n = 25	ECMO for hypothermic cardiac arrest	Any amount of bleeding requiring transfusion	Nil	Decannulation	Were not explicitly reported	Major bleeding events Circuit thrombosis Limb ischaemia Successful weaning Alive at follow-up	C
Tantway 2023	Saudi Arabia	Retrospective cohort study (1)	2009–2020	103/44 (42.7)	UFH- ACT (180–200)	Sepsis in post-cardiotomy ECMO	Nil	Nil	Hospital discharge	Were not explicitly reported	Abdominal bleeding Bleeding- need for intervention. Limb ischaemia Alive at follow-up	S
Tauber 2016	Austria	Prospective cohort study (1)	2010–2012	26	UFH- ACT (150–180)	Predictors of transfusion	ELSO definition	Nil	Decannulation	Were not explicitly reported	Major bleeding events	S

Thiele 2023	Germany	Prospective RCT (44)	2019–2022	209/170 (81.3)	UFH- APTT (60–80)	Early ECMO vs usual care for myocardial infarction associated shock	BARC 3-5	Stroke or systemic embolization and peripheral ischemic vascular complications warranting surgical or interventional therapy	30	Were used in >90% of cases	Major bleeding events ICH Bleeding- need for intervention. Major thrombosis DVT Ischaemic stroke Solid organ emboli Alive at follow-up	M
Uricchio 2023	USA	Retrospective cohort study (1)	2009–2021	143/102 (71.3)	UFH- anti-Xa (0.25–0.35) n = 89; bivalirudin-APTT (60–75) n = 54	UFH vs bivalirudin	ELSO definition	Deep vein thrombosis, pulmonary embolism, or ischemic stroke	30 days post-decannulation	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Major thrombosis Circuit thrombosis DVT LV thrombus Ischaemic stroke Successful weaning Alive at follow-up	M
Vandenbriele 2019 (a)	UK	Retrospective cohort study (1)	2011–2019	100/71 (71)	UFH- anti-Xa (>0.3)	Association between DAPT and bleeding	BARC 3-5	Clinically or radiographically overt arterial/venous thromboses	Decannulation	Were used in >50% of cases	Major bleeding events Major thrombosis Successful weaning Alive at follow-up	M
Vandenbriele 2019 (b)	UK	Retrospective cohort study (1)	2011–2019	51	UFH- not reported	ECMO vs impella	BARC 3-5	Nil	Decannulation	Were used in >90% of cases	Cannula site bleeding	M
Vondran 2019	Germany	Retrospective case series (2)	2012–2016	12/8 (66.7)	UFH- not reported	ECMO for constrictive pericarditis	Nil	Nil	30	Were not explicitly reported	ICH Thoracic bleeding Bleeding- need for intervention. Successful weaning Alive at follow-up	C
Wang 2013	China	Retrospective cohort study (1)	2004–2011	87/51 (58.6)	UFH- ACT (160–180)	ECMO in valvular surgical patients	Nil	Nil	Hospital discharge	Were not explicitly reported	ICH Bleeding- need for intervention. Ischaemic stroke Limb ischaemia	S
Wang 2021	China	Retrospective cohort study (1)	2015–2018	222/171 (77)	UFH- multimodal	DIC score and outcomes in post-cardiotomy patients	Need for thoracotomy	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Thoracic bleeding Bleeding- need for intervention. Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	S
Weber 2018	Germany	Retrospective (1)	2007–2015	281	UFH- multimodal	LV thrombus incidence	Nil	Nil	30	Were not explicitly reported	LV thrombus Alive at follow-up	M
Wilcox 2021	USA	Prospective cohort study (1)	2017–2020	52/32 (61.5)	UFH- APTT (60–85)	Incidence of acute brain injury	Nil	Limb ischaemia, intracardiac thrombus, PE/DVT, HIT, oxygenator clot, haemofilter clot	Hospital discharge	Were used in >50% of cases	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Thoracic bleeding Major thrombosis Circuit thrombosis DVT LV thrombus Ischaemic stroke Limb ischaemia Alive at follow-up	S
Wong 2017	USA	Retrospective cohort study (1)	2010–2015	103/68 (66)	UFH- ACT (180–220)	Cannula related complications	Cannula site bleeding requiring surgical intervention	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding Bleeding- need for intervention. Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	S

(*continued on next page*)

Table 1 (*continued*)

Study	Country of Origin	Study Design (number of centres)	Years of Data Collection	Sample/ Male (%)	Anticoagulation Strategy	Intervention or Observation Studied	Major Bleeding Definition Used	Major Thrombosis Definition Used	Longest Follow-Up	Antiplatelets	Outcomes of Interest Included in Final Analysis	Overall Risk of Bias[a]
Wood 2019	USA	Retrospective cohort study (1)	2011–2018	247/127 (51.4)	Nil, n = 20; UFH- Multimodal, n = 50	UFH vs no anticoagulation	Bleeding that required intervention and included haemorrhagic cerebral vascular accident, gastrointestinal bleeding, and 4 or more packed red blood cell (PRBC) transfusions in a 24-h period.	Ischemic cerebral vascular accident, limb thrombosis, intracardiac thrombus, and pulmonary embolism. Circuit clots were included as a thrombotic complication only if they required intervention or changes to the anti-coagulation strategy	Hospital discharge	Were not explicitly reported	Major bleeding events Abdominal bleeding ICH Respiratory bleeding Thoracic bleeding Major thrombosis Circuit thrombosis LV thrombus Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	M
Wu 2010	Taiwan	Retrospective cohort study (1)	2003–2009	110/78 (70.9)	UFH- ACT (180 −200)	Review of protocol for post-cardiotomy ECMO	Bleeding requiring reoperation	Nil	Hospital discharge	Were not explicitly reported	Major bleeding events Thoracic bleeding Bleeding- need for intervention. Limb ischaemia Successful weaning Alive at follow-up	S
Xin 2021	China	Retrospective case series (1)	2004–2016	15/12 (80)	UFH- ACT (160 −180)	Double distal perfusion cannulas in ECMO + IABP	Nil	Nil	Hospital discharge	Were not explicitly reported	Limb ischaemia Successful weaning Alive at follow-up	M
Yeo 2016	Korea	Retrospective cohort study (1)	2010–2015	151/90 (59.6)	UFH- monitoring not reported separately	Pre-emptive distal perfusion cannulas	Nil	Nil		Were used in <50% of cases	Major bleeding events Limb ischaemia Successful weaning Alive at follow-up	M
Yie 2016	South Korea	Prospective cohort study (1)	2008–2014	60	UFH- ACT (170 −210)	ACT in ECPR	Requiring 5 pints of packed red blood cells or FFP or Plts per day during ECPR	CVA, solid organ	Hospital discharge	Were not explicitly reported	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Major thrombosis Ischaemic stroke Solid organ emboli Successful weaning Alive at follow-up	S
Zhang 2023	China	Retrospective cohort study (1)	2018–2022	28/23 (82.1)	UFH- ACT (180 −200)	UFH loading dose in ECPR	Life threatening'	Complications of embolism were defined as complications in the ECMO pipeline or pump head, membrane oxygenator thrombosis, and venous thrombosis.	Hospital discharge	Were used in >50% of cases	Major bleeding events Cannula site bleeding Abdominal bleeding ICH Respiratory bleeding Major thrombosis Circuit thrombosis LV thrombus Ischaemic stroke Limb ischaemia Successful weaning Alive at follow-up	S
Zhao 2022	China	Retrospective cohort study (1)	2012–2020	42/20 (47.6)	UFH- not reported	Outcomes of patients transferred to ECMO center	ELSO definition	Nil	Hospital discharge	Were not explicitly reported	Cannula site bleeding ICH Circuit thrombosis Limb ischaemia Alive at follow-up	M
Zhu 2023	China	Prospective cohort study (1)	2019–2021	73/53 (72.6)	UFH- APTT (55 −65)	Serum Galectin-3	Nil	Nil	Hospital discharge	Were not explicitly reported	Abdominal bleeding Limb ischaemia Alive at follow-up	S
Zotzmann 2020	Germany	Retrospective cohort study (1)	2010–2017	103/71 (68.9)	UFH- APTT (50 −60)	Full body CT in ECPR	Nil	Nil	Hospital discharge	Were not explicitly reported	ICH Thoracic bleeding Bleeding- need for intervention. Ischaemic stroke Solid organ emboli Alive at follow-up	M

[a] Overall Risk of Bias: L = low, M = Moderate, S= Serious, C= Critical.

eligibility. Covidence software was used to collate search results, remove duplicates and record screening decisions at each stage.[13] Any disagreements were resolved by discussion and consensus prior to proceeding at each stage.

Through Covidence, a standardised data-extraction sheet was used, in line with the *Cochrane Handbook for Systematic Reviews of Interventions Version 6.3*.[14] Two review authors independently extracted information regarding trial design, the anticoagulation strategy, outcomes of interest (as reported below) and information relevant to the risk of bias grading. Where required, individual trial authors or organisations were contacted to obtain missing data. Any disagreements were resolved by discussion and consensus. All studies were assessed for country of origin, authors, primary institution, and years of data collection to ensure outcomes were not collected from overlapping cohorts.

Two review authors independently assessed methodological quality. Risk of bias was judged based on the anticoagulation strategy and this study's primary outcomes, rather than the objectives of the studies. Cochrane's Risk of Bias 2 (ROB 2) tool for RCTs was used.[15] For non-RCTs, the ROBINS-I tool was used.[16] For RCTs where patients were not randomised based on anticoagulation strategy, data was handled as observational, and the ROBINS-I tool was used. Bias surrounding deviation from intended intervention was anticipated, given observational studies are unlikely to report on intentional deviation from institutional protocols in patients with increased bleeding or thrombosis. 'Risk of Bias' summaries are presented using the 'Robvis tool',[17] as well as 'Risk of Bias' judgements for individual studies in the 'Characteristics of Included Studies' table.

2.4. Outcomes

Unless otherwise specified, outcomes were limited to the duration of the time spent on ECMO. The primary outcomes are related to the severity of the bleeding or thrombosis, whereas secondary outcomes are related to the anatomical location of the events.

1. Co-Primary Outcomes:
   A. Primary bleeding outcomes - Major Bleeding Events (as defined by the study), and intracranial bleeding.
   B. Primary thrombotic outcomes - Major thromboembolic events (as defined by the study) and ischaemic stroke.
2. Secondary Bleeding Outcomes (Bleeding Location)
   A. Cannula site bleeding
   B. Gastrointestinal, intraabdominal and retroperitoneal bleeding
   C. Respiratory tract bleeding (pulmonary, tracheobronchial and oropharyngeal)
   D. Thoracic bleeding
   E. Bleeding requiring procedural intervention (surgery, endoscopy, interventional radiology and new drain insertion)
3. Secondary Thrombotic Outcomes (Thrombosis Location)
   a. Major circuit thrombosis defined as a circuit or component change or thrombosis causing haemodynamic compromise
   b. DVT
   c. Embolic phenomena to solid organs
   d. Limb ischaemia
4. Tertiary outcomes
   A. Survival to decannulation-defined as weaning off ECMO, bridge to transplant or bridge to durable circulatory support.
   B. Mortality at longest follow-up

2.5. Data synthesis

Analyses were performed using STATA (MP version 18.1, College Station, TX, USA). It was anticipated that most studies would be single-arm cohort studies and as such, analysis was limited in these cases to incidences. Where multiple different anticoagulation strategies within the same study were included in a single analysis, these strategies were denoted on forest plots by numbers in parentheses following the author's name. For RCTs with anticoagulation strategies as the intervention, risk ratios and mean differences were planned to be reported. Incidences of bleeding complications, thromboembolic complications and mortality were calculated by pooling study-specific data. A random effects model was applied using DerSimonian and Laird for proportions, using the metaprop command in STATA, with 95% confidence intervals. Estimates are represented in forest plots. A sensitivity analysis low risk of bias studies was planned.

2.6. A subgroup analysis and investigation of heterogeneity

Where sufficient data was available, subgroup analyses were performed for primary outcomes based on:

1. Anticoagulant
2. Heparin monitoring test
3. Central cannulation
4. ECPR
5. Post-cardiotomy
6. Use of mechanical support for LV unloading

The incidence of major bleeding according to bleeding definition was also assessed.

Recognised formal bleeding definitions are more thoroughly outlined in the Appendix.

A post-hoc analysis was performed comparing the incidence of major bleeding events in post-cardiotomy patients to patients in studies that exclusively did not contain post-cardiotomy patients.

The I^2 test was utilised to assess statistical heterogeneity for each outcome [17]. We judged I^2 values as follows:

- 0%–40%: might not be important
- 41%–60%: may represent moderate heterogeneity
- 61%–90%: may represent substantial heterogeneity.

3. Results

3.1. Study selection and characteristics

The search identified 12195 studies, of which 159[1,5–10,18–184] were included in the final review, with 21,942 patients in the quantitative synthesis. The details of the search results are outlined in the PRISMA Diagram (Fig. 1). The details of the included studies are outlined in the Table of Characteristics (Table 1, Appendix). Of the 159 included studies, 20 were prospective and 3 were RCTs. None of the three RCTs were randomised to receive an anticoagulation strategy as the intervention. Of the included studies, 151 reported outcomes of interest for UFH[1,5–7,10,18–20,22–97,99–108,110–112,114–119,121–125,127–132,135–140,142,144–150,152–174,179,180,183], 8 for bivalirudin[5,6,8,9,27,132,170,184], 2 for argatroban[27,168], 2 for nafamostat[142,175] and 12 for no anticoagulation[27,32,84,109,121,122,125,127,133,150,163,180].

All included studies were English language studies. With regard to geographical location of publication, most studies originated from the United States of America (46), Germany (23), France (20) and South Korea (17). Other countries included China (11), Japan (6), Italy (5), Australia (3), Saudi Arabia (3), the United Kingdom (3), Canada (2), Taiwan (2) and the Netherlands (2). Croatia, Denmark, Finland, Hong Kong, India, Poland, Turkey and

the United Arab Emirates each published a study included in this manuscript (Table 1).

3.2. Risk of bias

The Risk of Bias assessments for RCTs and observational studies are outlined in Figs. 2 and 3 (Appendix). No study was identified as 'Low Risk of Bias' for the primary outcomes. Given none of the RCTs were randomised by anticoagulation strategy, all three were assessed using the ROBINS-I tool.

3.3. Outcomes

The incidence of the primary, secondary and tertiary outcomes are outlined in Table 2. The most common site of bleeding reported was thoracic bleeding (24%, 95%CI 1–66, $I^2 = 94.49\%$). The most common ischaemic complication was limb ischaemia (95%CI 1–33, $I^2 = 80.97$). In total, 58% (95%CI 24–96, $I^2 = 93.11$) of patients survived to decannulation.

Major Bleeding Events, as defined by individual studies, had an overall incidence of 40% (95% CI 36–44, $I^2 = 97.12$) (Table 2). Significant heterogeneity existed among Major Bleeding Events depending on the definition employed, but there was no between-group difference when only standardised definitions of Major Bleeding were assessed (44%, 95% CI 39–48, $I^2 = 90.66\%$, P = 0.60 between groups) (Fig. 4, Table 4, Appendix). Definitions for Major Bleeding Events used by individual studies were included in Table 1. The incidence of Major Bleeding Events differed significantly between cohorts based on the anticoagulant used due to a small number of nafamostat patients. UFH was by far the most used anticoagulant. In patients managed with UFH, the monitoring tests employed were not associated with a difference in incidence of Major Bleeding Events.

Major thrombotic events had an incidence of 17% (95%CI 14–19, $I^2 = 92.60\%$), with significant difference between anticoagulants, with the lowest incidence among the small nafamostat cohort. The highest incidence of major thrombotic events occurred with UFH (Table 3). In total, 121 papers did not define thrombotic events (Table 1). In studies of with UFH as the anticoagulant, the pooled incidence of major thrombotic events was similar across different monitoring tests.

Three per cent (95%CI 3–4, $I^2 = 64.03\%$) of patients developed ICH (Table 5). Study data was insufficient to analyse nafamostat and argatroban, but the incidence of ICH did not differ significantly between patients anticoagulated with heparin, bivalirudin, or no anticoagulation. Among patients anticoagulated with heparin, the monitoring test employed was not associated with a difference in incidence of ICH. Patients managed without anticoagulation had a lower incidence of ischaemic stroke than UFH (Table 5).

3.4. Subgroup analysis

Subgroup analyses were performed for primary outcomes among ECPR, post-cardiotomy, central cannulation and patients receiving LV unloading (Table 6). Post-cardiotomy represented the subgroup with the largest sample. The number of ECPR and patients receiving LV unloading were comparatively low. A post-hoc analysis comparing major bleeding events in post-cardiotomy studies to non-post-cardiotomy studies demonstrated a significantly higher incidence in the post-cardiotomy population, at 50% (95%CI 43–58) vs 37% (95%CI 31–43) (p = 0.01) (Fig. 5).

3.5. Assessing reporting bias

Funnel plots were generated for each of the co-primary outcomes (Figs. 6–9, Appendix). Asymmetry was evident in all four funnel plots.

4. Discussion

This systematic review and meta-analysis represent the most up-to-date and extensive analysis of anticoagulation practice in VA-ECMO, and included 21,942 patients in the final quantitative analysis. The identified incidence of major bleeding events of 40% and the overall incidence of major thrombosis of 17%. Ischaemic stroke and ICH had respective incidences of 6% and 3%. UFH was by far the most used anticoagulant in this study.

4.1. The incidence of major bleeding events and sites of bleeding

The identified incidence of major bleeding events of 40% was substantially higher than reported in a previous meta-analysis,[185] even when accounting for bleeding definitions employed. A subgroup analysis of major bleeding events reported according to recognised formal definitions such as ELSO, BARC, GUSTO and ISTH demonstrated no between-group heterogeneity. Thoracic bleeding

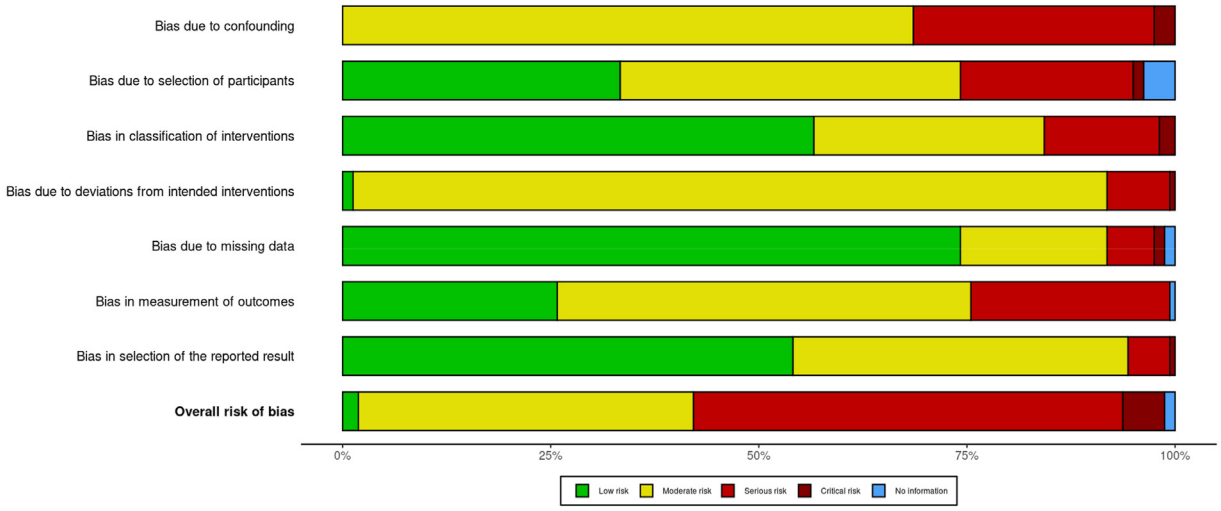

Fig. 2. ROBINS-I summary plot.

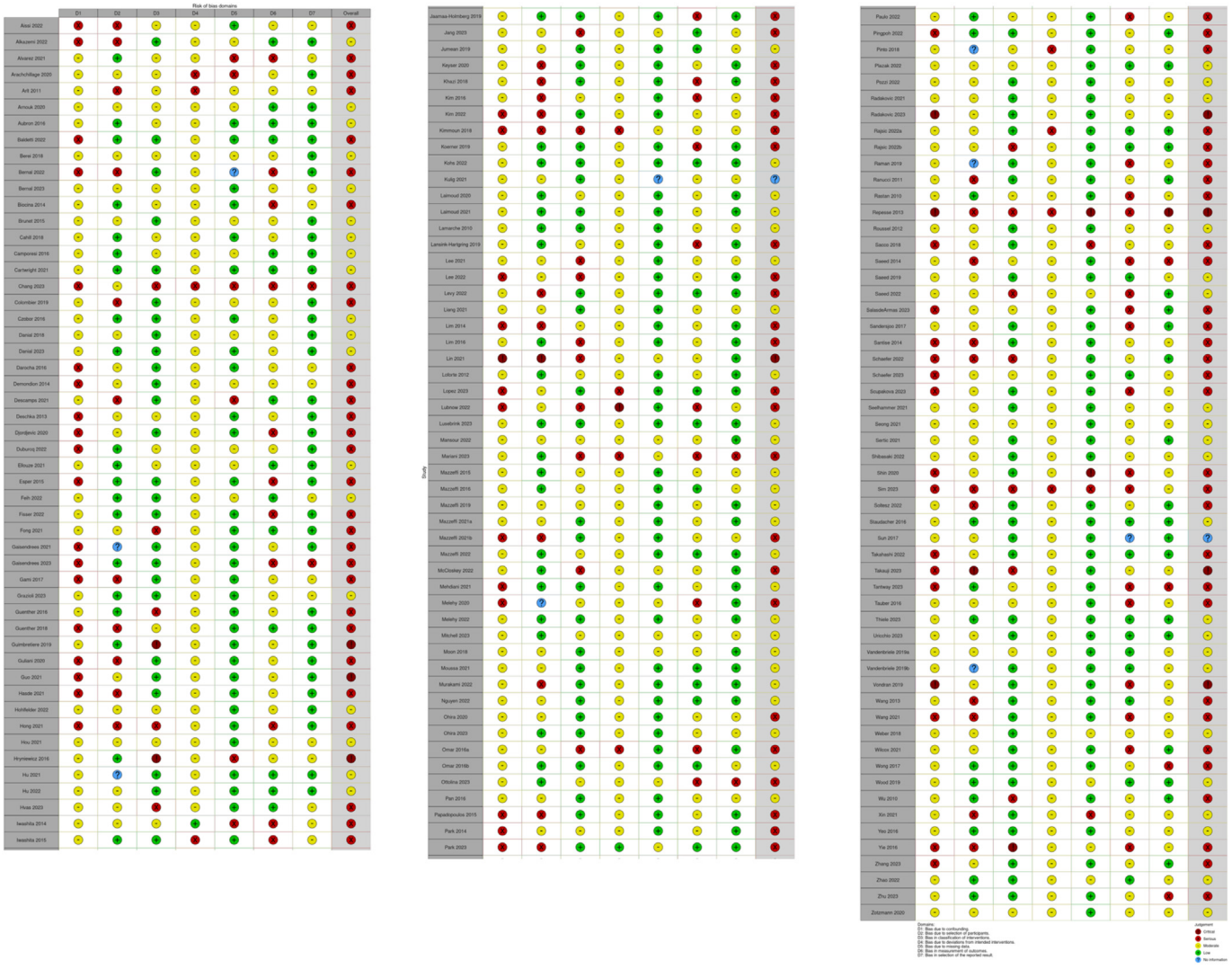

Fig. 3. ROBINS-I traffic light summary.

Table 2
Incidence of haemorrhagic and thrombotic complications in overall population as defined by study.

Event	N=	No. Events	Reported Range (%)	Pooled Estimate (%)	95% CI	I^2
Major bleeding events	12736	5006	2–92	40	36–44	97.12
Cannula site bleeding	8706	1370	2–73	18	16–21	91.93
Abdominal bleeding	4595	476	2–50	11	9–13	82.24
Intracranial haemorrhage	10035	381	1–25	3	3–4	64.03
Respiratory bleeding	2416	213	1–70	9	6–11	87.13
Thoracic bleeding	3550	476	10–66	24	19–30	94.49
Bleeding requiring procedural intervention	6289	2553	0–83	32	25–38	98.01
Major thrombotic events	6505	952	1–69	17	14–19	92.60
Major circuit thrombosis	4394	376	1–50	7	6–9	86.97
DVT	1823	301	0–21	6	4–8	78.50
Intracardiac thrombus	1795	91	1–10	4	3–6	53.75
Ischaemic stroke	10838	862	1–33	6	5–7	83.12
Solid organ emboli	4811	243	1–14	3	2–5	82.74
Limb ischaemia	11544	1197	1–33	9	8–11	80.97
Survival to decannulation	10853	6100	24–96	58	54–61	93.11
Survival at longest follow-up	17865	7866	14–100	46	40–52	92.8

represented the most common site of bleeding. Bleeding requiring procedural intervention occurred in 32%. These two findings may have been confounded by the inclusion of post-cardiotomy patients, as the bleeding in this cohort may reflect surgical bleeding requiring rethoracotomy for haemostasis. The post-hoc subgroup analysis comparing post-cardiotomy patients to non-post-cardiotomy patients demonstrated a significantly higher incidence of major bleeding events in the post-cardiotomy cohort (50 vs 37%,

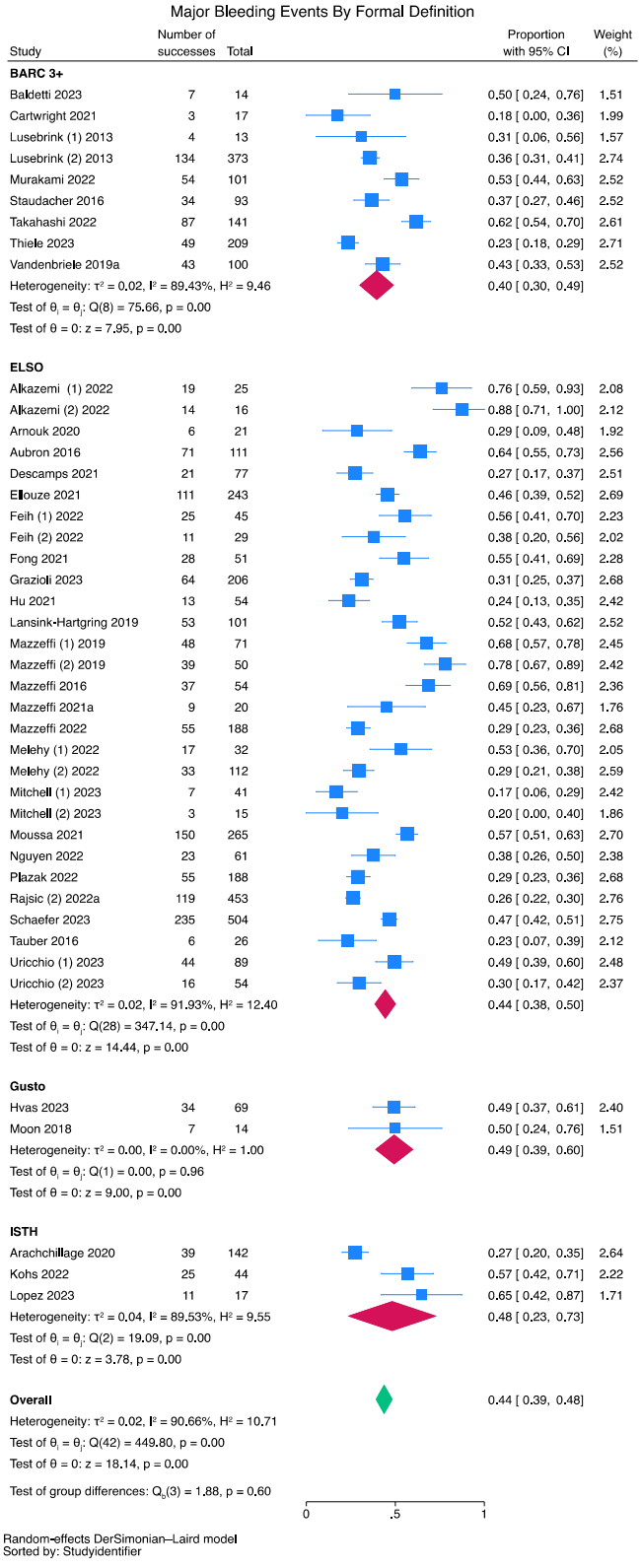

Fig. 4. Major bleeding events with formal definitions.

p = 0.01). Patients receiving additional mechanical left ventricular (LV) unloading had particularly high incidences of major bleeding events compared to the general population and other high-risk subgroups. Major bleeding events were similar across UFH, bivalirudin and anticoagulation-free cohorts. In patients anticoagulated with UFH, major bleeding events were similar across all reported monitoring tests.

4.2. The incidence of major thrombotic events and sites of thrombosis

This study similarly identified an incidence of major thrombotic events (17%) substantially higher than the previously reported 8%.[185] Limb ischaemia represented the most common ischaemic complication. Post-cardiotomy, central cannulation and LV unloading subgroups all demonstrated particularly high incidences of thrombotic complications. This review highlights the lack of consistency in defining major thrombosis in ECMO research, with 121 papers not providing a definition.

4.3. The incidence of neurological complications

The incidence of ischaemic stroke and ICH in this study was in keeping with rates published by the ELSO registry,[186] although the ELSO registry did not describe underlying anticoagulation strategies employed. The proportion of patients surviving decannulation and hospital discharge was in keeping with previously published data.[187] Patients receiving additional mechanical LV unloading had a notably high proportion of ischaemic strokes. Patients managed without anticoagulation interestingly reported a lower incidence of ischaemic stroke. This may represent a selection bias of low thrombotic risk patients being managed with this strategy.

4.4. Comparison to other studies

This meta-analysis reported substantially higher rates of major bleeding events (40% vs 27%) and thrombosis (17% vs 8%) when compared to the previous meta-analysis published by Sy et al[185] They included 26 studies (1496 patients) published between 1977 and 2016. Of these studies, 10 contained exclusively post-cardiotomy patients and 4 contained exclusively ECPR. The current meta-analysis contained only studies published from 2010 onwards to better reflect contemporary practice and technology and included over 20,000 patients. Since the previously published meta-analysis, there has been a sharp increase in published VA-ECMO literature. Sy was unable to assess an association between formal bleeding definitions and the incidence of major bleeding events. They reported an incidence of major bleeding post-cardiotomy of 31% and reported the need for surgical intervention as the most common type of major bleeding. This is a substantially lower incidence of post-cardiotomy major bleeding than the 50% reported in our study, however, we detected an incidence in the need for surgical intervention of 32%. We hypothesise that a lack of standardised bleeding definitions used by Sy et al. resulted in an under-reported incidence of major bleeding events. The proportion of patients surviving decannulation, and hospital discharge in our study was in keeping with previously published data,[187] which is a more objective outcome than bleeding, and we believe this adds to the external validity of this study.

4.5. Strengths and limitations

This meta-analysis represents the most comprehensive and up-to-date analysis of the topic. It followed a pre-published protocol and was completed according to the PRISMA guidelines.[11] This study has demonstrated novel findings relevant to contemporary practice, including the particularly high incidence of bleeding and thrombotic events in patients requiring left ventricular mechanical unloading. This study is also the first meta-analysis to assess the

Table 3
Incidence of major bleeding and thrombotic events by subgroups.

Major Bleeding Events	n=	No. Events	Pooled Estimate (%)	95% CI	I^2 (%)	P value
Overall population	12736	5006	40	36–44	97.12	NA
Overall population by formal definitions[a]	4549	1863	44	39–48	90.66	0.60
Heparin	12183	4848	41	36–46	97.39	<0.05
Bivalirudin	130	51	43	28–58	64.50	
Nafamostat	135	15	8	0–18	72.11	
No anticoagulation	251	84	38	18–58	93.56	
Monitored by APTT[b]	5463	1716	48	39–58	89.43	0.33
Monitored by ACT[b]	1216	502	38	24–51	96.83	
Monitored by anti-Xa[b]	1051	483	48	39–58	89.43	
Multimodal monitoring[b]	1815	813	44	30–58	98.04	
Major thrombosis	**n=**	**No. Events**	**Pooled estimate (%)**	**95% CI**	**I^2 (%)**	**P Value**
Overall population	6505	952	17	14–19	92.60	NA
Heparin	5968	901	19	15–22	93.12	<0.05
Bivalirudin	244	39	15	1–19	0.0	
Nafamostat	135	1	1	0–3	0.0	
No anticoagulation	158	11	6	0–13	76.9	
Monitored by APTT[b]	1621	326	22	16–29	90.74	0.33
Monitored by ACT[b]	580	104	14	6–23	94.94	
Monitored by anti-Xa[b]	993	244	21	15–27	79.79	
Multimodal monitoring[b]	638	91	15	8–22	83.20	

[a] Formal definitions for major bleeding events include ELSO definition, BARC 3+, GUSTO score, ISTH definition etc.
[b] Outcomes in patients managed with UFH according to monitoring test used.

Table 4
Incidence of major bleeding events by study definition.

Major Bleeding Events by Definition						
Anticoagulant	N=	No. Events	Pooled Estimate	95% CI	I^2	P value
ELSO definition	3202	1332	0.40	0.30–0.49	91.93	<0.05
BARC3+	1061	415	0.40	0.30–0.49	89.43	<0.05
MTP	593	150	0.29	0.10–0.48	NA	NA
Surgical intervention	479	94	0.27	0.13–0.40	92.20	<0.05
ISTH	203	75	0.48	0.23–0.73	NA	NA
GUSTO	83	41	0.49	0.39–0.60	NA	NA
Other	3142	1033	0.44	0.34–0.55	97.99	<0.05
No definition provided	3903	1859	0.38	0.27–00.48	97.88	<0.05

Table 5
Incidence of anticoagulation associated neurological complications.

ICH	n=	No. Events	Pooled Estimate (%)	95% CI	I^2 (%)	P value
Overall population	10035	381	3	3–4	64.03	NA
Heparin	9743	373	4	3–4	67.88	0.28
Bivalirudin	89	4	4	0–9	20.8	
No anticoagulation	166	3	2	0–4	0.0	
Monitored by APTT[a]	2825	370	3	2–4	60.67	0.05
Monitored by ACT[a]	1452	242	4	3–5	0.00	
Monitored by anti-Xa[a]	779	224	2	0–4	61.04	
Multimodal monitoring[a]	1198	180	5	3–7	68.21	
Ischaemic stroke	**n=**	**No. Events**	**Pooled estimate (%)**	**95% CI**	**I^2 (%)**	**P Value**
Overall population	10838	862	6	5–7	83.12	NA
Heparin	10428	848	7	5–8	85.16	<0.05
Bivalirudin	207	8	3	1–6	0.00	
No anticoagulation	166	4	2	2–4	0.00	
Monitored by APTT[a]	4321	310	7	5–9	88.68	0.66
Monitored by ACT[a]	1973	149	5	3–7	77.37	
Monitored by anti-Xa[a]	450	59	7	2–13	79.20	
Multimodal monitoring[a]	1574	108	6	4–8	59.54	

[a] Outcomes in patients managed with UFH according to monitoring test used.

incidence of major bleeding specifically in VA-ECMO per anti-coagulation strategy according to well-recognised definitions. The results may serve as a reference for power calculations for future studies in this field.

This meta-analysis highlights that no high-quality data assessing the relationship between anticoagulation strategies and outcomes exists. This is largely due to confounding bias, as populations with heterogenous indications for VA-ECMO

Table 6
Incidence of primary outcomes among high-risk subgroups.

Major Bleeding Events	n=	No. Events	Pooled Estimate (%)	95% CI	I^2 (%)
ECPR	796	367	41	25–58	96.94
Post-cardiotomy	5574	2368	50	43–58	96.57
Central cannulation	342	112	51	22–81	98.03
LV unloading	414	247	60	43–77	93.32
Major thrombosis	**N=**	**No. Events**	**Pooled estimate (%)**	**95% CI**	**I^2 (%)**
ECPR	623	112	13	6–21	90.00
Post-cardiotomy	853	179	23	12–34	90.89
Central cannulation	59	15	25	14–37	NA
LV unloading	194	41	21	15–27	0.00
ICH	**N=**	**No. Events**	**Pooled estimate (%)**	**95% CI**	**I^2 (%)**
ECPR	584	28	4	2–6	42.96
Post-cardiotomy	5059	174	3	2–4	55.82
Central cannulation	104	14	12	6–18	00.00
LV unloading	417	27	5	2–8	60.77
Ischaemic stroke	**N=**	**No. Events**	**Pooled estimate (%)**	**95% CI**	**I^2 (%)**
ECPR	664	25	3	2–4	0.00
Post-cardiotomy	4725	410	7	5–9	71.86
Central cannulation	158	16	8	3–14	33.10
LV unloading	717	104	13	7–19	81.80

inherently carry different risks of major bleeding, as demonstrated by this study. Future studies should attempt to include more homogenous populations. Another major limitation of this study is that it represents a meta-analysis of intention to follow departmental anticoagulation protocols, rather than an individual patient data meta-analysis. This paper is unable to account for the time spent with anticoagulation in the therapeutic range or individual clinicians' responses to major bleeding or thrombotic events. Similarly, transfusion triggers vary between centres and the requirement for transfusion as a definition of major bleeding is potentially problematic. Therefore at least a moderate risk of bias due to deviation from intended intervention was present in most studies. Heterogeneity was expected and we attempted to account for this where able. Variations in definitions and confounding biases of populations likely represent a large component of the heterogeneity encountered. However, over-interpretation of the I^2 test results reported in this study should be cautioned, as high I^2 results are typical for meta-analyses of proportions.[188]

Although this review assessed the overall incidence of mortality and survival to decannulation, we did not assess their association with individual anticoagulation strategies. This represents an important next step for an investigation to determine if anticoagulation strategies can be utilised to improve patient outcomes. Our study was not able to assess the relationship between bleeding or thrombosis site and outcomes. This study also did not assess the association between anticoagulation range and outcomes. This study has highlighted the need for high-quality prospective data assessing the association between specific bleeding and thrombotic events and patient-centred outcomes, and whether anticoagulation strategies are a modifiable risk factor for improving these outcomes. Although there were 3 RCTs included in our analysis, the intervention to which patients were randomised in each was not anticoagulation.

The sample sizes for novel anticoagulation strategies such as direct thrombin inhibitors and nafamostat were limited, and it is

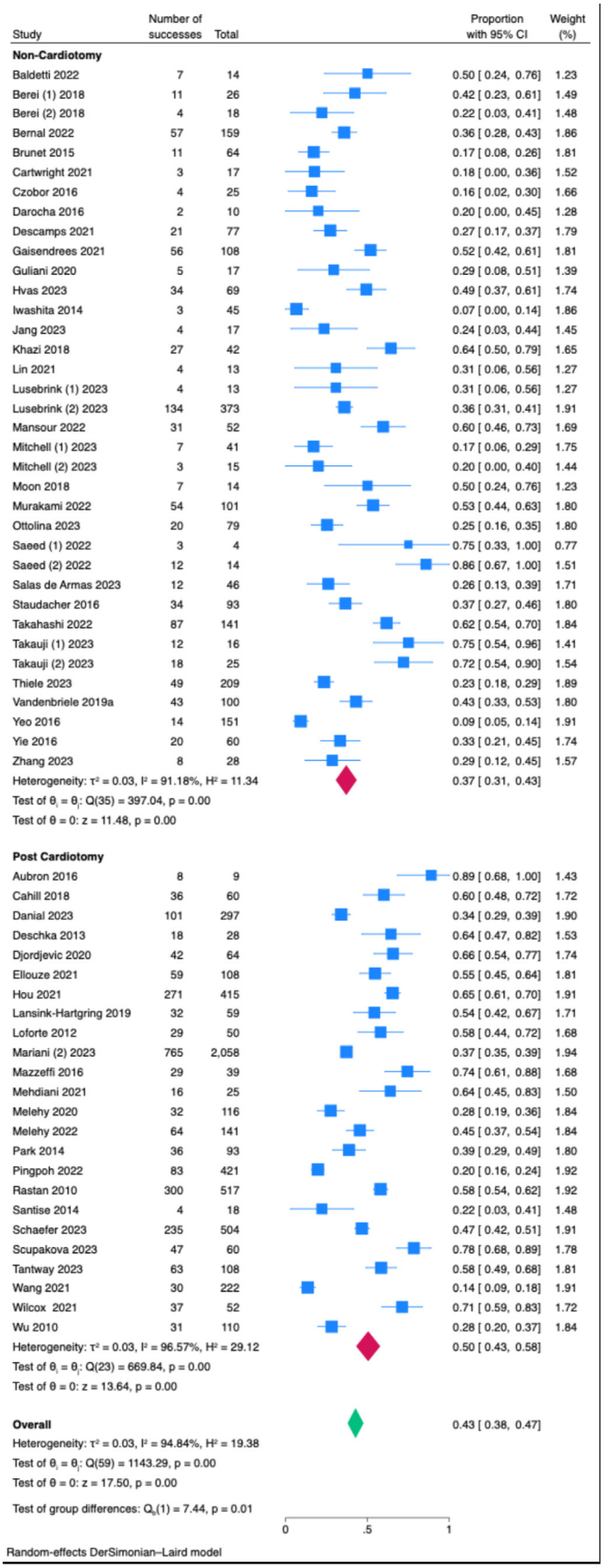

Fig. 5. Major bleeding events in post-cardiotomy vs non-cardiotomy patients.

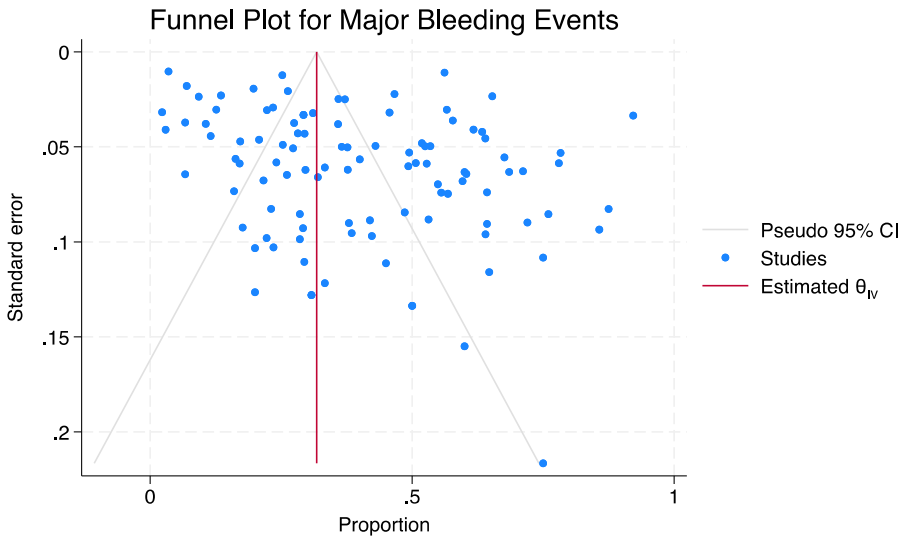

Fig. 6. Funnel plot for Major Bleeding Events.

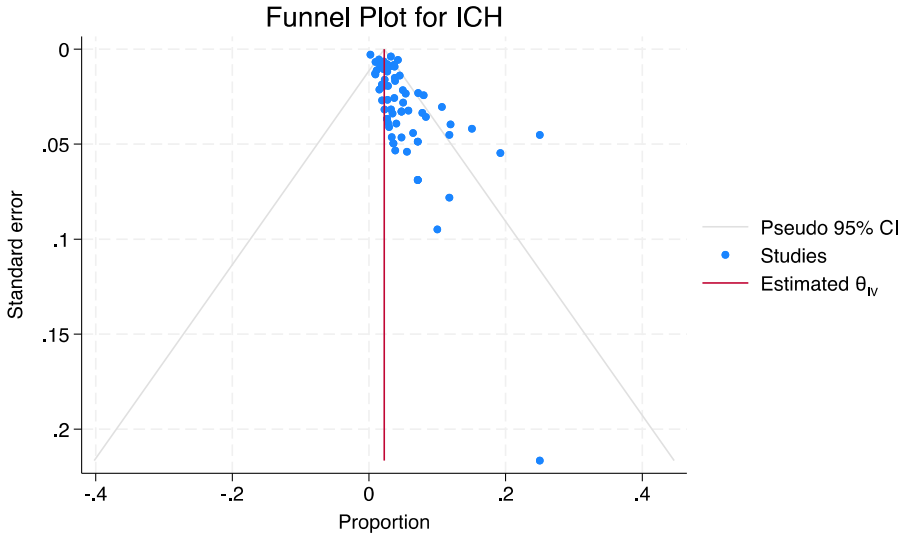

Fig. 7. Funnel plot for ICH.

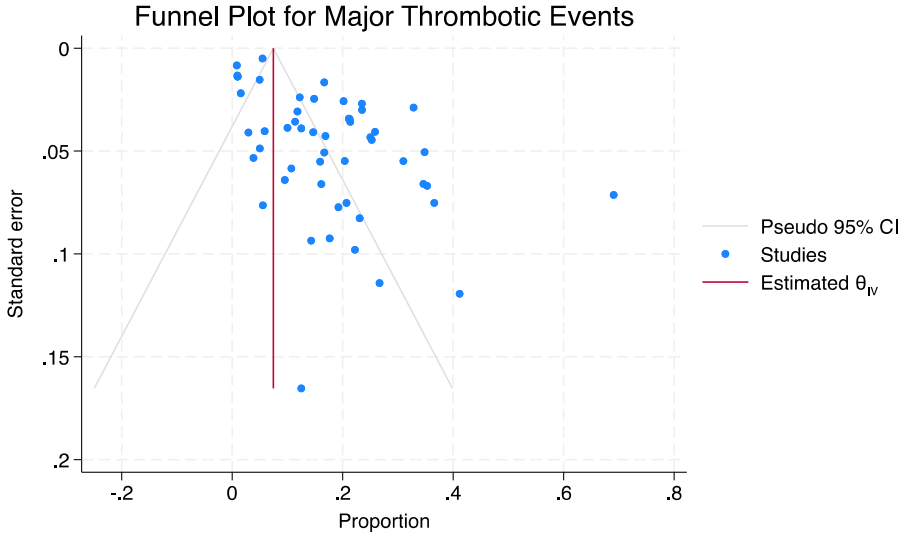

Fig. 8. Funnel plot for major thrombotic events.

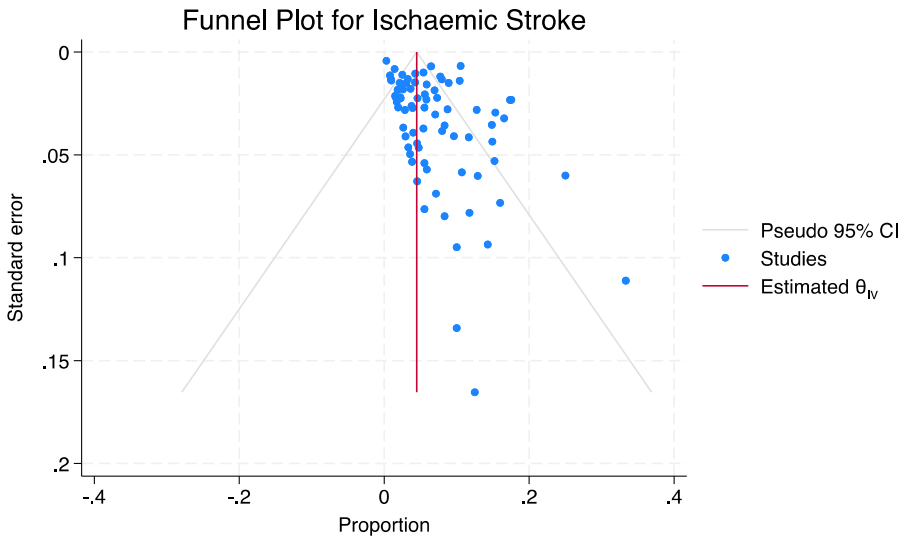

Fig. 9. Funnel plot for ischaemic stroke.

difficult to draw firm conclusions on these cohorts, especially regarding outcomes with lower incidences such as neurological complications.

In conclusion, the incidence of major bleeding identified in this study is higher than previously reported. Post-cardiotomy patients, those that underwent LV unloading, and central cannulation had particularly high incidences of Major Bleeding. The incidence Major Bleeding Events, Major Thrombotic Events and ICH were similar among UFH, bivalirudin and anticoagulation-free VA-ECMO, and did not differ between UFH monitoring tests. The numbers reported for patients managed with non-UFH-based strategies were low.

Conflict of 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.The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Prof John Myburgh declares he is part of the CC&R editorial team as an associate editor. The other 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.

Author contribution statement

Author contribution to this manuscript is as listed:

Dr Ruan Vlok- Writing (original draft), conceptualisation, formal analysis, data collection and curation, project administration.

A/Prof Hergen Buscher- Conceptualisation, methodology, review and editing of the manuscript, visualisation.

A/Prof Anthony Delaney- Review and editing of the manuscript, visualisation, supervision of formal analysis, methodology.

Dr Tessa Garside- Review and editing of the manuscript, visualisation, methodology, formal analysis.

Dr Gabrielle McDonald- Data collection and curation, review and editing of the manuscript.

Dr Richard Chatoor- Data collection and curation, review and editing of the manuscript.

Prof John Myburgh- Methodology, review and editing of the manuscript, supervision.

A/Prof Priya Nair- Supervision, review and editing of the manuscript, conceptualisation, project administration.

On behalf of the authors of this manuscript, all authors provided a substantial contribution to the production of this manuscript and have reviewed the final manuscript for submission.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ccrj.2024.10.003.

SUPPLEMENTAL MATERIAL

Search Strategy in Ovid Format:

Database: Ovid MEDLINE(R) ALL <1946 to Present>
Search Strategy:

1 ECMO.tw. or Extracorporeal Membrane Oxygenation/
2 (ECLS or Extracorporeal Life Support).tw.
3 extracorporeal.tw. or Extracorporeal Circulation/
4 'Extracorporeal cardiopulmonary resuscitation'.tw.
5 ECPR.tw.
6 1 or 2 or 3 or 4 or 5
7 anticoagula*.tw. or Anticoagulants/
8 (heparin or UFH or unfractionated).tw. or Heparin/
9 bivalirudin.tw.
10 Nafamostat.tw.
11 prostacyclin.tw.
12 epoprostenol.tw.
13 argatroban.tw.
14 APTT.tw. or Partial Thromboplastin Time/or Blood Coagulation/ or Blood Coagulation Tests/or Prothrombin Time/
15 (TEG or thromboelastography).tw.
16 (ROTEM or thromboelastometry).tw.
17 viscoelastic.tw. (16726)
18 (activated clotting time or ACT).tw.
19 anti$XA.tw.
20 Platelet Function Tests/
21 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20
22 Bleed*.tw.
23 Gastrointestinal Haemorrhage/
24 Haemostasis/or h*emosta*.tw.

25 Postoperative Complications/or Postoperative Haemorrhage/or Reoperation/
26 ('return to theatre' or 'rethoracotomy').tw.
27 Thrombosis/or thromb*.tw.
28 Intracranial Thrombosis/or Embolic Stroke/or Haemorrhagic Stroke/or Ischemic Stroke/or Stroke/or Thrombotic Stroke/
29 Venous Thrombosis/or Pulmonary Embolism/or Venous Thromboembolism/
30 (DVT or deep vein thrombosis).tw.
31 Ischemia/or Peripheral Arterial Disease/or Arterial Occlusive Diseases/
32 Blood Component Transfusion/or Blood Transfusion/or Erythrocyte Transfusion/or Platelet Transfusion/(69654)
33 transfus*.tw.
34 ('massive transfusion' or MTP).tw.
35 'bleeding event'.tw.
36 'thrombotic event'.tw.
37 BARC.tw.
38 thromb$s.tw.
39 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38
40 6 and 21 and 39

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