# Economic Evaluation of Anticoagulation with Bivalirudin vs. Heparin during Pediatric Extracorporeal Membrane Oxygenation

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## Abstract

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Extracorporeal membrane oxygenation (ECMO) is an invasive technology used to replace heart and/or lung function in critically ill patients with potential reversible causes of cardiac or respiratory failure. Anticoagulation is required during ECMO to prevent formation of blood clots as the body is exposed to foreign materials of the ECMO circuit. The delicate balance between bleeding and clotting can be difficult to achieve in pediatric patients who have developmentally immature clotting cascades. While heparin has traditionally been used for anticoagulation during ECMO, there is new interest in Bivalirudin, an alternate anticoagulant. Bivalirudin has a different mechanism of action with potential benefits of more consistent therapeutic effect and easier dosing. Costs are the most commonly cited disadvantage of using bivalirudin as the patent for the medication lasts until 2028. The purpose of this work was to evaluate the clinical and financial implications of using bivalirudin rather than heparin during pediatric ECMO. The

PEDECOR dataset was queried for patients placed on ECMO from 2011-2020. Subjects were restricted to individuals who were age 0-18 years old, with only a single ECMO run. Exposure was defined based on the percentage of the ECMO run for which a patient received bivalirudin, using greater than 50% as the definition of bivalirudin exposure. Standardized costs were applied to various components of care in order to characterize the costs per hospitalization for each patient. Clinical outcomes, resource utilization, survival to discharge and costs were assessed for two groups: those who received bivalirudin for greater than 50% of the ECMO run and those who did not. Sensitivity analyses were conducted using different definitions of bivalirudin exposure. There were 1151 patients who met inclusion criteria from the dataset. Of these 48 received bivalirudin, with 22 receiving bivalirudin for greater than 50% of their ECMO run. Patients who received bivalirudin for greater than 50% of their ECMO run had a significantly decreased incidence rate of clinical complications per ECMO-day, and decreased utilization of laboratory assays and blood products per-ECMO day compared to the non-exposed group. However, there were no differences in survival or costs between the two groups. While further investigation is needed to justify switching to bivalirudin-based anticoagulation strategies based on financial implications, there are clear clinical benefits to using this approach in pediatric patients.

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# Chapter 1. INTRODUCTION

Extra-corporeal membrane oxygenation (ECMO) is a technology used to support heart and/or lung function in individuals who have severe cardiac or pulmonary failure as a result of potentially treatable disease processes. This technology uses a series of pumps and membranes to replace the circulation and gas-exchange functions of the heart and lung respectively. Patients are connected to the circuit via large diameter vascular cannulas through which blood is removed and returned to the body. ECMO has been used in pediatric patients to treat cardiac or respiratory failure associated with a wide range of conditions including treatable congenital anomalies, infections, and drug overdoses.[1]

Achieving a balance between bleeding and clotting during ECMO can be challenging, particularly in pediatric patients.[2,3] Unfractionated heparin (heparin) has traditionally been used for pharmacologic anticoagulation during ECMO to prevent formation of blood clots.[4,5] Heparin is an activator of antithrombin III (AT3) which allows AT3 to inhibit the activity of the clotting factor thrombin, that contributes to blood clot formation. Developmental immaturity of AT3 makes using heparin in pediatric populations is difficult, such that similar dosing of heparin may have different pharmacologic effects in patients of different ages.[6] As a result, heparin effect is not always predictable for a particular patient.

Inconsistent therapeutic effect of anticoagulants during ECMO can cause two potential problems: clotting and bleeding.[2,3] Insufficient anticoagulation results in development of blood clots both in the patient and the ECMO circuit. When this occurs in the vascular cannulas or the circuit, the affected components need to be changed, and the patient must temporarily be off of ECMO support during the process. If clot burden within the circuit requires changing to a

new circuit, blood must be used to prime the circuit before it is connected to the patient, exposing the patient to additional blood products. When clots occur in patients, the medication used for anticoagulation must be changed to both prevent clot propagation in the affected area and to prevent additional clots from forming elsewhere in the body.

On the other hand, supratherapeutic anticoagulant effect increases the risk of bleeding complications.[2,3] Significant bleeding often occurs only within the patient, but can have devastating effects depending on the anatomic location. Bleeding in body cavities such as the thorax, pericardium or abdomen may require surgical intervention. Bleeding in the brain can cause strokes, which can lead to significant neurologic morbidity or death.[7]

There are currently two strategies to address developmental variation in heparin effect. Some institutions administer exogenous AT3 to improve heparin activity. Studies of AT3 supplementation in pediatric patients demonstrate decreased heparin dose requirements, but no significant changes in clinical outcomes of bleeding or clotting.[8–10] Other institutions have solved this problem by investigating alternate anticoagulant medications. (Per personal discussion with Adam Vogel from Texas Children's Hospital, Houston, TX; David Kays from John's Hopkins All Children's Hospital, St. Petersburg, FL; Arul Thirumoorthi from C.S. Mott Children's Hospital, Ann Arbor, MI; and Rachel Chapman from Children's Hosptial Los Angeles, CA).

Bivalirudin is one such medication that has been proposed for use in both adult and pediatric patients on ECMO.[11–18] This medication is a synthetic analog of the active component of leech saliva that inhibits clotting, hirudin. Bivalirudin is manufactured by the Medicines Company and was first evaluated in clinical trials starting in 2000. The patent for the current manufacturing process and formulation of the drug was granted in 2009 by the U.S.

Patents Office (Patent #7,582,727, and Patent #7,598,343), and is expected to expire in 2028, with pediatric exclusivity lasting until 2029.[19,20] Initial FDA approval was limited to patients undergoing percutaneous coronary intervention, and patients who develop an immune reaction to heparin known as heparin-induced thrombocytopenia (HIT). Unlike heparin, which indirectly inhibits thrombin function, bivalirudin acts directly on thrombin to inhibit its function. Bivalirudin has been suggested as an alternate anticoagulant because its direct effect on thrombin allows for more consistent therapeutic effect across age groups.[6] Use of this medication for anticoagulation during ECMO is only starting to be formally studied in clinical trial contexts (ClinicalTrials.gov protocols NCT03318393 and NCT03965208). Some institutions have chosen to use this medication off-label for this purpose (per personal discussion with providers from Children's Hospital Los Angeles, C.S. Mott Children's Hospital and John's Hopkins All Children's Hospital).

In non-ECMO patient populations, bivalirudin has been shown to have a better safety profile than heparin, and has been shown to have similar costs per episode of care.[21–26] This prior work has been done in adult patients undergoing percutaneous coronary intervention (PCI), such as cardiac catherization with angioplasty or stent placement.[21–24,26,27] In these studies, bivalirudin was consistently shown to provide a safety benefit, particularly with respect to bleeding complications in adult patients undergoing PCI. Both secondary analysis of clinical trial data, and analysis of data submitted by the Medicines Company to the National Institute for Health and Clinical Excellence (NICE) have demonstrated a 30-day and hospital-stay cost-benefit to using bivalirudin, despite higher costs of the drug itself.[21,24,26] NICE is a governmental body from the United Kingdom that specifically evaluates cost-effectiveness of different therapies. As a result of the NICE evaluation, the appraisal committee for the National

Health Service gave a positive recommendation for use of bivalirudin for adults undergoing PCI in the UK.[21] This safety-benefit has been so consistently demonstrated that cardiac interventionalists now recommend use of bivalirudin as a first-line anticoagulant for these patients.[28,29]

While it can be life-saving, ECMO is a cost-intensive technology that requires specialized personnel and equipment. ECMO complications increase both equipment-related and procedure-related costs of care. Clinicians cite the cost of the medication as a barrier to use of bivalirudin in the pediatric ECMO population specifically. Additionally, the evidence to support bivalirudin use as a primary anticoagulant during pediatric ECMO is not robust. Given the demonstrated benefit of bivalirudin use in select adult patients, and the theoretical benefit expected by switching to a direct thrombin inhibitor in pediatric patients, this project aims to assess the economic implications of using bivalirudin rather than heparin for anticoagulation during pediatric ECMO.

# Chapter 2. METHODS

## *2.1* HYPOTHESIS

When assessed per hospitalization, it is less expensive to use bivalirudin than heparin for anticoagulation during pediatric ECMO, and patients who receive bivalirudin for anticoagulation have improved outcomes compared to those who receive heparin.

## *2.2* STUDY DESIGN AND SUBJECTS

This study will be conducted using the Pediatric ECMO Outcomes Registry (PEDECOR) dataset maintained by the Research Informatics Core in the Research Resources Office (RRO) of

the Department of Pediatrics at Baylor College of Medicine.[30,31] PEDECOR is an observational data registry of all ECMO patients treated at several children's hospitals in the United States. The hospitals included are Texas Children's Hospital (TCH), Children's Hospital of Atlanta (CHOA), Johns Hopkins University (JHU), Washington University in St. Louis (Wash U), Medical College of Wisconsin (MCW), University of Nebraska at Omaha, University of Minnesota, Children's Hospital of Richmond at Virginia Commonwealth University (VCU), University of Louisville, Arkansas Children's Hospital, Helen DeVos Children's Hospital (HDCH), Duke University (Duke), University of Oklahoma Health Sciences Center (OUHSC), and Lucille Packard Children's Hospital at Stanford University (LPCH). This is an active observational registry, with member hospitals contributing data prospectively. All member institutions have access to the registry to perform research projects. For this project the dataset was queried for all patients placed on ECMO from 2011-2020. All patients age 0-18 years old who were placed on ECMO and who had data submitted to PEDECOR were included in this analysis. No patients were excluded based on indication for ECMO. Descriptive variables included age, sex, reason for ECMO, comorbidities, and ECMO mode (venovenous vs. venoarterial).

### *2.3* Resource Utilization and Cost Assessment

The PEDECOR dataset collects data about various components of hospitalization including length of hospital stay, length of ICU stay, ventilator days, diagnostic studies that are performed, and various interventions to treat complications of ECMO. PEDECOR does not contain cost or charge data, so standardized costs of each component of care were applied. A standard cost of treatment was used for each hospital day, each ICU day, and each day requiring a ventilator.[32–34] Costs of diagnostic studies were obtained from the Centers for Medicare and

Medicaid Services fee schedules for laboratory and diagnostic tests.[35] The daily dose of anticoagulants and blood products was recorded in PEDECOR for each drug used. Standardized costs of medications were obtained based on average wholesale unit price for each drug from Micromedex.[36] Standardized costs of blood products were obtained from a microcosting study evaluating acquisition, processing and administration costs associated with transfusion of various blood products for the purposes of analysis.[37] Device costs for ECLS included costs of the circuits, obtained from a prior costing study.[38]

The PEDECOR dataset contains multiple assessments of bleeding and clotting. Bleeding is captured by the BASIC bleeding score, a score to qualify bleeding severity during ECMO [39]. Pharmacologic treatment of bleeding and clotting was captured by the dataset through daily records of blood products and medications administered. Surgical bleeding was captured through the combination of the bleeding score and the location. Individuals with a bleeding score of 3 or greater and whose bleeding location included the terms “washout”, “hemothorax”, “Peritoneal”, “Chest Tube”, “Mediastinal”, “abdominal”, “Surgical”, “chest” or “exploration” were considered to have a surgical intervention for bleeding. A standardized cost for exploratory laparotomy was used for surgical cost for all surgical patients regardless of the site of surgery based on a 2016 study of the costs of emergency general surgery. [40] All costs were converted to, and reported in, 2020 US Dollars. Table 1 has a list of costs for various supplies and services including the references from which these were obtained.

### *2.4* Cost Frame

The total costs of care were considered accounting for the costs associated with the ECMO run and the hospitalization. This was generated as the sum of estimated costs for ECMO services, Ventilator services, ICU services, labs, blood products, anticoagulant medications,

imaging studies and days on the acute care hospital ward. The incremental cost calculated was the difference in raw costs between individuals who receive bivalirudin for the majority of the ECMO run and those who do not, over the total hospitalizations. This cost frame provides an absolute difference in costs of treatment that may be easier for providers to immediately interpret. This frame is also important to consider because different routes of ECMO have different reimbursement rates. As of 2019 the reimbursement rate for cannulation directly into the mediastinum (central cannulation) is almost 10-times higher than it is for cannulation in other blood vessels (peripheral cannulation).[41,42] The case-mix at a particular institution may therefore make heparin or bivalirudin a more favorable option for anticoagulation.

### *2.5* EXPOSURE

Patients were grouped by the medication used for anticoagulation for the majority of the ECMO run either unfractionated heparin or bivalirudin. Patients were excluded if they did not receive pharmacologic anticoagulation during the ECMO run. In total, 13 patients were excluded for this reason. Figure 1 provides a CONSORT diagram outlining how the final analysis dataset was generated. There are two clinical trials comparing bivalirudin and heparin use in ECMO patients currently, one focusing on adult patients (NCT03965208) and another focusing on pediatric patients (NCT03318393). Information for these trials is only available on clinicaltrials.gov, as both trials are currently recruiting patients and published protocols are not available. It is therefore impossible to apply a definition from either trial to bivalirudin exposure in this observational dataset.

Prior observational studies in children use various definitions of bivalirudin exposure. One study in the U.S. used a pre-post-policy change analysis after a change in anticoagulation practice at the institutional level.[43] Their analysis assumes that patients treated after a specific

time-point received bivalirudin while those treated before that time received heparin. Another study in children defined bivalirudin exposure for each ECMO-day rather than the entirety of the ECMO run.[44] In this analysis laboratory values of interest were only considered to reflect the drug of interest after the initial anticoagulation was cleared from the system based on pharmacologic principles. Finally, a prior observational study in adults restricted analysis to cases without change in anticoagulation strategy mid-ECMO run.[45]

The definitions of exposure described in prior observational studies are challenging to apply in this analysis given the outcome of interest, survival to discharge, and the cost-effectiveness goal of this study. The multi-institutional nature of the PEDECOR patients makes applying a pre-post analytic strategy challenging, because the various institutions have different approaches to anticoagulation policy that are not apparent from the data available in PEDECOR. Restricting to a per-ECMO-day analysis is also challenging because it would limit the ability to determine the per-hospitalization ICER. Given these limitations, an alternate definition of bivalirudin exposure was chosen. The primary exposure variable was a binary indicator of using bivalirudin for the majority of the run, characterized as at least 50% of ECMO-days with bivalirudin. Figure 2 provides a histogram of proportion of days with bivalirudin exposure among the patients who received bivalirudin. This definition of bivalirudin exposure was chosen because drug costs are cited as a limitation to widespread adoption of bivalirudin-based anticoagulation strategies, and the 50% definition allows us to capture the effects of the medication that was used for the majority of the ECMO run on the total resource and cost utilization for each patient. An indicator of any bivalirudin exposure was also assessed for the purpose of sensitivity analysis.

## *2.6* OUTCOME MEASURES

The primary outcome of interest is survival to hospital discharge. While a traditional cost-effectiveness evaluation would use a quality-adjusted life-year outcome, quality-of-life data that can be mapped to utility scores are not available in PEDECOR. Several functional assessments are available, but incremental differences in these outcomes are less meaningful, and missingness in these data makes them poor options for outcomes in a study with a limited sample size. The functional assessments described in the PEDECOR database include the pediatric overall performance category (POPC), pediatric cerebral performance category (PCPC), and pediatric functional status score (FSS). [46,47] POPC and PCPC were collected on all patients at the time of admission and the time of discharge from the hospital. FSS was only collected for patients with prior known functional status at the time of admission and the time of discharge, so these data are not available for neonates. In contrast, survival to discharge is known for all patients because the date of admission, and date of discharge or death are available for all patients in the dataset.

## *2.7* STATISTICAL ANALYSIS

To calculate the incremental cost-effectiveness ratio associated with using bivalirudin, the following quantities were first determined: 1. Survival effect associated with bivalirudin, and 2. Cost difference associated with using bivalirudin rather than heparin. These quantities will be determined in the following ways.

### 2.7.1 *Survival effect associated with bivalirudin:*

The survival effect was in determined in two ways. First traditional logistic regression analysis was used to estimate the association between anticoagulant and survival to hospital

discharge. Given the small sample size of the treatment group, covariates weren't included in the initial model, given the risk for model non-convergence with the addition of predictor variables. To address potential confounding by indication both propensity-score-based methods and instrumental variable (IV) techniques were considered. Propensity-score based methods use a two-step regression process, first regressing the treatment of interest on various potential confounders of treatment and outcome to build a model that predicts the probability of treatment. Propensity scores are calculated from this model and two options then exist for analysis: 1. Study participants in the treatment arm are matched to individuals in the non-treatment arm and outcomes are assessed, or 2. Traditional regression analysis with a weighting factor for the propensity score is employed.[48,49] The small sample size of one treatment group makes it challenging to build a propensity model that stably predicts treatment exposure across the population, so this technique was ultimately deemed inappropriate for this analysis.

An instrumental variable (IV) analysis was instead chosen and performed. This type of analysis uses a variable called the instrument as a proxy for assignment to treatment groups. Ideal instruments are strongly correlated with the exposure of interest, and not related to the outcome of interest except through the exposure.[50] For this analysis the selected instrument was hospital formulary status, an indicator of whether the hospital had bivalirudin available as an anticoagulant for ECMO or not. A research report from the Agency for Healthcare Quality and Research (AHRQ) suggests using hospital formulary status as an instrumental variable if some hospitals add a medication to the formulary while others do not, if there is potential for confounding by indication because the new medication is likely to be used in patients with the poorest prognosis, and if the side effects of interest are rare and a traditional cohort study is challenging to perform.[51] Use of bivalirudin for anticoagulation during ECMO in the pediatric

population meets all of these parameters, so formulary status was considered as a potential instrument.

While hospital formulary status is not independently captured in PEDECOR, hospitals can be categorized as bivalirudin "users" or "non-users" based on whether any patients from the hospital receive bivalirudin for any portion of their ECMO run. Patients at hospitals that never use bivalirudin cannot receive that treatment, so the instrument is correlated with the treatment of interest, meeting the first criterion for an appropriate instrument. Patients are also unaware of hospital treatment practices prior to presenting for care, so from the patient perspective, treatment assignment determined by the instrument is approximately random. For the second criterion, hospital formulary status conceptually is unrelated to patient survival in this analysis. Studies of children's hospitals have shown that morbidity and mortality from ECMO are strongly associated with a hospital's total pediatric ECMO volume.[52,53] All of the hospitals included in this study are large children's hospitals, with well-established ECMO programs that manage several ECMO patients per year. We would therefore expect all hospitals to have similar survival outcomes from ECMO, and would not expect observed survival effect to be related to formulary status, but rather to other factors associated with ECMO care. Instrument validity was tested by comparing observed characteristics of patients from hospitals with access to bivalirudin to characteristics of patients from hospitals without bivalirudin. Using this variable as the instrument, two-stage linear regression analysis was then performed. Model 1 regresses treatment (anticoagulant medication) on the instrument (formulary status). Model 2 then regresses the outcome of interest (survival to discharge) on the treatment values predicted by model 1 to determine the incremental survival effect associated with bivalirudin.

### 2.7.2 *Cost differences associated with bivalirudin vs. heparin.*

To determine the incremental costs associated with bivalirudin compared to heparin, two gamma regression models were created to describe costs as a function of medication exposure. This method is an alternative to ordinary least squares regression for analyzing data that is right-skewed and strictly positive.[54] Both simulations and analyses of data from large clinical repositories demonstrate that standard linear regression techniques produce biased results when used to analyze healthcare costs, because cost data does not follow a symmetric normal distribution.[54–56] The gamma regression accounts for the skewed distribution of the data by taking the form of a generalized linear model using a log-link function. The first gamma regression model used raw costs as the response variable, while the second model used the individual difference between reimbursements and costs as the response variable. Exponentiating the coefficient from a gamma regression model provides the relative difference in costs between the two treatment groups. To determine the incremental cost difference of the treatments on the absolute scale, the average marginal effect was calculated for each model using the method of recycled predictions.[57] This method uses the regression model to estimate the costs of treatment for all subjects under both treatment assignments, and then calculates the difference between the mean costs on the additive scale.

### 2.7.3 *Sensitivity Analyses*

Given the observational nature of the data, an imperfect definition of bivalirudin exposure was used for this analysis. This definition may have attenuated cost differences if the per-day cost of bivalirudin use was high enough to bias global costs in the heparin group. This source of potential bias was addressed by performing two sensitivity analyses. In the first

sensitivity analysis the definition of exposure was changed. Rather than limiting to patients who only received bivalirudin for greater than or equal to 50% of their ECMO run, exposure was defined as any receipt of bivalirudin during the ECMO run. The second sensitivity analysis compared patients who received bivalirudin for at least 50% of their ECMO run to the group of patients who received no bivalirudin. This sensitivity analysis sought to remove potential effects of minimal bivalirudin use from the group of patients who received heparin for the majority of ECMO. The survival difference, incremental costs, and ICER were then re-calculated using the more liberal definition of bivalirudin exposure. For both sensitivity analyses both traditional regression and IVA were used. All statistical analyses were performed in R version 3.6.1. [58]

# Chapter 3. RESULTS

## *3.1* PATIENT CHARACTERISTICS

There are 1307 patients in the PEDECOR dataset from 2010-2020. After applying exclusion criteria, the final dataset had 1151 patients (Figure 2), with 13 patients excluded because they did not receive any pharmacologic anticoagulation. Of these, 48 patients received bivalirudin, with 22 patients receiving bivalirudin for at least 50% of their ECMO run. Twelve patients received bivalirudin for the entirety of the run. Table 2 provides demographic characteristics for the two groups based on the proportion of the run for which they received bivalirudin, and based on hospital formulary status, the intended instrumental variable. Numerical variables are summarized with means and standard deviations. Categorical variables are summarized with counts and proportions. On average, patients who received bivalirudin for the majority of their ECMO run were older, had longer time on ECMO, spent slightly longer in

the ICU, and had longer hospital stays. When the groups were defined based on hospital formulary status these differences largely disappear.

## *3.2* Clinical Outcomes

Table 3 summarizes counts and incidence rate ratio (IRR) of complications per ECMO-day for the two groups. All relative risks are reported as estimates and 95% confidence intervals. From this table we see that per ECMO-day, the incidence rate of complications was significantly lower when patients received Bivalirudin for at least 50% of their ECMO run. These differences are most prominent for deep vein thromboses (IRR 0.50, 95% CI: 0.31-0.77), intracranial hemorrhage (IRR: 0.56, 95% CI: 0.35-0.84) and surgeries (IRR: 0.51, 95% CI: 0.34-0.72). These results indicate that despite the longer overall duration of ECMO therapy in patients whose primary anticoagulant was bivalirudin, the incidence rate of complications was lower with this medication.

## *3.3* Resource Utilization

Table 4 summarizes resource utilization per ECMO-day based on the primary anticoagulant used. Per ECMO-day, patients who received bivalirudin for the majority of their ECMO run had fewer labs checked and required a smaller volume of transfused blood products. In particular, bivalirudin patients required fewer checks ACT (relative difference 0.44, 95% CI: 0.38-0.52) and PTT (relative difference 0.58, 95% CI: 0.51-0.65), the two labs checked to evaluate therapeutic effect of anticoagulants. In fact, procalcitonin, a laboratory assay that assesses for inflammation in the setting of bacterial infection, was the only test that was performed more frequently in bivalirudin patients than heparin patients. In terms of

neuroimaging studies, there were no differences in the per ECMO-day use of Head CT, brain MRI or head ultrasound between the two groups.

Transfused volume of all blood products was also significantly lower for bivalirudin patients than heparin patients. This difference was most prominent for cryoprecipitate (relative difference 0.09, 95% CI: 0.07-0.10), but was present for packed red blood cells (relative difference 0.32, 95% CI: 0.32-0.33), fresh frozen plasma (relative difference 0.17, 95% CI: 0.16-0.17), and platelets (relative difference 0.32, 95% CI: 0.31-0.32).

## *3.4* Costs

Table 5 summarizes the per-patient costs of care for both the entire hospitalization and the various components of care. The total cost per episode for patients receiving bivalirudin was $462,285 (range: $71,485 - $1,700,186), while the cost per episode for patients receiving heparin was $501,873 (range $20,827 - $4,452,965). These data indicate costs for ECMO therapy can be quite variable from patient to patient. Examining the costs of various components of care, the incremental costs of blood products, medications, and surgery are cheaper for patients receiving bivalirudin, although these differences are not statistically significant.

## *3.5* Incremental Cost and Effect using 50% cutoff for Bivalirudin exposure

Table 6 summarizes the incremental cost and survival differences based on bivalirudin exposure classification and statistical analytic technique. Gamma regression analysis was used to determine incremental costs of using bivalirudin for greater than 50% of the ECMO run compared to the reference group. Summary costs over the total hospitalization were similar for the bivalirudin group compared to the heparin group (Relative difference: 0.92, 95% CI: 0.61-

1.48). The incremental cost difference between these two treatments is $40,150, with bivalirudin being cheaper, but this difference is not statistically different. When survival was evaluated, the relative survival difference between patients who received bivalirudin and those who received heparin for the majority of their ECMO run was 1.08 (95% CI: 0.46-2.63). This corresponds to an incremental survival difference of 2.1 percentage points, which is not statistically significant. Using the instrumental variable technique, the prior regression models were created again. Under the IVA the cost difference between bivalirudin and heparin is $4,778 (95% CI: - $5,460 - $15,017). The incremental difference in chance of survival with bivalirudin is 0 percentage points (95% CI: -0.01 – 0.01). Incremental cost-effectiveness ratios were not calculated because the differences in cost and survival were not significant between the groups.

### *3.6* Sensitivity Analysis

Sensitivity analysis was performed using both traditional logistic regression and IVA. With traditional logistic regression for sensitivity analysis, the relative cost of using bivalirudin is 0.63 times that of using heparin (95% CI: 0.46-0.84) with an incremental cost difference of $227,205. The relative difference in survival is 1.23 times higher with bivalirudin than heparin (95% CI: 0.69-2.20), with an incremental difference of -5 percentage points. Using IVA techniques, sensitivity analysis shows an incremental difference of $4,810 (95% CI: -$5,498 - $15,119). Under the IV sensitivity analysis the incremental survival difference was 0.0 percentage points (95% CI: -0.01 – 0.01).

Comparing individuals who received bivalirudin for greater than 50% of their ECMO run to those who only received heparin, the relative cost of using bivalirudin is 0.94 times that of using heparin (95% CI: 0.63-1.51) with an incremental cost difference of - $29,022. The relative difference in survival for bivalirudin patients is 1.08 that of heparin patients (95% CI: 0.46-2.63),

with an incremental difference of 1.9 percentage points. Using IVA techniques, the second sensitivity analysis shows an incremental difference of $4,141 (95% CI: -$5,864 - $14,147). Under the second IV sensitivity analysis the incremental survival difference was 0.0 percentage points (95% CI: -0.01 – 0.01).

# Chapter 4. DISCUSSION

Comparing results from the six different analyses only one of the cost analyses demonstrated a statistically significant difference in cost per episode of care for pediatric ECMO patients. We are unable to identify a difference in survival from any of these analyses. These results are surprising given reports of favorable cost and clinical outcomes of bivalirudin use in other populations.[22,23] Evaluation of clinical outcomes and resource utilization show fewer complications, and fewer resources utilized per ECMO-day for bivalirudin recipients. The bivalirudin recipients in this analysis had longer ECMO runs and hospital stays, however, which may have offset the decreased cost of resources in this population, leading to the lack of cost difference.

Despite our inability to identify a cost or survival difference from these analyses, there are several important findings from this work. Per ECMO-day, the risk of adverse events in bivalirudin patients was lower than it was for heparin patients across all event types, a finding that was statistically significant. Adverse neurological events include strokes and intracranial hemorrhage which can have devastating consequences for patients and families.[7] While quality-of-life was not assessed as part of the PEDECOR dataset, we would anticipate improved post-ECMO quality of life among bivalirudin patients and their families because of the decreased frequency of adverse events that cause significant morbidity.[7]

Blood product utilization was also significantly different between the two groups. In pediatric patients, blood products are administered as a volume per kilogram of body mass.[59] From our results we see that patients who received heparin for the majority of their ECMO runs were generally younger and lower weight than patients who received bivalirudin. We would therefore expect the volume of blood transfused per ECMO-day to be lower for these patients than for the bivalirudin patients. We found the reverse, making the decreased volume of blood transfused clinically significant. In this context this finding further supports anecdotal reports of less bleeding with bivalirudin among ECMO patients.[60]

Careful use of blood products is necessary to prevent adverse effects of transfusion. Transfusion-related acute lung injury and transfusion-associated circulatory overload both carry significant risk of mortality and can adversely affect ECMO outcomes by impairing heart and lung function.[61–63] Repeated transfusions also carry risks of alloimmunization, the process of developing antibodies to transfused products.[63] The risk of transfusion reactions increases with the development of alloimmunity, making it increasingly difficult to find appropriately matched blood for these patients. Limiting transfusions has a clear immune benefit for patients and decreases the risk of potentially lethal adverse events.

Although costs of bivalirudin are often cited as a reason for lack of use, this analysis actually found medication costs to be cheaper for the bivalirudin group than the heparin group. One possible explanation for these findings is the more consistent therapeutic effect that can be achieved with bivalirudin. The consistency of therapeutic effect has been described previously, documented by various markers of anticoagulant activity. [60] Using heparin results in greater variability of these markers. Clinicians respond to the variability by administering blood products, or additional medications to prevent excessive bleeding and clotting. These results

demonstrate that patients who receive bivalirudin do not require adjunct medications such as desmopressin (DDAVP) and protamine to augment the therapeutic effect of the anticoagulant. Aminocaproic acid and tranexamic acid use were greater per ECMO-day for bivalirudin recipients than heparin recipients, but these medications are cheaper per dose than DDAVP and protamine.[36] This explanation is further supported by the smaller number of labs checked per ECMO-day for bivalirudin patients. In particular, ACT and PTT were checked much less frequently for bivalirudin patients than heparin patients. These laboratory assays are specifically used to evaluate therapeutic effect of anticoagulants, and fewer checks suggest less variability between different measurements.[13,64,65]

A final important observation from these data relates to the way patients were classified. From the histogram of bivalirudin use we see that the proportion of bivalirudin use among patients varies from zero to 100. Twelve patients received bivalirudin for the entirety of their run, so the remaining patients likely represent patients in whom initial anticoagulation with heparin failed and bivalirudin was used as a salvage option. In this case, some portion of the adverse events in bivalirudin patients may have occurred during a period of heparin exposure. Among these patients we might traditionally accept slightly worse outcomes because of failure of the initial therapy and inability to use another medication. In this setting, the finding of decreased adverse events and blood transfused becomes more meaningful. Our findings would suggest the true incidence of adverse events, true use of laboratory assays and true volume of blood products required to care for patients who receive bivalirudin for the entirety of their ECMO run is lower than what we observed, and thus the incremental difference in outcomes is likely greater than what we observed.

The most notable limitation of this work is the small sample size of one of the groups. There were only 22 patients who received bivalirudin for greater than 50% of their ECMO run, and only 48 who received bivalirudin at all. This small sample limits our power to identify small differences in costs or survival as statistically significant, particularly relative to costs of ECMO which are quite high. The small sample size also limits our ability to perform multivariate modeling that adjusts for various confounders because of risks of model nonconvergence. While we employed other strategies to account for unobserved confounding, a larger sample size would allow for more sophisticated statistical techniques.

Using the *pwr* package in R we can determine the sample size necessary to identify the differences seen in this study. To detect a survival difference of 5 percentage points with a significance level of 0.05 and 80% power, a sample size of 1570 participants per arm would be required. Identifying smaller differences in survival would require much larger sample sizes per arm. Given the number of pediatric patients who receive ECMO annually, it would be challenging to conduct a randomized trial with 80% power in a timely manner to answer this question. In the absence of such a trial, the decision to switch anticoagulation strategy can be challenging to make.

Despite the advanced statistical techniques employed in this analysis the potential for residual confounding still exists. In particular, the IVA does not fully address selection bias. Bivalirudin patients in this study had longer duration of ECMO, longer time in the ICU, and longer hospital stays. On average, these patients are sicker than the remaining patients in this analysis. Table 2 indicates that stratification on the instrument balances some of discrepancy in ECMO duration, ICU stay and length of hospital stay between the two groups, so IVA removes

confounding due to different durations of care. We do not know for certain, however, that IVA balances differences due to illness severity as this variable is not directly captured in the dataset. Another limitation of this work is the lack of a quality-adjusted outcome in this dataset. Economic evaluations typically use quality-adjusted life years (QALYs) as an outcome because QALYs of different treatments can be compared on a unified scale.[66,67] PEDECOR does collect functional status data on children, but missingness of these variables, and the difficulty translating these scores into QALYs prevented us from performing a traditional cost-effectiveness analysis. The interpretation of cost and survival differences is challenging in this context. These values are also difficult to compare to other study results because of this limitation.

Our work also offers some notable strengths. To date this is one of the larger studies of bivalirudin use during pediatric ECMO. There is one other study from Snyder et. al. with 42 patients receiving bivalirudin, but all of the patients in the Snyder study had a primary diagnosis of congenital diaphragmatic hernia (CDH).[60] While CDH is an important diagnosis in neonatal patients, the results of this study are not necessarily applicable in other patient populations. Our findings augment these results by identifying potential benefits in other populations as well.

# Chapter 5. CONCLUSIONS

We were able to identify benefits to using bivalirudin in terms of clinical complications and resource utilization. In particular, patients receiving bivalirudin had a decreased incidence rate of deep vein thromboses, intracranial hemorrhage and surgeries compared to patients receiving heparin. Bivalirudin recipients also had fewer labs drawn, and a smaller volume of transfused blood products per ECMO-day compared to patients who received heparin. The

decrease in utilization of these resources, as well as the decreased medication costs with bivalirudin suggests less variability in therapeutic effect of bivalirudin compared to heparin.

While we were unable to find differences in overall costs or survival between groups of patients that received different anticoagulants, these clinical differences are important to providers and patients because they represent opportunities to improve outcomes and resource utilization. The decreased number of laboratory assays in bivalirudin patients, particularly ACT and PTT assays, also represents a savings in human labor because clinicians do not have to interpret additional results. The time saved can then be used to prioritize other aspects of patient care.

A larger sample is necessary to adequately detect the survival differences seen here as statistically significant. If this work is repeated and there are truly no differences in cost or survival between these two medications then improvement in clinical outcomes with bivalirudin and the decrease in medication costs would justify switching to primarily bivalirudin-based anticoagulation practices for pediatric ECMO.

Figure 1: Consort Diagram of Study Participants

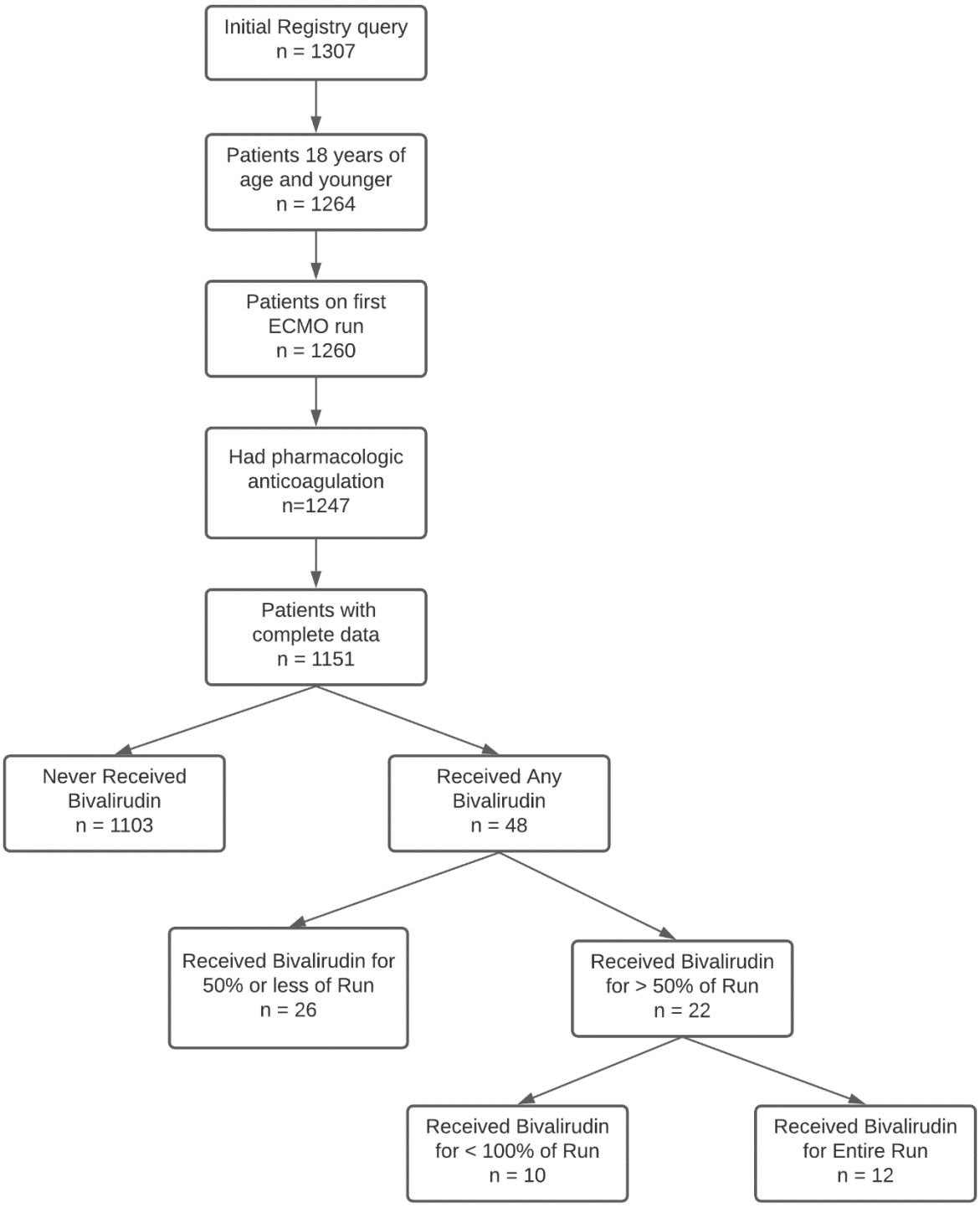

Figure 2: Histogram of distribution of bivalirudin use in bivalirudin recipients.

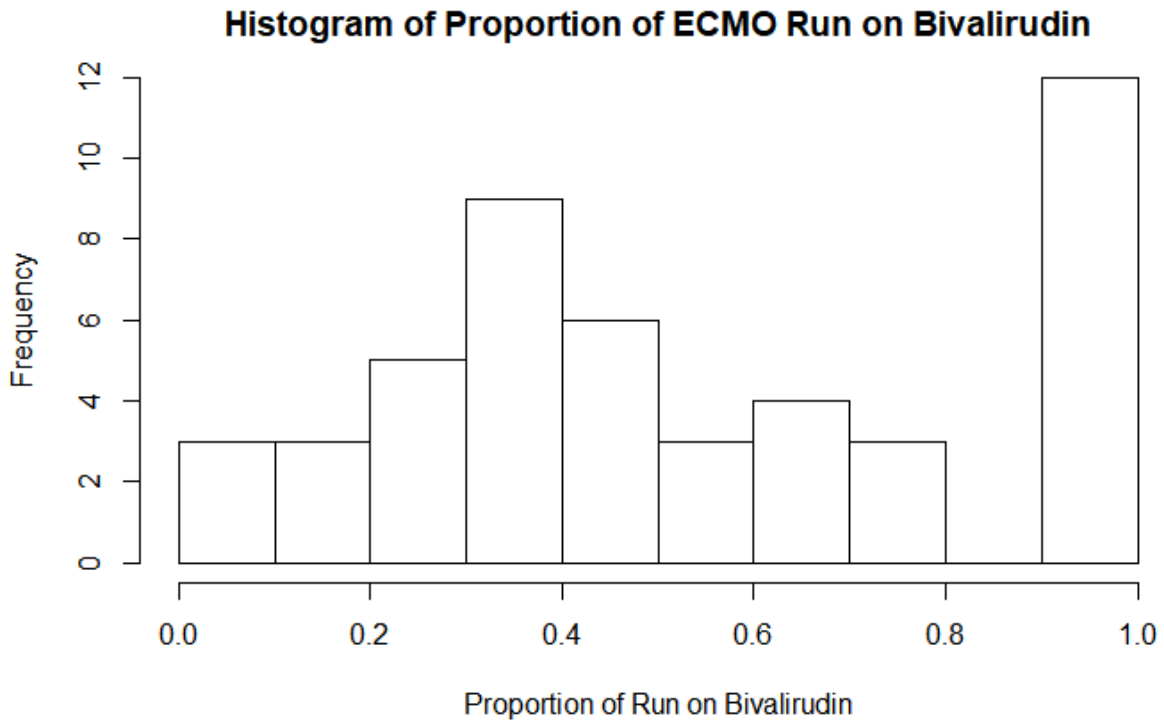

Table 1: Cost of each component of care and references

| Component | Cost (2020 US Dollars) | References |
|---|---|---|
| **Medications** | | |
| Bivalirudin (250 mg vial) | 240 | [36] |
| Heparin (10 mL) | 15 | [36] |
| Aminocaproic acid (100 mL) | 54 | [36] |
| Desmopressin (1 mL) | 71 | [36] |
| Protamine (100 mL) | 235 | [36] |
| Tranexamic acid (100 mL) | 250 | [36] |
| Argatroban (240 mg vial) | 245 | [36] |
| **Labs** | | |
| Activated Clotting Time (ACT) | 4.28 | [35] |
| Complete Blood Count (CBC) | 7.77 | [35] |
| Plasma Free Hemoglobin (PFHB) | 7.31 | [35] |
| Erythrocyte Sedimentation Rate (ESR) | 4.27 | [35] |
| C-Reactive Protein (CRP) | 5.18 | [35] |
| Prothrombin Time/International Normalized Ratio (PT/INR) | 4.29 | [35] |
| Partial Thromboplastin Time (PTT) | 6.47 | [35] |
| Fibrinogen | 9.72 | [35] |
| Anti factor Xa level (Anti-Xa) | 13.09 | [35] |
| D-Dimer | 10.18 | [35] |
| Lactate | 11.57 | [35] |
| Antithrombin III level (AT3) | 11.85 | [35] |
| Procalcitonin | 27.22 | [35] |
| Bilirubin | 5.02 | [35] |
| Thromboelastography (TEG) | 24.91 | [35] |
| Rotational thromboelastometry (ROTEM) | 24.91 | [35] |
| **Blood Products** | | |
| Packed Red Blood Cells (pRBCs) | 267 | [37] |
| Fresh frozen plasma (FFP) | 212 | [37] |
| Platelets (PLTs) | 195 | [37] |
| Cryoprecipitate (Cryo) | 126 | [37] |
| **ECMO Circuit** | 15,198 | [38] |
| **Imaging** | | |
| Head CT | 164 | [35] |
| Brain MRI | 318 | [35] |
| Head US | 166 | [35] |
| **Surgery cost** | 24,243 | [40] |
| **Per-day hospital costs** | | |
| Ventilator Day | 5,612 | [34] |
| ICU Day | 3,554 | [33] |
| Hospital Day | 2,738 | [32] |

Table 2: Demographic characteristics of groups based on bivalirudin exposure and formulary status.

| | Based on Medication Received | | Based on Formulary Status | |
|---|---|---|---|---|
| | **50% or less Bivalirudin (N=1129)** | **Greater than 50% Bivalirudin (N=22)** | **No Bivalirudin on Formulary (N=67)** | **Bivalirudin on Formulary (N=1062)** |
| **Sex Male, n (%)** | 577 (51.1%) | 15 (68.2%) | 32 (47.8%) | 551 (51.9%) |
| **Age (years), mean (SD)** | 2.99 (5.04) | 7.27 (6.35) | 4.15 (5.68) | 3.01 (5.06) |
| **Weight (kg), mean (SD)** | 15.9 (22.5) | 36.3 (29.1) | 16.7 (25.1) | 16.8 (23.1) |
| **ECMO Days, mean (SD)** | 6.77 (7.97) | 14.2 (16.8) | 6.75 (6.43) | 6.91 (8.38) |
| **ECMO Hours, mean (SD)** | 175 (192) | 352 (408) | 174 (154) | 178 (202) |
| **Ventilator Days, mean (SD)** | 27.7 (49.9) | 28.2 (28.8) | 21.3 (26.5) | 28.4 (51.0) |
| **ICU Length of Stay, mean (SD)** | 47.8 (63.3) | 56.9 (82.9) | 42.6 (52.4) | 48.8 (64.6) |
| **Hospital Length of Stay, mean (SD)** | 60.2 (70.4) | 70.2 (95.5) | 54.9 (57.7) | 61.5 (71.9) |
| **Pulmonary Hypertension, n (%)** | 152 (13.5%) | 0 (0%) | 10 (14.9%) | 139 (13.1%) |
| **Chromosomal Abnormalities, n (%)** | 155 (13.7%) | 2 (9.1%) | 11 (16.4%) | 144 (13.6%) |
| **Mitochondrial Disorders** | 4 (0.4%) | 1 (4.5%) | 0 (0%) | 5 (0.4%) |
| **Cardiac Diagnoses, n (%)** | 468 (41.5%) | 5 (22.7%) | 21 (31.3%) | 442 (41.6%) |
| **Pre-Admission oxygen use, n (%)** | 21 (1.9%) | 0 (0%) | 1 (1.5%) | 20 (1.9%) |
| **Comorbid malignancy, n (%)** | 26 (2.3%) | 1 (4.5%) | 1 (1.5%) | 26 (2.4%) |
| **Out of Hospital Cardiac Arrest, n (%)** | 58 (5.1%) | 1 (4.5%) | 2 (3.0%) | 56 (5.3%) |
| **Survived to Discharge, n (%)** | 634 (56.2%) | 13 (59.1%) | 39 (58.2%) | 605 (57.0%) |

Table 3: Clinical Outcomes based on proportion of ECMO run with Bivalirudin.

| | **50% or less Bivalirudin (N=1129)** | **Greater than 50% Bivalirudin (N=22)** | **Relative Risk (95% CI)** |
|---|---|---|---|
| **ECMO Days (total)** | 7640 | 313 | -- |
| **Component Changes (per 100 ECMO-days)** | 40.4 | 36.1 | 0.81 (0.67-0.97) |
| **Cardiac Clots (per 100 ECMO-days)** | 9.6 | 6.7 | 0.64 (0.40-0.95) |
| **Limb Ischemia events (per 100 ECMO-days)** | 9.8 | 6.7 | 0.62 (0.39-0.93) |
| **Pulmonary Embolism (per 100 ECMO-days)** | 9.3 | 6.1 | 0.59 (0.36-0.90) |
| **Deep Vein Thromboses (per 100 ECMO-days)** | 10.9 | 6.1 | 0.50 (0.31-0.77) |
| **Strokes (per 100 ECMO-days)** | 9.6 | 7.0 | 0.66 (0.42-0.98) |
| **Intracranial Hemorrhage (per 100 ECMO-days)** | 10.8 | 6.4 | 0.56 (0.35-0.84) |
| **Surgeries (per 100 ECMO-days)** | 15.5 | 8.6 | 0.51 (0.34-0.72) |

Table 4: Resource utilization per ECMO-day based on anticoagulant.

| | 50% or less Bivalirudin (N=1129) | Greater than 50% Bivalirudin (N=22) | Relative Difference (95% CI) |
|---|---|---|---|
| **ACT (per ECMO-day)** | 1.04 | 0.46 | 0.44 (0.38-0.52) |
| **Platelet level (per ECMO-day)** | 1.20 | 0.78 | 0.65 (0.57-0.74) |
| **Hemoglobin level (per ECMO-day)** | 1.20 | 0.78 | 0.65 (0.57-0.74) |
| **ESR (per 1000 ECMO-days)** | 7 | 6 | 0.90 (0.15-2.90) |
| **CRP (per ECMO-day)** | 0.12 | 0.10 | 0.88(0.60-1.23) |
| **PT (per ECMO-day)** | 2.57 | 1.61 | 0.62 (0.57-0.68) |
| **PTT (per ECMO-day)** | 1.54 | 0.89 | 0.58 (0.51-0.65) |
| **Fibrinogen (per ECMO-day)** | 1.03 | 0.68 | 0.67 (0.58-0.76) |
| **Anti-Factor Xa (per ECMO-day)** | 0.94 | 0.23 | 0.25 (0.19-0.31) |
| **D-Dimer (per ECMO-day)** | 1.54 | 0.89 | 0.58 (0.51-0.65) |
| **Lactic acid (per ECMO-day)** | 0.95 | 0.66 | 0.70 (0.61-0.80) |
| **Procalcitonin (per 100 ECMO-days)** | 3.6 | 7.9 | 2.20 (1.43-3.25) |
| **Bilirubin (per ECMO-day)** | 0.55 | 0.47 | 0.85 (0.72-1.00) |
| **Thromboelastrography (per ECMO-day)** | 0.55 | 0.50 | 0.90 (0.77-1.06) |
| **Rotational Thromboelastometry (per 100 ECMO-days)** | 12.4 | 9.9 | 0.79 (0.54-1.11) |
| **Computed Tomography (per 100 ECMO-days)** | 4.2 | 3.8 | 0.92 (0.49-1.55) |
| **Magnetic Resonance Imaging (per 100 ECMO-days)** | 3.8 | 3.5 | 0.92 (0.47-1.60) |
| **Ultrasound (per 100 ECMO-days)** | 4.2 | 3.8 | 0.91 (0.48-1.55) |
| **Aminocaproic Acid, mg (per ECMO-day)** | 0.82 | 4.92 | 0.12 (0.12-0.12) |
| **Desmopressin, mL (per ECMO-day)** | 3.0 | 0.0 | -- |
| **Protamine, micrograms (per ECMO-day)** | 0.22 | 0.00 | -- |
| **Tranexamic Acid, micrograms (per ECMO-day)** | 8.15 | 489 | 1.17 (1.13-1.21) |
| **PRBCs Transfused, ml (per ECMO-day)** | 135 | 44 | 0.32 (0.32-0.33) |
| **FFP Transfused, ml (per ECMO-day)** | 93 | 29 | 0.17 (0.16-0.17) |
| **Platelets Transfused, ml (per ECMO-day)** | 59 | 10 | 0.32 (0.31-0.32) |
| **Cryoprecipitate, ml (per ECMO-day)** | 6.4 | 0.56 | 0.09 (0.07-0.10) |

Table 5 Costs per patient and the incremental cost differences for various components of care based on anticoagulant.

| | 50% or less Bivalirudin (N=1129) | Greater than 50% Bivalirudin (N=22) | Incremental |
|---|---|---|---|
| **Lab Costs** | 853 | 1,066 | 213 |
| **Device Costs** | 62,826 | 92,982 | 30,156 |
| **Blood Costs** | 1,734 | 954 | -790 |
| **Medication Costs** | 137,838 | 39,973 | -97,865 |
| **Surgical Costs** | 25,359 | 29,670 | 4,311 |
| **Imaging Costs** | 176 | 339 | 163 |
| **Total Costs** | 501,873 | 461,723 | -40,150 |

Table 6 Incremental cost and survival differences comparing bivalirudin to heparin under four different analytic frameworks: standard generalized regression and instrumental variable analysis using 50% cutoff for bivalirudin, and using any bivalirudin during the ECMO run.

| Analysis | Bivalirudin Definition | Incremental Cost Difference (2020 USD) | Incremental Difference in Probability of Survival (Absolute Scale) |
|---|---|---|---|
| **Traditional Regression Analysis** | 50% Cutoff | -40,150 | 0.021 |
| **Instrumental Variable Analysis** | 50% Cutoff | 4,778 | 0.00 |
| **Traditional Regression Analysis** | Any Bivalirudin vs. no Bivalirudin | 227,205 | -0.05 |
| **Instrumental Variable Analysis** | Any Bivalirudin vs. no Bivalirudin | 4,810 | 0.00 |
| **Traditional Regression Analysis** | > 50% Bivalirudin vs. no Bivalirudin | 29,022 | 0.019 |
| **Instrumental Variable Analysis** | > 50% Bivalirudin vs. no Bivalirudin | 4,141 | 0.00 |

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