Analysis of Current Anticoagulation Practices in Extracorporeal Membrane Oxygenation

by

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Abstract

Management of anticoagulation in patients undergoing extracorporeal membrane oxygenation (ECMO) is controversial despite more than 50 years of ECMO experience. According to the most recent Extracorporeal Life Support Organization (ELSO) guidelines from 2021, there are currently no standardized protocols for anticoagulation agents or monitoring. ELSO currently lists heparin as the most commonly used primary anticoagulant for pediatric and adult ECMO, but they also state many centers have switched to using direct thrombin inhibitors (DTIs) as their primary anticoagulant. The goal of this project was to survey currently licensed and practicing perfusionists in the United States (U.S.) to determine current practices of anticoagulation during ECMO. In addition to determining the most common primary anticoagulant and anticoagulation test used, the survey aimed to glean insights into individual perfusionist preference regarding ECMO anticoagulation.

After the research project was approved by the Milwaukee School of Engineering Institutional Review Board (IRB), responses were collected from November 2023 through January 2024. A recruitment letter explaining the goals of the investigation and survey as well as a link to the survey was posted on a variety of perfusion platforms including Perfusion.com and the Women in Perfusion Facebook group. The survey link was also distributed to perfusionists at Aurora St. Luke's Medical Center, Froedtert Hospital, and Children's Hospital of Wisconsin. Multiple perfusionists from the same institution were allowed to participate in order to focus on individual beliefs. Questions were modeled after two recent surveys focused on anticoagulation practices in ECMO, one an international adult survey by Esper *et al.* from 2017 and the other a 2022 U.S. pediatric survey by Frazier *et al.*

Similar to the results from other surveys conducted in 2017 and 2022, this survey found the majority of respondents (73%) use heparin as their center's primary ECMO anticoagulant and activated partial thromboplastin time (aPTT) as the predominant monitoring test. When asked about individual preference, the majority of respondents (36%) selected heparin as their preferred anticoagulant on ECMO while 27% selected bivalirudin. Almost one third (32%) did not prefer one anticoagulant over another. In this survey, 24% of respondents indicated bivalirudin as their center's primary ECMO anticoagulant, which is a significant increase from just 2% and 8% from the 2017 and 2022 surveys, respectively. These percentages indicate there may be a downward shift in the use of heparin as the primary ECMO anticoagulant and an increase in bivalirudin usage. Continued research and implementation of DTIs is necessary before ECMO anticoagulation practices can be standardized.

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Nomenclature

ACT: Activated clotting time

aPTT: Activated partial thromboplastin time

ATIII: Antithrombin III

ARDS: Acute respiratory distress syndrome

CO_2: Carbon dioxide

CPB: Cardiopulmonary bypass

DTI: Direct thrombin inhibitor

ECLS: Extracorporeal life support

ECMO: Extracorporeal membrane oxygenation

ELISA: Enzyme-linked immunosorbent assay

ELSO: Extracorporeal Life Support Organization

FFP: Fresh frozen plasma

HIT: Heparin-induced thrombocytopenia

IU: International unit

IRB: Institutional Review Board

MSOE: Milwaukee School of Engineering

mL: Milliliter

O_2: Oxygen

PF4: Platelet factor 4

PT/INR: Prothrombin time/internationalized normalized ratio

PVC: Polyvinyl chloride

RBC: Red blood cell

ROTEM: Rotational thromboelastometry

SRA: Serotonin release assay

TACO: Transfusion-associated circulatory overload

TEG: Thromboelastography

TRALI: Transfusion-related acute lung injury

U.S.: United States

VA: Veno-arterial

VV: Veno-venous

WHO: World Health Organization

1.0 Introduction

Extracorporeal membrane oxygenation (ECMO), also referred to as extracorporeal life support (ECLS), is an advanced life support therapy in which a heart-lung machine takes over the work of a patient's lungs and/or heart to allow them to recover from illness or wait for a transplant [1]. ECMO is utilized in children and adults and can be used anywhere from days to weeks to even months at a time [1]. The interaction of a patient's blood with the non-biological surfaces of the ECMO circuit leads to an increased rate of blood clot formation (thrombosis) in both the patient and ECMO circuit and can cause a variety of complications [2]. To prevent thrombosis, ECMO patients are placed on an anticoagulant.

The two most common anticoagulants used in ECMO patients are heparin and direct thrombin inhibitors (DTIs) [2]. Heparin is an indirect thrombin inhibitor and remains the predominant anticoagulant used in ECMO patients due to its low cost, familiarity of use, and easy reversibility with protamine [2]. Heparin also comes with several potential disadvantages including unpredictable anticoagulant response, heparin resistance, and heparin-induced thrombocytopenia (HIT) [3]. New data show some centers have switched to using a DTI, most commonly bivalirudin or argatroban, as opposed to heparin as their primary anticoagulant in ECMO [4]. DTIs have several advantages over heparin including a more predictable anticoagulation response, no risk of HIT, and no antithrombin III (ATIII) monitoring or supplementation [4]. However, there are a number of limitations regarding DTIs including no pharmacologic antidote to reverse their effects, higher cost, and less familiarity with use [5].

Management of anticoagulation in patients undergoing ECMO is controversial despite more than 50 years of ECMO experience [1]. The Extracorporeal Life Support Organization (ELSO) is an international nonprofit organization that provides current guidelines in management of ECMO patients, continuing education to those delivering ECMO support, and a comprehensive registry of ECMO patient data [4]. According to the most recent ELSO guidelines published in 2021, there are currently no standardized protocols for anticoagulation in patients requiring ECMO [4]. ELSO currently lists heparin as the most commonly used primary anticoagulant for pediatric and adult ECMO, but they also report an increase in centers using DTIs as their primary anticoagulant [4].

There are two recent surveys analyzing current anticoagulation practices in ECMO, one from 2017 and the other from 2022. The first, published in 2017 by Esper *et al.*, was an adult ECMO international survey that found 45 of 47 responding institutions (95.7%) used heparin as their primary ECMO anticoagulant [6]. The other, published in 2022 by Frazier *et al.*, was a pediatric ECMO survey in the U.S. and found 35 of 38 (92.1%) responding pediatric clinical pharmacists used heparin as their primary ECMO anticoagulant [7]. Although these studies are recent, trends in coagulation management often shift quickly.

The goal of this project was to survey currently licensed and practicing perfusionists in the United States (U.S.) to determine current practices of anticoagulation in ECMO. The survey was modeled after those published in 2017 by Esper *et al.* and in 2022 by Frazier *et al*. In addition to determining the most common primary anticoagulant and primary anticoagulation test used at various centers in the U.S., individual

perfusionist preferences regarding ECMO anticoagulation were assessed in an effort to better understand if personal preferences aligned with institutional protocols.

2.0 Background

2.1 Types of ECMO

There are two main types of ECMO: veno-venous (VV) and veno-arterial (VA). VV ECMO is used for pulmonary support only, whereas VA ECMO provides both pulmonary and cardiac support [8]. Common indications for VV ECMO include acute respiratory distress syndrome (ARDS), acute lung injury, hypoxia/hypercarbia, and bridge to lung transplant [8]. For patients without preserved cardiac function, in which case VV ECMO is not an option, VA ECMO may be utilized to provide complete cardiopulmonary support. Common indications for VA ECMO include failure to wean from cardiopulmonary bypass (CPB), cardiogenic shock, and acute heart failure [9]. Not all patients are candidates for ECMO, and the risks and benefits must be carefully weighed prior to putting someone on ECMO. Contraindications for VV and VA ECMO are not absolute but typically include overwhelming sepsis, multisystem organ failure, non-survivable neurologic injury, advanced malignancy diagnosis, elderly age (typically over 70 years), contraindications to anticoagulation, and more [8].

For both VV and VA ECMO, deoxygenated blood is drained from the patient's venous system via a venous cannula, pumped across a membrane oxygenator that adds oxygen (O_2) and removes carbon dioxide (CO_2) from the blood, and then returns oxygenated blood back to the patient [9]. In VV ECMO, oxygenated blood is returned to the patient's venous system via a venous reinfusion cannula, and with VA ECMO this oxygenated blood is returned to the patient's arterial system via an arterial reinfusion cannula [8]. There are a variety of different cannulation strategies for ECMO including central, femoral, and other peripheral cannulation [8].

2.2 Pathophysiology of Thrombosis in ECMO

The ECMO circuit consists of a drainage cannula, centrifugal blood pump, membrane oxygenator, heat exchanger, and reinfusion cannula, which are all connected together with polyvinyl chloride (PVC) circuit tubing [10]. In humans, endothelium helps regulate hemostasis and prevents excessive bleeding or clotting [11]. Unfortunately, when a patient is on ECMO and their blood is constantly exposed to the foreign components of the ECMO circuit, these protective endothelial mechanisms no longer contribute to hemostasis. Exposure to the artificial surface results in activation of platelets, leukocytes, neutrophils, and cytokines as well as initiation of coagulation and complement systems [5]. Turbulent flow and shear forces within the ECMO circuit also contribute to thrombus formation [11]. Overall, the result of ECMO is an inherent prothrombotic state that can result in a variety of patient and circuit complications including oxygenator failure, stroke, heart attack, blood clots in the lungs, reduced flow to limbs resulting in possible amputation, and more [5]. To decrease the risk of clots in the patient and ECMO circuit, patients are placed on an anticoagulant.

A significant challenge of ECMO is trying to achieve the perfect balance of adequate anticoagulation to prevent clots in the circuit and patient without over anticoagulating and causing bleeding [12]. Some of the most common risks that occur with ECMO include severe bleeding (up to 29%), circuit thrombosis (up to 13%), and intracranial hemorrhage (up to 10%) [13]. Common sites of bleeding include cannulation sites, intracranial, gastrointestinal, intrathoracic, and retroperitoneal [13]. As seen in Figure 1, thrombotic and bleeding complications during ECMO are common and have a significant impact on patient outcomes [12].

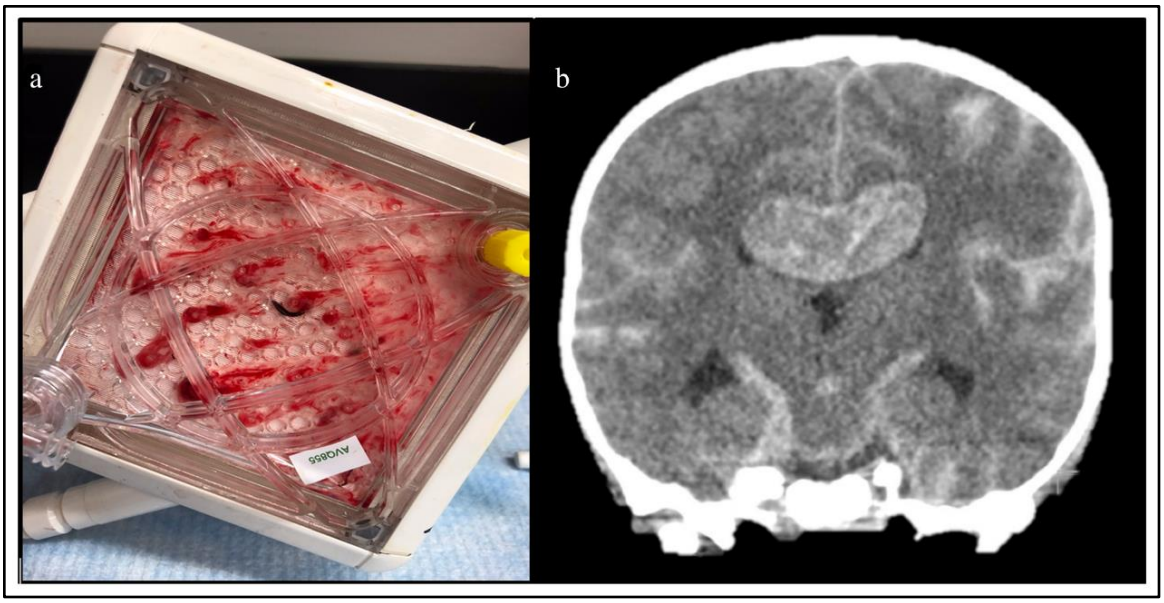

Figure 1: Balance Between Thrombotic and Bleeding Complications on ECMO [12]. Picture (a) demonstrates significant thrombus in the oxygenator and (b) demonstrates a large intraventricular hemorrhage.

2.3 Types of Anticoagulants Used in ECMO

The two most common anticoagulants used in ECMO patients are heparin and DTIs [2]. Heparin is an indirect thrombin inhibitor and acts by binding to several proteins, most notably a small protein called ATIII, which neutralizes the enzymatic activity of thrombin [14]. Inactivating thrombin blocks the conversion of fibrinogen to fibrin which prevents the formation of blood clots [15]. Heparin increases the anticoagulation activity of ATIII by 1,000 to 2,000 fold [12, 16, 17]. Heparin remains the predominant anticoagulant used in ECMO patients due to its low cost, familiarity of use, and easy reversibility with protamine [2]. Heparin also comes with several potential disadvantages including unpredictable anticoagulant response, heparin resistance, and HIT [3].

New data show some centers have switched to using a DTI, most commonly bivalirudin or argatroban, as opposed to heparin as their primary anticoagulant in ECMO [4]. In contrast to heparin, which requires adequate levels of ATIII to exert its anticoagulant effect, DTIs directly bind to thrombin independently of ATIII [17]. The mechanisms of action of indirect and direct thrombin inhibitors are compared in Figure 2 [18]. DTIs have several advantages over heparin including a more predictable anticoagulation response, no risk of HIT, and no ATIII monitoring or supplementation [4]. However, there are a number of limitations regarding DTIs including no pharmacologic antidote to reverse their effects, higher cost, and less familiarity with their use [5].

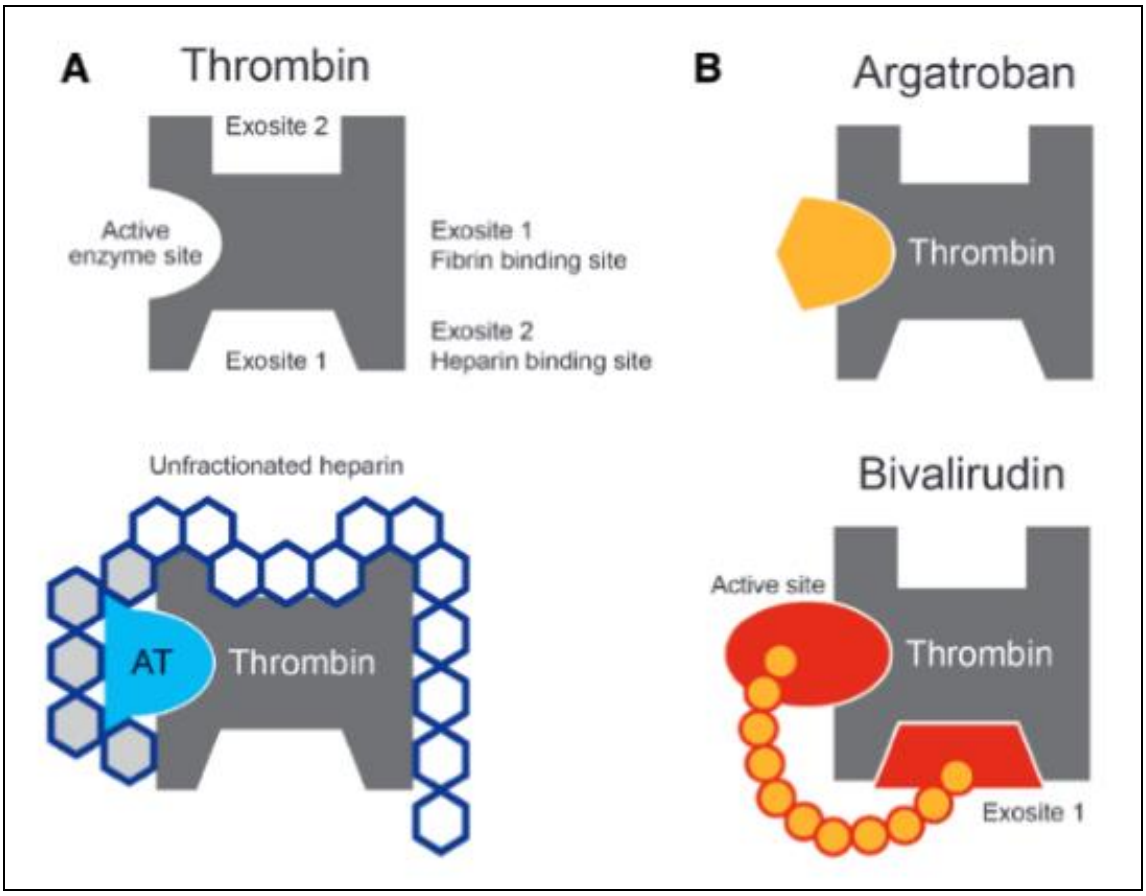

Figure 2: Mechanisms of Action of Indirect and Direct Thrombin Inhibitors [18]. (A) Indirect inhibition of thrombin by antithrombin (AT), which is activated via heparin. (B) Direct inhibition of thrombin by argatroban and bivalirudin. Argatroban directly inhibits thrombin via univalent binding to thrombin's active site. Bivalirudin directly inhibits thrombin by binding to both its active site as well as secondary binding site (exosite).

2.4 Advantages and Limitations of Heparin

Heparin is the predominant anticoagulant used in ECMO due to its low cost, familiarity of use, and easy reversibility with protamine. Heparin, derived from porcine mucosa, is one of the cheapest anticoagulants available, costing only a fraction of the price of DTIs [19]. Its onset of action is immediate when administered intravenously and it has a relatively short half-life of 60 to 90 minutes [15]. In cases of severe bleeding or adverse reactions, heparin's effects can be easily reversed with administration of

protamine [20]. Since the development of ECMO over 50 years ago, heparin has been the primary anticoagulant used and seems to be the anticoagulant the majority of healthcare professionals are most comfortable using [5]. While heparin has its advantages, there are also a number of limitations including unpredictable anticoagulant response, heparin resistance, and HIT [3].

2.4.1 Unpredictable Anticoagulant Response

As previously mentioned, heparin is an indirect thrombin inhibitor and acts by binding to several proteins. In addition to binding ATIII and inhibiting thrombin and factor Xa to exert its anticoagulant effect, heparin also binds to various plasma proteins including fibronectin, glycoproteins, apolipoproteins, and complement factors C3 and C4b as well as endothelial cells and macrophages, all of which can contribute to an unpredictable anticoagulant response [20]. In critically ill patients, the concentration of these proteins is elevated, resulting in increased binding of heparin to these proteins and further reduction in heparin's ability to provide adequate anticoagulation [20]. In the later phase of illness, heparin can be released from these proteins and cause an increase of heparin binding to ATIII, resulting in severe bleeding [20]. Additionally, heparin does not inhibit thrombin already bound to fibrin [18]. This means fibrin-bound thrombin remains active and clot growth can continue despite heparin therapy [18, 20]. The inability of heparin to inactivate fibrin-bound thrombin and the high degree of heparin binding to plasma proteins, endothelial cells, and macrophages results in a relatively unpredictable heparin response [12, 20].

2.4.2 Heparin Resistance

Heparin resistance is a phenomenon observed in up to 50% of ECMO patients in which standard heparin dosing does not yield sufficient anticoagulation and increased doses of heparin are required to achieve adequate anticoagulation for the safe conduct of ECMO [20, 21]. It is most recognizable in situations where the patient previously responded to heparin, but after reaching a certain threshold, no additional, or only a minimal increase, in anticoagulation is observed with additional heparin [20]. This phenomenon is most frequently caused by low levels of ATIII (defined as levels less than 70% of normal) and requires administration of ATIII either in the form of fresh frozen plasma (FFP) or ATIII concentrate [12].

FFP is far less expensive than ATIII concentrate, with an approximate cost of $410 per dose compared to thousands of dollars per dose of concentrate [22, 23, 24]. Although more affordable, FFP carries the risk of transfusion reactions and transmission of viral infections [20]. Additionally, there is variability in the amount of ATIII in FFP and thus greater amounts of FFP may be required to achieve adequate ATIII levels, which could lead to transfusion-associated circulatory overload (TACO) or transfusion-related acute lung injury (TRALI) [12]. ATIII concentrate, on the other hand, contains a known amount of ATIII and undergoes a pasteurization process to eliminate the risk of viral transmission [20].

The two most common ATIII concentrates are Thrombate and Atryn [12]. Thrombate is a human plasma-derived form of ATIII and supplied as 500-international units (IU) and 1,000-IU vials, with an approximate cost of $2,330 and $4,660 per vial, respectively [23]. Atryn is a recombinant form of ATIII developed from goat milk and is

supplied as 525-IU or 1,750-IU vials, with an approximate cost of $3,275 and $10,900 per vial, respectively [24]. Regardless of whether ATIII is supplemented via FFP or concentrate, administration requires close patient monitoring and likely adjustment of the heparin infusion rate to prevent bleeding [20]. If heparin resistance occurs, careful administration of ATIII or switching to a different anticoagulant is recommended [20].

2.4.3 Heparin-Induced Thrombocytopenia (HIT)

HIT is another serious, potentially life-threatening complication of heparin [4]. HIT is described as an autoimmune thrombocytopenic syndrome resulting from exposure to heparin [25]. HIT can be classified as either Type I or Type II. Type I is a transient, non antibody-mediated reaction that occurs in 10% to 20% of all patients treated with heparin [20]. It presents as a mild decrease in platelet count within the first two days of exposure to heparin and results from heparin-induced microaggregation of platelets [25]. Type I is reversible, does not result in any thrombi formation or other serious complications, and does not usually require intervention or a switch to a different type of anticoagulant [20].

Type II is a more severe and complex complication caused by antibodies directed against molecular complexes containing heparin and an endogenous platelet protein, platelet factor 4 (PF4) [20]. The IgG antibody is the primary mediator of Type II and binds specifically to heparin-PF4 complexes [26]. These complexes lead to abnormal and irreversible platelet activation and aggregation, activation of endothelial cells, monocytes, and macrophages, and release of tissue factor and other proaggregatory stimuli, all of which can result in severe venous and/or arterial thrombotic complications [20].

Thrombotic complications develop in 30% to 70% of patients with confirmed Type II HIT [26]. The mechanism of Type II HIT is illustrated in Figure 3 [26].

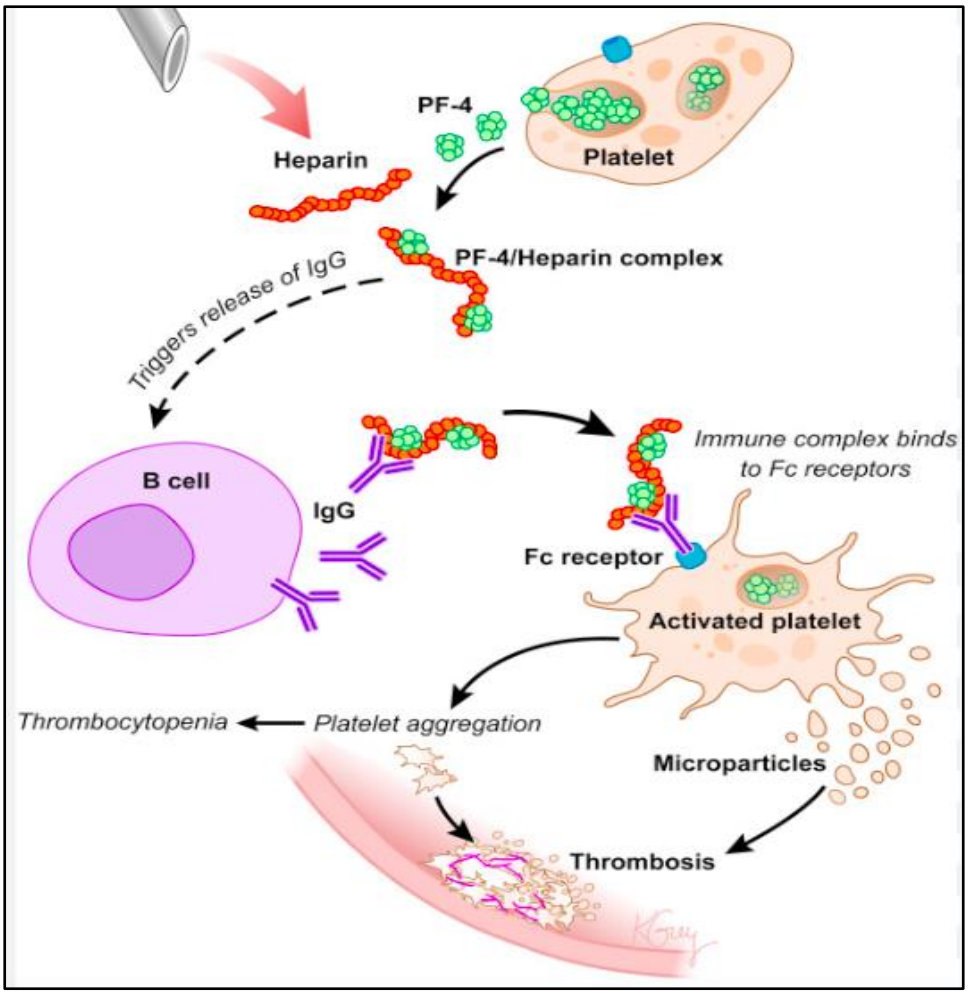

Figure 3: Mechanism of Type II HIT [26]. Administration of heparin causes platelet release of PF-4. Heparin binds to PF-4 and results in PF4-heparin complexes. IgG antibodies are released from B cells and bind specifically to PF4-heparin complexes. These immune complexes lead to platelet activation and aggregation, release of proaggregatory stimuli, and ultimately result in thrombosis and thrombocytopenia.

Type II HIT typically develops within the first five to ten days after exposure to heparin and is characterized by severe thrombocytopenia, with a decrease in platelet count over 50% or a platelet count of less than 50,000 per microliter of blood [20, 25]. Type II HIT occurs in up to 5% of ECMO patients and results in mortality rates between 10 to 30% of those affected [27, 28]. The risk factors for development of HIT include five or more days of heparin use, post cardiac surgery, and female gender [29]. Patients with suspected HIT should be screened with an enzyme-linked immunosorbent assay (ELISA) for PF4 and a serotonin release assay (SRA). The ELISA PF4 is an antigen-based assay that is extremely sensitive for detecting antibodies against heparin-PF4 complexes and yields results in as little as 90 minutes [28]. Despite its impressive sensitivity and quick turnaround time, the ELISA PF4 is limited by low specificity and a high number of false positive results [25]. This high number of false positives is a reason why most centers will also run an SRA if HIT is suspected. The SRA is a highly specific test for pathogenic HIT antibodies and is considered the gold standard for diagnosing HIT, but unfortunately results can take days to come back [30]. If HIT is suspected or confirmed, heparin must be immediately discontinued and the patient should be switched to another type of anticoagulant, most commonly a DTI [20, 30].

2.5 Advantages and Limitations of Direct Thrombin Inhibitors (DTIs)

Bivalirudin and argatroban are the most popular DTIs used and have several advantages compared to heparin, including a more predictable response, no ATIII monitoring or supplementation, no risk of HIT, and the ability to neutralize both free thrombin and fibrin-bound thrombin [4, 18, 31]. However, there are a number of limitations regarding DTIs including no pharmacologic antidote to reverse their effects and less familiarity of use [5]. Furthermore, DTIs are significantly more expensive than heparin, with an average daily cost of $1,500 for bivalirudin and $1,250 for argatroban, which is almost ten times the daily cost of heparin ($150) [19].

Bivalirudin is a small synthetic peptide derived from the naturally occurring drug hirudin, which is found in leech saliva [31]. Bivalirudin directly inhibits thrombin by binding to both its primary active site as well as secondary binding site (exosite) [18]. Bivalirudin has a quick onset of action of two to four minutes and unlike heparin and argatroban, which both bind to plasma proteins in addition to thrombin, bivalirudin only binds to thrombin. This allows for more predictable dosing and anticoagulant response [32]. Approximately 80% of bivalirudin is eliminated by enzymatic cleavage and ~20% is renally eliminated [18]. The elimination half-life of bivalirudin is ~25 minutes in the presence of normal renal function but can increase to 60 up to 240 minutes in patients with severe renal dysfunction or failure [18]. In addition to renal failure patients, bivalirudin should not be used in low flow states due to its rapid cleavage and possible result of thrombosis in low flow or stagnant blood [32].

Argatroban is a synthetic nonpeptide derivative of the amino acid L-arginine that directly inhibits thrombin via univalent binding to the active site [18]. Argatroban has a

slightly longer onset of action compared to heparin and bivalirudin, taking approximately 30 minutes to exert its anticoagulant effects [33]. In addition to binding thrombin, argatroban is 54% bound to the serum proteins albumin and alpha1-acid glycoprotein [32]. Despite binding to other proteins, argatroban still has a more predictable anticoagulant effect than heparin [4]. Unlike bivalirudin, argatroban is primarily metabolized in the liver and is a good alternative for patients with renal impairment [18]. Argatroban has a relatively short elimination half-life of ~45 minutes, but this can be prolonged in patients with severe hepatic dysfunction [18]. In addition to its independence from renal dysfunction, another advantage of argatroban over bivalirudin is the lack of thrombotic events associated with low blood flow [20]. The clinical and pharmacologic properties, advantages, and disadvantages of the major anticoagulants used in ECMO are summarized in Table 1 [18, 32].

Table 1: Summary of Properties, Advantages, and Disadvantages of Anticoagulants Used in ECMO [18, 32].

	Heparin	Bivalirudin	Argatroban
Mechanism of Action	Indirect thrombin inhibitor, potentiates ATIII by 1,000 to 2,000 fold	DTI	DTI
Onset of Action	Immediate	2 to 4 min	30 min
Plasma half-life	60 to 90 min	~25 min	~45 min
Binding to Other Proteins	Yes	No	Yes
Antidote	Protamine	None	None
Advantages	Inexpensive, well known, has a reversal agent	More predictable response, no ATIII monitoring or supplementation, no risk of HIT, able to inhibit free thrombin and fibrin-bound thrombin	More predictable response, no ATIII monitoring or supplementation, no risk of HIT, able to inhibit free thrombin and fibrin-bound thrombin
Disadvantages	Unpredictable response, ATIII monitoring and supplementation, risk of heparin resistance and/or HIT, only able to inhibit free thrombin	Expensive, less familiarity of use, no reversal agent, risk of thrombosis in low flow states, not recommended in renally impaired patients	Expensive, less familiarity of use, no reversal agent, not recommended in hepatically impaired patients

2.6 Methods for Anticoagulation Monitoring in ECMO

Laboratory testing is used to help achieve an appropriate balance between thrombosis and bleeding in ECMO patients. In addition to standardized tests such as hemoglobin/hematocrit, platelet count, and others, there are specific anticoagulation diagnostic tests including activated clotting time (ACT), activated partial thromboplastin time (aPTT), anti-factor Xa (anti-Xa), prothrombin time and international normalized ratio (PT/INR), and viscoelastic tests such as thromboelastography (TEG) and rotational thromboelastometry (ROTEM) that are used to optimize patient management [12]. While these tests are beneficial in guiding anticoagulation, they do not always accurately predict clinical hemostasis-related outcomes including thrombin formation or excessive patient bleeding [34]. The most widely used monitoring tests to assess hemostasis for patients on ECMO will be individually reviewed.

2.6.1 Activated Clotting Time (ACT)

The ACT test is performed by adding whole blood to a tube containing a surface activator, most commonly kaolin, which stimulates the contact activation pathway and evaluates intrinsic coagulation [12]. The ACT is a clot-based assay that measures the time for initial fibrin formation in seconds [12]. This test provides a global functional test of hemostasis, incorporating the effects of red blood cells (RBCs) and platelets, thus it is not specific for assessing heparin activity [5]. Multiple factors can prolong ACT independent of heparin or DTI use including hypothermia, hemodilution, anemia, decreased platelet function and number, hypofibrinogenemia, and coagulation factor deficiencies [5, 12, 34]. In contrast to the 400 to 480 second target for CPB, the suggested ACT range for

ECMO is 180 to 200 seconds [34]. ACT can yield rapid, bedside results and is relatively inexpensive compared to other tests. Although ACT is a commonly used point-of-care test at most institutions, ACTs in this lower range often do not correlate with other coagulation tests including aPTT and anti-Xa and thus ACT may not be the most reliable tool to monitor heparin anticoagulation on ECMO [12, 34].

2.6.2 Activated Partial Thromboplastin Time (aPTT)

The aPTT test is performed by mixing citrated plasma with an activator (silica or ellagic acid) and calcium to initiate clot formation, which is determined based on either mechanical or optical clot detection [12]. Similar to the ACT, an aPTT test evaluates contact activation and intrinsic coagulation and is affected by antithrombin, factor VIII, factor XII, and fibrinogen levels [12, 34]. However, unlike the ACT, which is a whole blood test, aPTT is a plasma-based test and thus it is not influenced by hemoglobin/hematocrit or platelet count [34]. This is thought to be one of the reasons that aPTT has shown better correlation with heparin concentrations during ECMO compared to ACT [5]. In addition to monitoring heparin, aPTT is also useful for evaluating DTI anticoagulation [34]. Different analytical methods to monitor aPTT exist and thus therapeutic ranges differ between hospitals. The most common aPTT range for ECMO is 60 to 80 seconds in patients with a standard bleeding risk and can decrease to 40 to 60 seconds in patients at an increased bleeding risk [5].

2.6.3 Anti-factor Xa (anti-Xa)

Anti-Xa is a functional assay that directly measures heparin's ability to catalyze ATIII inhibition of factor Xa [5]. It is considered the "gold standard" for monitoring heparin anticoagulation on ECMO as it has shown better correlation with heparin concentration compared to ACT or aPTT [17, 35]. Suggested target values during ECMO range between 0.3 to 0.7 IU per milliliter (mL) [34]. Testing and results can be influenced by ATIII deficiency, hyperlipidemia, hyperbilirubinemia, and high plasma free hemoglobin levels secondary to hemolysis [12, 34]. While anti-Xa is a direct measure of heparin effect, it does not include clot formation or other coagulation parameters nor does it represent the overall hemostatic state of the patient [35].

2.6.4 Prothrombin Time and International Normalized Ratio (PT/INR)

PT measures the time, in seconds, for clot formation to occur after adding a patient's plasma to thromboplastin (a mixture of tissue factor, calcium, and phospholipid) [36]. There are many different preparations of thromboplastin reagents, which can result in different PT results even with the same patient plasma [36]. To make PT results more universal and easily understandable, the World Health Organization (WHO) created the INR, which is a way to standardize the results of PT results no matter the testing method [37]. Unlike ACT and aPTT, which evaluate intrinsic coagulation, PT/INR is used to evaluate the extrinsic and common pathways of coagulation [37].

2.6.5 Viscoelastic Tests

TEG and ROTEM are viscoelastic tests performed by mixing whole blood with an activator (kaolin or tissue factor) and calcium [12]. These tests evaluate whole blood clot formation and provide a thorough evaluation of the coagulation process from the onset of clot formation through clot lysis. A comprehensive assessment of coagulation is obtained including rate of clot formation, strength and stability of clot, platelet function, fibrinogen deficiency, and fibrinolysis [5]. The test contains multiple channels with different activators. One of the channels contains heparinase, an enzyme that neutralizes heparin, which allows for evaluation of hemostasis in both the presence and absence of heparin [12]. This allows for patient evaluation of heparin therapy by comparing the differences in clotting times with and without heparinase and allows for adjustments in heparin dosing [12]. In addition to assisting in anticoagulant management, TEG and ROTEM are commonly used to guide transfusion management including plasma, platelets, and fibrinogen [34].

3.0 Project Statement

The 2021 ELSO anticoagulation guidelines show that treatment decisions about anticoagulation are highly individualized by center and patient [12]. Despite these guidelines, there are currently no standardized protocols for anticoagulation agents or anticoagulation monitoring for ECMO patients [4]. The goal of this project was to survey currently licensed and practicing perfusionists in the U.S. to determine current practices of anticoagulation in ECMO including primary anticoagulant and primary monitoring test. The survey was modeled after those published in 2017 by Esper *et al.* [6] and in 2022 by Frazier *et al.* [7]. In addition to determining the most common primary anticoagulant and primary anticoagulation test used at various centers in the U.S., individual perfusionist preferences regarding ECMO anticoagulation were assessed in an effort to better understand if personal preferences aligned with institutional protocols.

4.0 Methods

4.1 Survey Development

Many survey questions associated with this investigation were modeled after two surveys previously used to look into anticoagulation practices during ECMO. The first was an international survey about adult ECMO anticoagulation by Esper *et al.*, with results published in 2017 [6]. The other was a pediatric ECMO survey conducted in the U.S. by Frazier *et al.*, who published their findings in 2022 [7]. Similar to these surveys, questions were designed to assess demographics of the respondent perfusionists and their institutions (length of practice as a perfusionist, patient populations, number of ECMO cases per year, etc.) as well as their institution's anticoagulation practices.

Additionally, questions regarding individual beliefs about ECMO anticoagulation were modeled after questions from a survey on calcium salt usage with CPB by 2021 Milwaukee School of Engineering (MSOE) graduate Natalie Neisen [38]. These additional questions were aimed at better understanding the individual beliefs of the perfusionist regarding ECMO anticoagulation, specifically, if the perfusionist had a personal preference of using one anticoagulant over another on ECMO and why. The full list of survey questions is located in Appendix A.

4.2 Survey Distribution

Prior to survey distribution, human subject research training and protocol application approval from the MSOE Institutional Review Board (IRB) was obtained. Following approval, the online survey was created using MSOE's Qualtrics survey software account. Testing of the survey prior to distribution was deemed unnecessary

because it featured many of the same questions posted in the surveys by Esper *et al.* [6] and Frazier *et al.* [7]. A recruitment letter explaining the goals of this investigation and survey as well as a link to the survey was posted on a variety of perfusion platforms including Perfusion.com and the Women in Perfusion Facebook group. The survey link was also distributed to perfusionists at Aurora St. Luke's Medical Center, Froedtert Hospital, and Children's Hospital of Wisconsin. Currently licensed and practicing perfusionists in the U.S. with ECMO experience were qualified to participate in this study. Multiple perfusionists from the same institution were allowed to participate in order to focus on individual beliefs.

All participants completed an abbreviated informed consent and were authorized to skip any question they chose to not answer for any reason. Any identifying information was removed to preserve the anonymity of responses. The survey was ended if participants responded that they were not a currently licensed and practicing perfusionist in the U.S. or if they indicated they did not have ECMO experience. All participants who completed the survey were offered the opportunity to include any additional comments at the end. The survey was available for eight weeks from November 2023 through January 2024. The email recruitment letter used is located in Appendix B.

4.3 Analysis of Survey Data

Data from the survey are here presented in aggregate as either the number or the percentage of respondents for each question. Five participants chose to provide information in the open-ended question and their responses are listed.

5.0 Results

5.1 Participant Demographics

A total of 96 individuals participated in the survey. Of the 96 responses, 85 participants identified themselves as currently licensed and practicing perfusionists in the U.S. and were allowed to continue answering the remaining questions of their choosing, but not all respondents answered all questions. The number of years participants have been practicing perfusion varied greatly as depicted in Table 2, with over half of respondents having ten years or less of experience.

Table 2: Number of Years of Experience Survey Participants Have as a Practicing Perfusionist. N = 85.

Years of Practice	# of Respondents	% of Total Respondents
1-5	28	33%
6-10	21	25%
11-20	16	19%
>20	20	23%

Multiple questions aimed to identify the hospital demographics where perfusionists currently practice. The majority of respondents (60 of 85, or 71%) work solely with adult populations, 9% (8 of 85) work solely with pediatric populations, and the remaining 20% (17 of 85) work with both adult and pediatric populations. The average number of ECMO cases per year at respondents' institutions was split almost evenly. Only 22% (17 of 78) of respondents reported their current institution does more

than 100 ECMO cases per year. The pie chart in Figure 4 depicts the responses for typical patient population and Table 3 shows the responses for the number of ECMO cases performed each year.

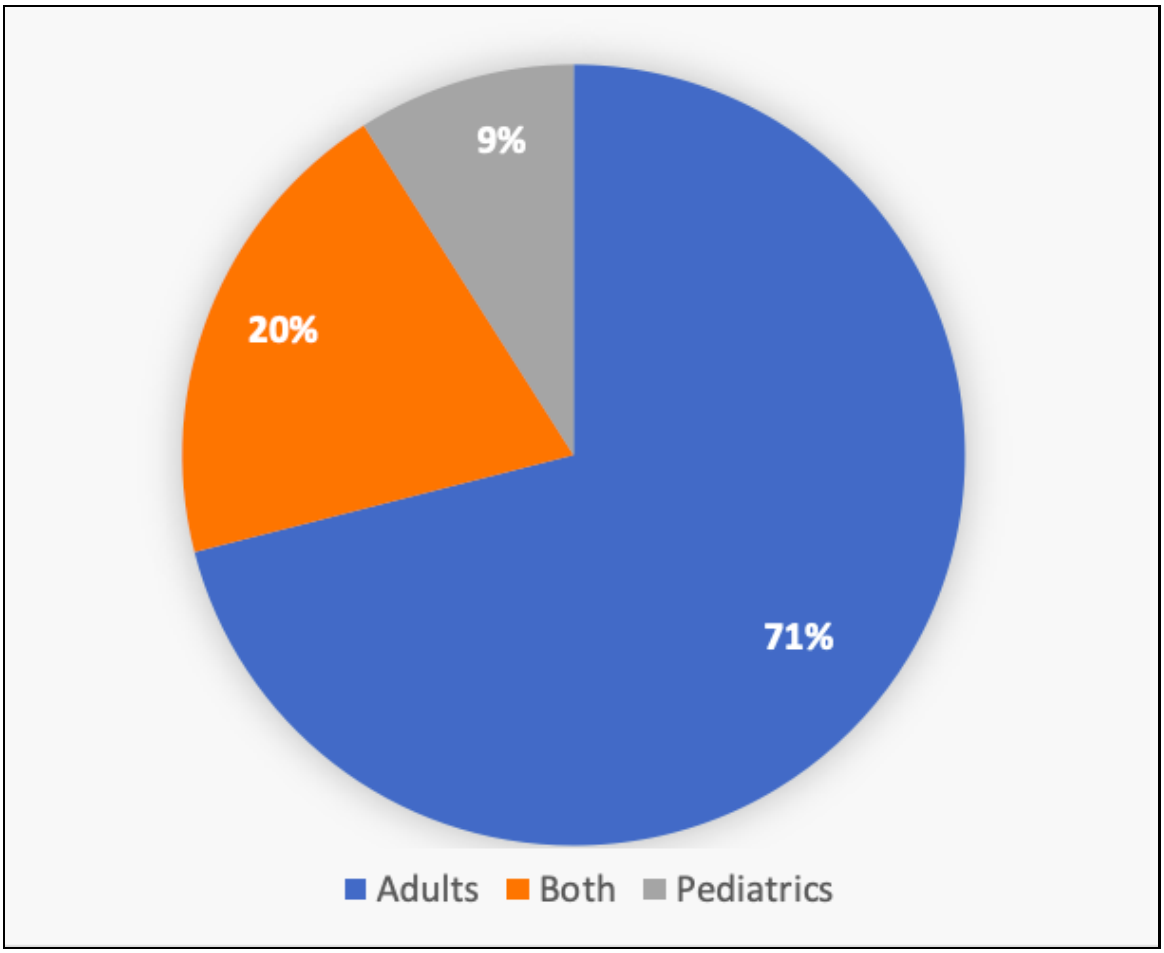

Figure 4: Patient Population Distribution of Survey Participants' Hospitals. N = 85.

Table 3: Average Number of ECMO Cases per Year at Participants' Hospitals. N = 78.

# of ECMO Cases per Year	# of Respondents	% of Total Respondents
0-10	17	22%
11-25	12	15%
26-50	18	23%
51-100	14	18%
101+	17	22%

5.2 Primary and Secondary Anticoagulants Used

The majority of respondents (57 of 78, or 73%) reported that their institution's primary anticoagulant on ECMO is heparin. The next most commonly used primary anticoagulant was bivalirudin, accounting for 24% (19 of 78) of responses. Argatroban and "other" both received only one response and accounted for 1% each of total responses. Participants' hospitals primary anticoagulants used on ECMO are visually depicted in Figure 5.

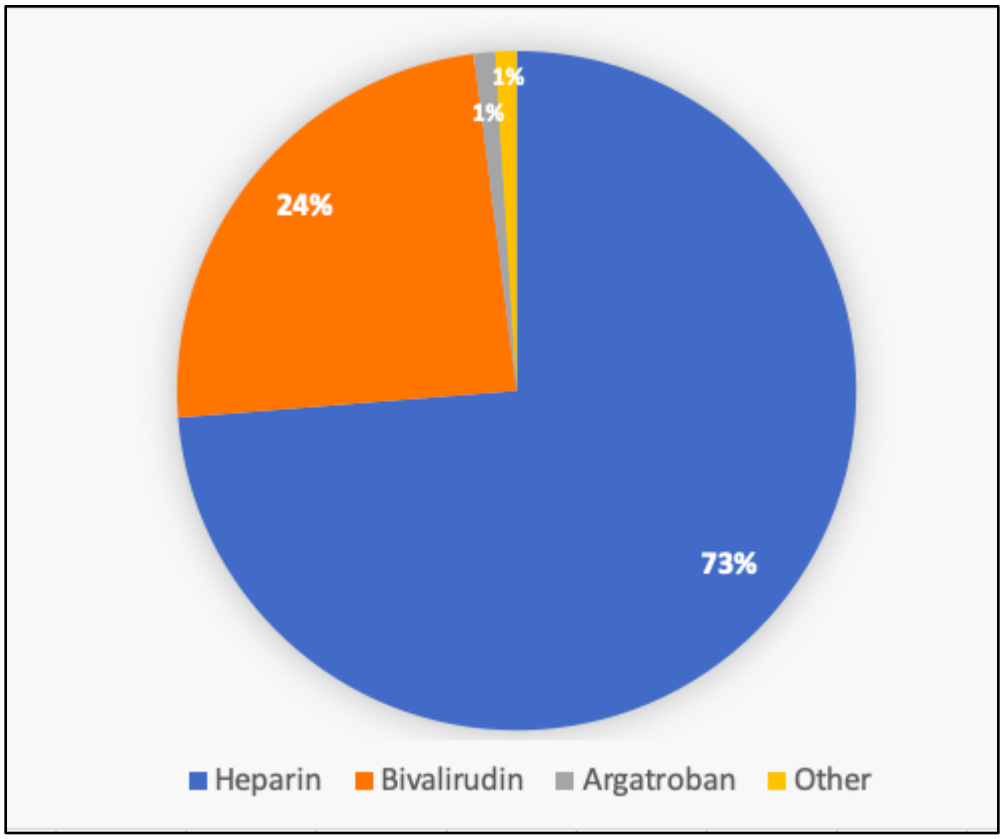

Figure 5: Participants' Hospitals Primary Anticoagulant on ECMO. N = 78.

When asked about switching to secondary anticoagulants at participants' hospitals, 42% (33 of 78) selected bivalirudin as their hospital's secondary anticoagulant of choice, 15% (12 of 78) selected argatroban, and 17% (13 of 78) selected bivalirudin or argatroban. The remaining respondents selected either switching to heparin (15 of 78, or 19%) or "other" (5 of 78, or 6%). In a "select all that apply" question asking the rationale for switching from heparin to bivalirudin or argatroban, a total of 151 responses were collected. The main reason selected for switching was heparin resistance due to ATIII deficiency, accounting for 29% (44 of 151) of responses. The second most common reason for switching and selected by 19% (29 of 151) of respondents was due to being

unable to achieve therapeutic anticoagulation (unable to meet ACT, aPTT, etc.) on heparin. Additional reasons for switching from heparin to bivalirudin or argatroban included excessive bleeding (17%, or 25 of 151), more predictable dosing and response (11%, or 17 of 151), circuit clots (9%, or 13 of 151), no platelet activation/no HIT (9%, or 13 of 151), personal preference (4%, or 6 of 151), and patient clots (3%, or 4 of 151). The bar graph in Figure 6 depicts the responses for rationale behind switching from heparin to bivalirudin or argatroban.

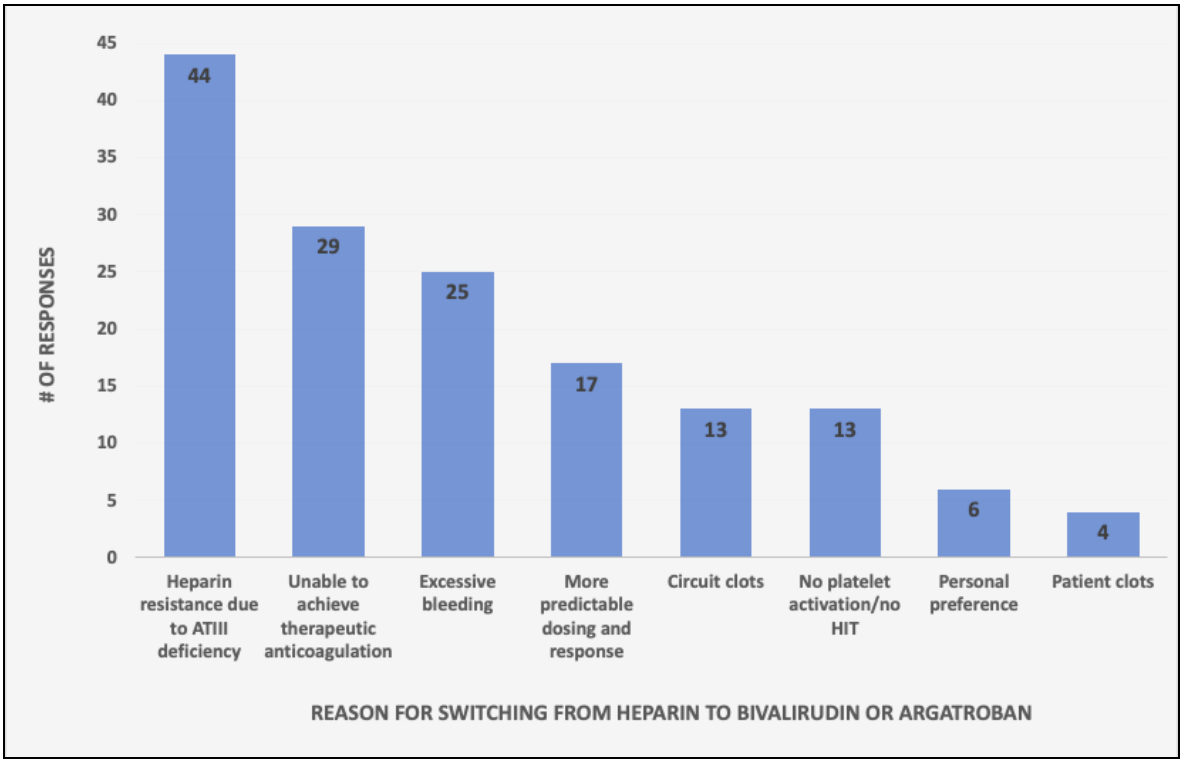

Figure 6: Rationale for Switching from Heparin to Bivalirudin or Argatroban on ECMO.

5.3 Methods of Anticoagulation Monitoring

Responses for primary tests used to monitor heparin anticoagulation on ECMO varied. Over one third of respondents (39%, or 24 of 62) who use heparin listed aPTT as their institution's primary monitoring test for heparin. The next most commonly used tests for heparin monitoring were ACT (31%, or 19 of 62) followed by anti-factor Xa (19%, or 12 of 62), TEG (6%, or 4 of 62), and PT/INR (5%, or 3 of 62).

For respondents who use bivalirudin, 72% (42 of 58) reported using aPTT as their primary test to monitor bivalirudin anticoagulation. ACT and anti-factor Xa were tied for the next most common tests used, accounting for 9% (5 of 58) of responses each. PT/INR was the primary test used for 7% (4 of 58) of respondents followed by TEG, which was selected by 3% (2 of 58) of respondents.

For respondents who use argatroban, just over half (52%, or 15 of 29) reported aPTT as their hospital's primary test to monitor argatroban anticoagulation. The next most frequently used tests for argatroban monitoring were anti-factor Xa (24%, or 7 of 29), PT/INR (10%, or 3 of 29), TEG (7%, or 2 of 29), ACT (3%, or 1 of 29), and other (3%, or 1 of 29).

5.4 ATIII Monitoring and Supplementation

Of the respondents who use heparin, the majority (39%, or 24 of 61) only monitor ATIII levels if they are unable to achieve therapeutic anticoagulation. Fewer than half of perfusionists (43%, or 26/61) reported regular monitoring of ATIII levels as part of a set protocol. Of those that do monitor ATII levels regularly, 25% (15 of 61) reported once a day monitoring, 11% (7 of 61) reported less than once a day monitoring, and 7% (4 of 61) reported more than once a day monitoring. The remaining 18% (11 of 61) reported never monitoring ATIII levels. The frequency of ATIII monitoring is shown in Figure 7.

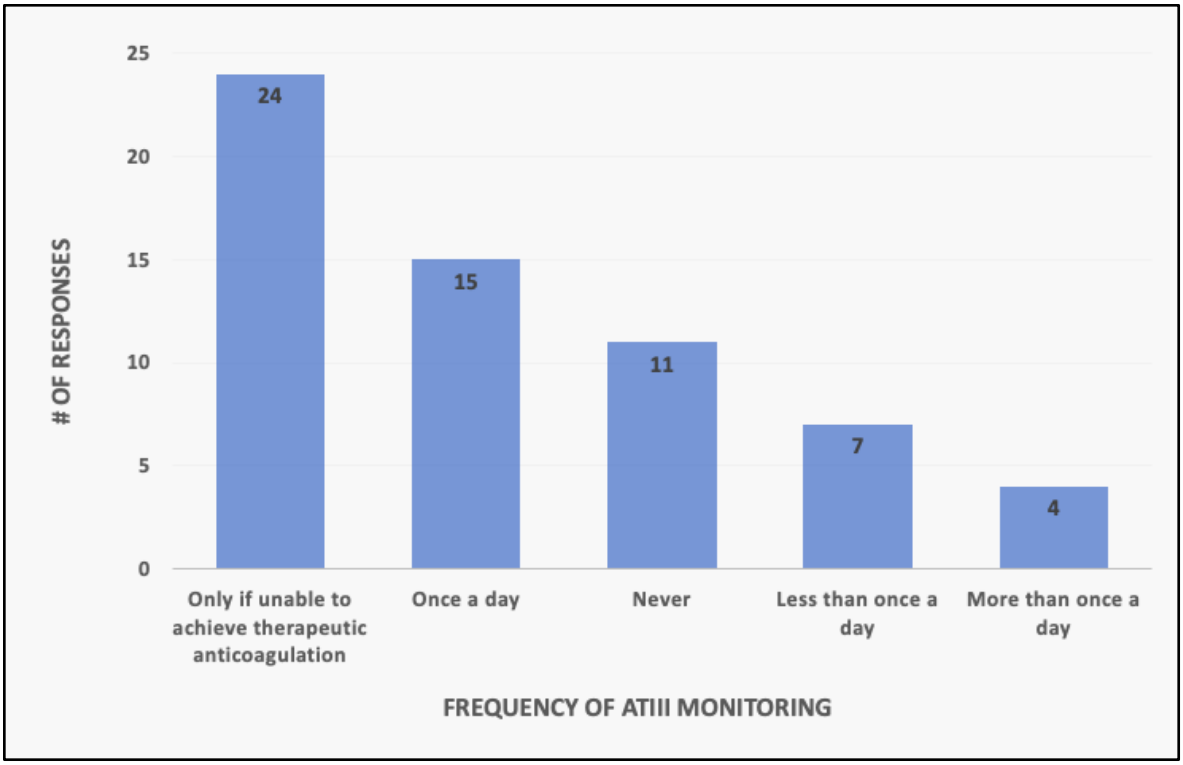

Figure 7: Frequency of ATIII Monitoring on ECMO.

There was an almost even split between respondents who have and those who do not have a documented protocol for ATIII administration at their institution. Roughly 54% (34 of 63) of respondents stated their institution does have an official ATIII administration protocol while the other 46% (29 of 63) stated their institution does not have an official ATIII administration protocol. For respondents who use heparin, the majority (74%, or 45 of 61) report administering ATIII less than 10% of the time. Roughly 21% (13 of 61) administer ATIII 11% to 25% of the time, 3% (2 of 61) administer ATIII 26% to 50% of the time, and only 2% (1 of 61) administer ATIII over 75% of the time. Figure 8 depicts the number of respondents at institutions with a documented ATIII administration protocol.

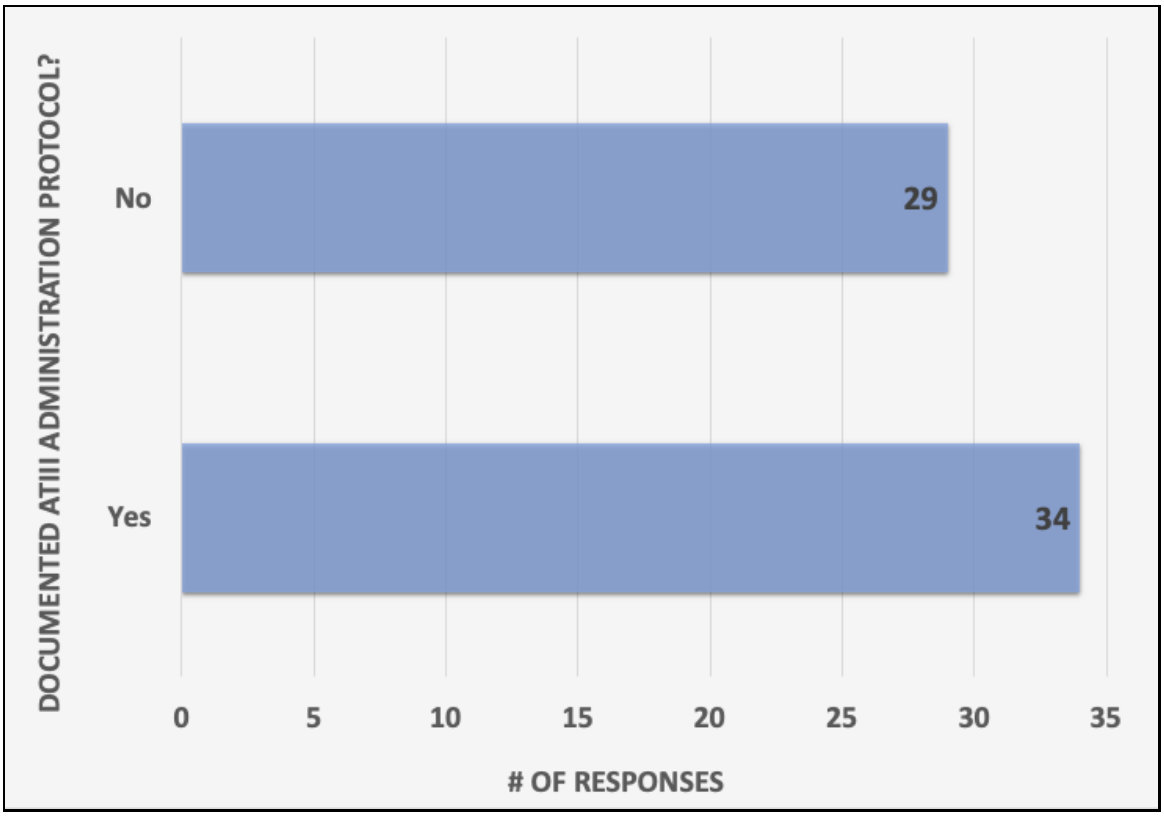

Figure 8: Institutions with a Documented ATIII Administration Protocol.

5.5 Personal Preference of Perfusionists when it comes to ECMO Anticoagulation

Over one third of respondents (21 out of 59, or 36%) selected heparin as their preferred anticoagulant on ECMO while 27% (16 out of 59) selected bivalirudin. Almost one third of respondents (19 out of 59, or 32%) did not prefer one anticoagulant over another. Only 3% (2 out of 59) preferred argatroban and 2% (1 out of 59) selected "other." Individual perfusionist preference for preferred anticoagulant on ECMO is visually depicted in Figure 9.

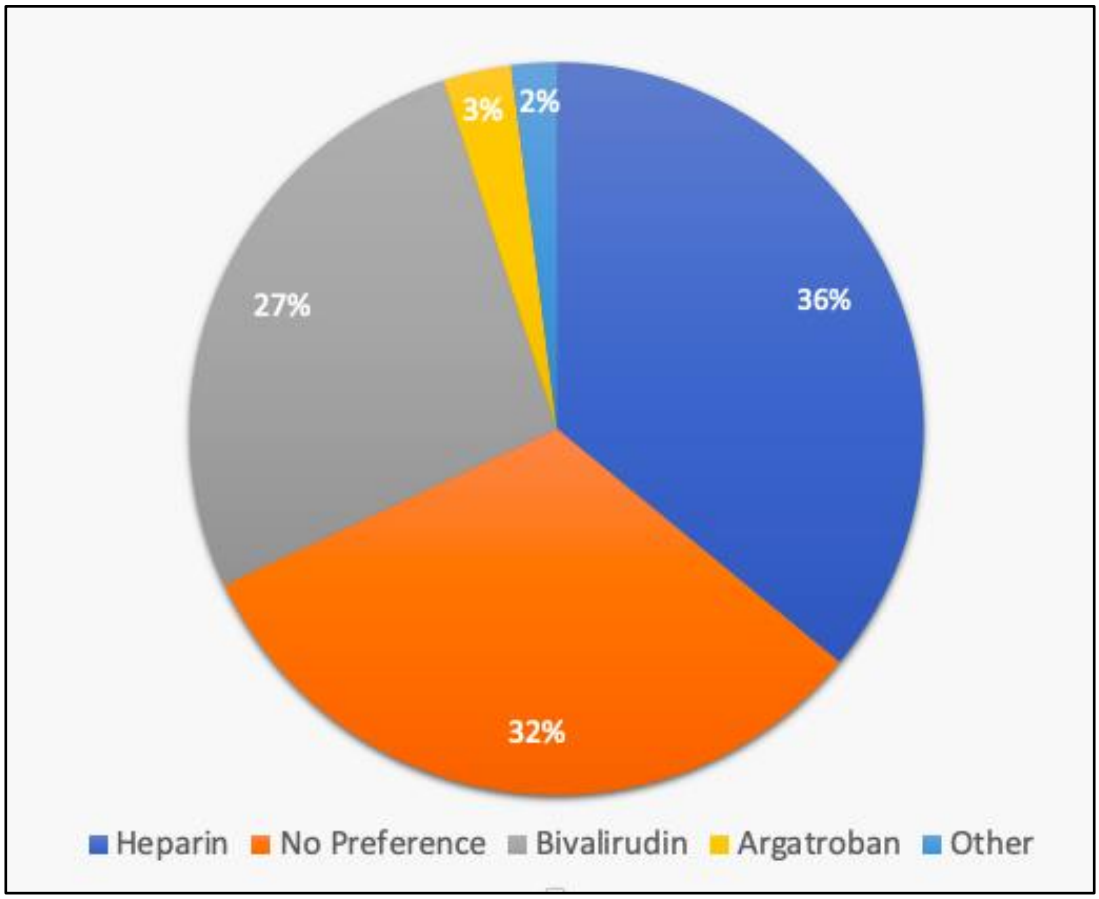

Figure 9: Perfusionist Preference of Using One Anticoagulant over Another on ECMO. N = 59.

For perfusionists who personally prefer using bivalirudin or argatroban on ECMO over heparin, a “select all that apply” question was asked to better understand why. A total of 111 responses were collected. The most selected reason for preferring bivalirudin or argatroban over heparin was no risk of HIT (20%, or 22/111). The next most selected reasons were more predictable dosing and response (18%, or 20/111) and fewer bleeding complications (17%, or 19/111). Additional reasons included easier anticoagulation monitoring (14%, or 16/111), no ATIII monitoring or supplementation (13%, or 15/111), fewer circuit clots (10%, or 11/111), and fewer patient clots (7%, or 8/111). These data are summarized in Figure 10.

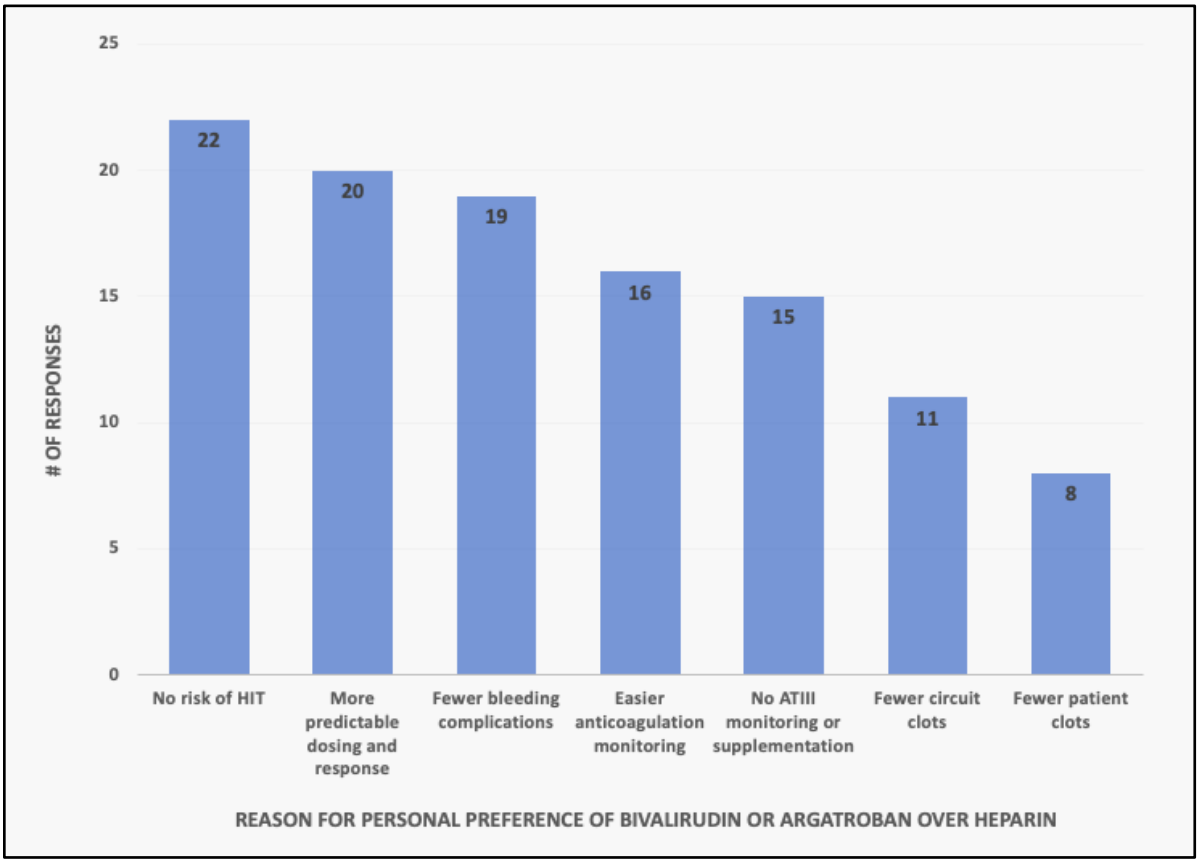

Figure 10: Perfusionist Reasoning for Preference of Bivalirudin or Argatroban on ECMO over Heparin.

Following completion of the survey, participants were prompted to freely provide any additional information about anticoagulation practices on ECMO. Only five participants elected to answer this question, and Table 4 includes the five responses received.

Table 4: Additional Information Provided about Anticoagulation Practices on ECMO. N = 5.

Response
We keep our PTT on ECMO 60 to 80 using bivalirudin.
I would prefer to initiate with heparin and then switch to a DTI. This would simplify management, and although there is no reversal the half-life is short enough that I personally don't find that to be an issue.
Anti-Xa levels and ATIII levels are monitored regularly in the pediatric patient. They are not done as frequently in the adult population.
Comfort level with bivalirudin was definitely increased during COVID pandemic when we started using it more widely.
We initiate with an ACT of 250 to 300 using heparin then switch to Xa inhibitors and track PT/PTT.

6.0 Discussion

6.1 Comparison to Previous Research

This study served as a complement to the ones conducted by Esper *et al*. [6] and Frazier *et al*. [7] while expanding on their questions by asking about individual perfusion preferences regarding ECMO anticoagulation. The 2017 survey by Esper *et al.* was sent to 166 institutions and focused on adult ECMO anticoagulation and transfusion techniques. Of the responding 47 adult ECMO institutions, 96% reported using heparin as their primary ECMO anticoagulant [6]. Primary tests for monitoring heparin anticoagulation varied, with an even split between ACT and aPTT (41.7%, or 20/47 each) being the most common [6]. Their survey did not have questions regarding rationale for switching to alternative agents nor did it ask about individual preference regarding anticoagulants.

The second survey, published by Frazier *et al.* [7] in 2022, was sent to U.S. pediatric clinical pharmacists with experience managing ECMO patients. The survey focused on pediatric ECMO anticoagulation and antimicrobial prophylaxis. It was completed by 38 respondents from 33 U.S. health systems. The majority of respondents (92%, or 35 of 38) reported heparin as their center's primary ECMO anticoagulant [7]. Often, a combination of tests was used to monitor heparin anticoagulation, with anti-Xa being the most commonly used [7]. The main reason for switching from heparin to a DTI was due to adverse drug reactions and/or heparin resistance [7]. This survey did not contain questions regarding individual preference or opinion regarding ECMO anticoagulants.

Similar to the results from the 2017 international adult survey and 2022 U.S. pediatric survey, this survey found the majority of respondents use heparin as their center's primary ECMO anticoagulant. One key difference noted between this survey compared with the two previous surveys is the decreased percentage of respondents reporting heparin as their center's primary ECMO anticoagulant. Only 73% (57/78) of respondents reported heparin as their center's primary ECMO anticoagulant in this survey, which is substantially less than the 96% and 92% that Esper *et al.* and Frazier *et al.* reported, respectively. In this survey, 24% (19/78) of respondents indicated bivalirudin as their center's primary ECMO anticoagulant, which is a significant increase from just 2% and 8% reported in the Esper *et al*. and Frazier *et al*. surveys, respectively. These percentages indicate there may be a downward shift in the use of heparin as the primary ECMO anticoagulant and an increase in bivalirudin usage. These contrasts, as well as results from other questions replicated within this survey, are compared in Table 5 [6, 7].

Table 5: Comparison of Survey Results to Those of 2017 International Adult Survey by Esper *et al.* [6] and 2022 U.S. Pediatric Survey by Frazier *et al.* [7].

Question	2017 International Adult Survey	2022 U.S. Pediatric Survey	Project Survey
Center's primary anticoagulant	Heparin: 96% (45/47) Heparin and bivalirudin: 2% (1/47) Bivalirudin: 2% (1/47)	Heparin: 92% (35/38) Bivalirudin: 8% (3/38)	Heparin: 73% (57/78) Bivalirudin: 24% (19/78) Argatroban: 1% (1/78) Other: 1% (1/78)
Main reason for switching from heparin to bivalirudin or argatroban	N/A	Adverse drug reactions and/or heparin resistance: 79% (30/38)	Heparin resistance due to ATIII deficiency: 29% (44/151) Unable to achieve therapeutic anticoagulation: 19% (29/151) Excessive bleeding: 17% (25/151) More predictable dosing and response: 11% (17/151)
Center's Primary Test to Monitor Heparin	ACT: 41.7% (20/54) aPTT: 41.7% (20/54) Anti-Xa: 10% (5/54) TEG: 8% (4/54) PT/INR: 2% (1/54) Combination: 8% (4/54)	Anti-Xa: 34% (12/35) aPTT, anti-Xa, and ACT: 29% (10/35) aPTT and anti-Xa: 17% (6/35) aPTT and ACT: 9% (3/35) ACT, anti-Xa: 9% (3/35) ACT: 3% (1/35)	aPTT: 39% (24/62) ACT: 31% (19/62) Anti-Xa: 19% (12/62) TEG: 6% (4/62) PT/INR: 5% (3/62)
% of Respondents Whose Institutions have a Set Protocol for ATIII Administration	53% (20/38)	69% (25/36)	54% (34 of 63)

6.2 Survey Limitations

One caution with this study was its method of recruitment. Participation in the survey was recruited through direct posts to a variety of perfusion platforms including Perfusion.com and the Women in Perfusion Facebook group. The survey link was also distributed to perfusionists at Aurora St. Luke's Medical Center, Froedtert Hospital, and Children's Hospital of Wisconsin. This resulted in data collected via convenience sampling, which is a method of data collection that relies on participants who are conveniently available and willing to respond [39]. A limitation of this method is findings can only be generalized to the subpopulation from which the sample is drawn and not to the entire population [39]. A random sampling of the perfusion community may have provided a more accurate representation of the individual beliefs and practices of perfusionists.

Additionally, in an attempt to preserve anonymity and make participants as comfortable as possible in answering questions truthfully, there were no questions asked about the location of participants or at which center they practice. This means multiple perfusionists from the same hospital could have completed the survey. Although this allows for better focus on individual beliefs regarding ECMO anticoagulation practices, it also means there could have been repeat answers regarding the institution's practices and resulted in skewed data for questions pertaining to hospital protocols.

6.3 Future Research

With the significant increase in ECMO use over the past two decades, the search for the perfect balance between thrombosis and bleeding is becoming more important. Research on current practices as well as other avenues such as surface coating and new drug technologies may further hold the answer and improve patient outcomes. In addition to research about heparin, DTIs, and alternative anticoagulants for ECMO, there is a new focus on developing a biomembrane that mimics healthy vascular endothelial tissue in the ECMO circuit [11]. Nitric oxide (NO) and prostacyclin are potential circuit coatings that could make the circuit more similar to healthy endothelial tissue and allow for regulation of hemostasis to prevent excessive bleeding or clotting [11]. Earlier research in animal models showed NO coating may be promising in the prevention of thrombus formation and preservation of platelet function, but human research is still limited [40]. Additionally, antibodies targeting factor XII have shown promise and have an advantage over anticoagulants since they do not increase the risk of bleeding [2]. Emerging preclinical data focusing on the role of antibodies targeting factor XII have shown promise in animal ECMO circuits, yet data in humans are still missing [2].

7.0 Conclusion

Despite decades of research and advancements in ECMO, there is still not enough evidence to standardize anticoagulation administration and monitoring of ECMO patients. Similar to the results from the 2017 international adult survey by Esper *et al.* and 2022 U.S. pediatric survey by Frazier *et al.*, this survey found the majority of respondents use heparin as their center's primary ECMO anticoagulant. Although heparin is still the predominant anticoagulant utilized in ECMO, heparin resistance and HIT are just two of its major limitations. Inability to achieve therapeutic anticoagulation, excessive bleeding, and unpredictable dosing and response have also contributed in the shift toward increased bivalirudin and DTI use. In the current survey, 24% of respondents indicated bivalirudin as their center's primary ECMO anticoagulant, which is a significant increase from just 2% and 8% reported in the Esper *et al*. and Frazier *et al*. surveys, respectively. However, the percentages from this current survey may be skewed since the number of sites sampled is unknown and multiple perfusionists from the same hospital could have completed the survey. But taken at face value, the results of this survey indicate there may be a downward shift in the use of heparin as the primary ECMO anticoagulant and an increase in bivalirudin usage. Unfortunately, these next-generation anticoagulants also have their shortcomings, including lack of antidote, short half-life, and decreased familiarity of use. Continued research and implementation of DTIs is necessary before ECMO anticoagulation practices can be standardized.

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Appendix A: Survey Questions

1. Are you currently a licensed and practicing perfusionist in the United States?
    a. Yes
    b. No

If they answer "No," a prompt will appear thanking them for their time, but their survey will end there.

2. How long have you been a practicing perfusionist?
    a. 1-5 years
    b. 6-10 years
    c. 11-20 years
    d. >20 years

3. What is your center's patient population?
    a. Adults
    b. Pediatrics
    c. Both

4. Do you have experience with ECMO?
    a. Yes
    b. No

If they answer "No," a prompt will appear thanking them for their time, but their survey will end there.

5. How many ECMO cases does your center do per year?
    a. 0-10
    b. 11-25
    c. 26-50
    d. 51-100
    e. 101+

6. What is your center's primary anticoagulant on ECMO?
    a. Heparin
    b. Bivalirudin
    c. Argatroban
    d. Other

7. What secondary anticoagulant(s) does your center use on ECMO?
    a. Bivalirudin
    b. Argatroban
    c. Bivalirudin or Argatroban
    d. Heparin
    e. Other

8. Rationale for switching from heparin to bivalirudin or argatroban on ECMO (**select all that apply**):
    a. Heparin resistance due to ATIII deficiency
    b. Excessive bleeding
    c. Patient clots
    d. Circuit clots
    e. Unable to achieve therapeutic anticoagulation (unable to meet ACT, aPTT, etc.)
    f. No platelet activation/no HIT
    g. More predictable dosing and response
    h. Personal preference

9. What is your center's primary test to monitor **heparin** anticoagulation on ECMO?
    a. aPTT
    b. ACT
    c. Anti-factor Xa
    d. PT/INR
    e. TEG
    f. ROTEM
    g. Other
    h. Heparin not used

10. What is your center's primary test to monitor **bivalirudin** anticoagulation on ECMO?
    a. aPTT
    b. ACT
    c. Anti-factor Xa
    d. PT/INR
    e. TEG
    f. ROTEM
    g. Other
    h. Bivalirudin not used

11. What is your center's primary test to monitor **argatroban** anticoagulation on ECMO?
    a. aPTT
    b. ACT
    c. Anti-factor Xa
    d. PT/INR
    e. TEG
    f. ROTEM
    g. Other
    h. Argatroban not used

12. If you use heparin, how often do you monitor ATIII levels on ECMO?
    a. Less than once a day
    b. Once a day
    c. More than once a day
    d. Only if you are unable to achieve therapeutic anticoagulation
    e. Never

13. If you use heparin, does your center have a set protocol for ATIII administration?
    a. Yes
    b. No

14. If you use heparin, in what percentage of ECMO patients do you administer ATIII?
    a. 0-10%
    b. 11-25%
    c. 26-50%
    d. 51-75%
    e. 76-100%

15. Do you have a **personal preference** of using one over another on ECMO?
    a. Heparin
    b. Bivalirudin
    c. Argatroban
    d. No preference
    e. Other

16. If you personally prefer using bivalirudin or argatroban over heparin, please select why (**select all that apply**):
    a. More predictable dosing and response
    b. Easier anticoagulation monitoring
    c. No ATIII monitoring or supplementation
    d. No risk of HIT
    e. Fewer bleeding complications
    f. Fewer patient clots
    g. Fewer circuit clots

17. If you would like to provide additional information about anticoagulation practices on ECMO, please enter it here.

Appendix B: Recruitment Letter

Hello, my name is Rachel Christopherson. I am a second-year perfusion student at Milwaukee School of Engineering. As part of my thesis project, I am conducting a survey to analyze current anticoagulation practices in ECMO. The goal of the survey results is to determine the current most used primary anticoagulant in ECMO at different centers across the United States as well as individual preference on anticoagulants used in ECMO.

Your participation is voluntary. You have the right to decline to answer any question you do not want to answer for any reason and to end participation at any point by closing out of the online survey. The survey contains a maximum of 17 multiple choice questions and should only take about 5 minutes of your time.

The possible risks or discomforts associated with this study are minimal.

All responses will be recorded via Qualtrics. No identifying information such as name, email, or IP address will be recorded. No one will be able to identify you or your responses.

After completion of the survey, you will be able to enter your name and email into a drawing for 1 of 4 $25 Amazon gift cards. If you choose to enter, your contact information will not be linked to any of your responses.

If you have any questions about the survey, you may contact my thesis advisor, Dr. Gerrits, via email at gerrits@msoe.edu or myself at christophersonr@msoe.edu.

Your participation in this survey indicates that you have read the above information and you voluntarily agree to provide your answers.

Thank you! I really appreciate your time and responses!

Thesis Approval Form

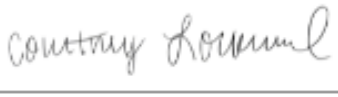
Master of Science in Perfusion–MSP

Milwaukee School of Engineering

This thesis, entitled "Analysis of Current Anticoagulation Practices in Extracorporeal Membrane Oxygenation," submitted by the student Rachel Christopherson, has been approved by the following committee:

Faculty Advisor:  Date: 03/08/2024

Dr. Ron Gerrits, PhD

Faculty Member:  Date: 03/08/2024

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