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Article title: Identification of clinical factors predicting warfarin sensitivity after cardiac surgery

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Abstract

Objectives: Warfarin is commonly initiated post-cardiac surgery to reduce the risk of intra-cardiac thrombus formation. Studies have found that sensitivity is increased after cardiac surgery and anti-coagulation is subsequently difficult to manage. This study set out to identify clinical markers of increased warfarin sensitivity in patients' post-cardiac surgery, and build a model that can predict warfarin sensitivity, and improve safety in this setting. **Methods:** The study was an observational, retrospective cohort design. Clinical parameters including Left Ventricular Ejection Fraction (LVEF), cross-clamp time, age, serum albumin and C-reactive protein concentrations were collected from consenting patients who had undergone cardiac surgery and prescribed post-operative warfarin. Warfarin Dose Index (WDI) was calculated for each patient from their INR and warfarin dose, as a measure of sensitivity. **Results:** 41 patients were recruited to the study. Logarithmically transformed WDI (log WDI) significantly correlated with LVEF, cardiopulmonary bypass (CPB) time, cross-clamp time, baseline INR and co-administration of amiodarone ($p<0.05$). When added to a linear regression model, LVEF and cross-clamp time produced a model that accounted for 41% of variance in log WDI ($R^2=0.41$), $p=0.0002$). Applying a log WDI cut-off value of -0.349 discriminated between patients who develop an INR >4 and those who do not with a sensitivity of 75% and a specificity of 70%. **Conclusions:** This single centre study has highlighted two risk factors for increased warfarin sensitivity post-cardiac surgery. Further research is needed to confirm these findings in a wider, more diverse population, and to validate this model.

Keywords: Warfarin; anticoagulation; anticoagulants; risk-prediction; adverse drug reactions; cardio-thoracic surgery; surgery

1. Introduction

Warfarin is an anticoagulant medication used for the treatment and prevention of thromboembolic disorders such as deep vein thrombosis and pulmonary embolism [1]. It inhibits the enzyme Vitamin K Epoxide Reductase (VKOR), blocking the formation of reduced vitamin K, which is necessary for the synthesis of the clotting factors II, VII, IX, X, and of the anticoagulants protein C and protein S [2]. There is wide inter-patient variability in the response to warfarin, and as a consequence dosing needs to be tailored to individual patients. Factors that are known to affect warfarin response include diet, co-administration of interacting drugs and single nucleotide polymorphisms for the genes that code Cytochrome P450 isoenzyme CYP2C9 and VKOR [1].

Another factor which is increasingly recognised as affecting the sensitivity to warfarin is a recent history of cardiac valve surgery. Studies have found that in the initial post-operative period following valve replacement, certain patients show an exaggerated response to warfarin when compared to non-surgical patients [3-5]. The sensitivity appears to be prolonged, and can lead to poor control in the 3-month period after valve replacement [6]. However, after this period, sensitivity is thought to return to normal. There is therefore a critical window for potential harm, especially during period of warfarin loading. There is variation in this population however, and whilst some patients show increased sensitivity to warfarin, others do not. A universal, bespoke dosage regimen in this population may therefore be inappropriate.

Theories for the increased sensitivity include myocardial dysfunction and fluid overload during surgery, which has been hypothesized to lead to hepatic congestion which then may affect warfarin metabolism or the synthesis of clotting factors [3-7]. As warfarin is 99% bound to plasma proteins (mainly albumin), hypoalbuminemia, caused by an inflammatory response or haemodilution as a consequence of cardiopulmonary bypass (CPB), may also be implicated [3-4,8]. Interacting drugs

commonly used after cardiac surgery are also expected to influence sensitivity [9, 14-15]. In studies looking at factors influencing sensitivity in this patient group, baseline INR, serum albumin, amiodarone and antimicrobial prophylaxis have been identified as risk factors [3, 9-11].

Despite studies finding increased sensitivity in patients after cardiac valve surgery, and the identification of various factors that may contribute to altered response, guidance on dosing in this patient group remains limited, and, as a consequence, anticoagulation is poorly managed. A recent study by Roberts et al investigated the implementation of a warfarin dosing protocol post-valve surgery, suggesting a 30% reduction in warfarin doses in all patients. However, this strategy, whilst reducing the risk of bleeding complications, may leave some non-sensitive patients under-anticoagulated, and at risk of thrombus formation [12]. Another study by Meijer et al developed a specific dosing algorithm post valve-surgery. Despite improving the individual time in therapeutic range, patients in the algorithm group spent more time with a supra-therapeutic INR compared with the non-algorithm group [13]. Identifying clinical and biochemical markers that are associated with increased postoperative sensitivity, and then incorporating them into a risk prediction tool could therefore aid the personalization of dosing in this setting and minimize the risk of over-anticoagulation and the associated risk of bleeding.

The published evidence of increased sensitivity is currently limited to patients that have undergone cardiac valve surgery, however, many of the hypotheses to explain the increased sensitivity are pertinent to patients undergoing other types of cardiac surgery, for example, coronary artery bypass graft. Here, damage to the myocardium as a result of ischaemia during aortic clamp may lead to an acute deterioration in left ventricular function, and hepatic congestion, and altered sensitivity to warfarin. The purpose of the current study was therefore to identify clinical and biochemical markers of increased warfarin sensitivity in patients that have undergone

a range of cardiac surgeries, and to build a model that could, after validation, be used to predict the risk of warfarin sensitivity in the immediate post-operative period. The model could also be used to provide guidance on warfarin dosing.

2. Methods

The study was a non-interventional, retrospective cohort study. It received approval from the National Health Service Research Ethics Service (REC approval number: 15/EE/0082). Data were collected as a convenience sample, between April 2015 and September 2015, from consenting patients.

2.1 Inclusion criteria

1. Inpatient admission following cardiac surgery (not limited to valve repair/replacement)
2. Prescribed postoperative warfarin
3. Over 18 years
4. Capacity to consent as determined by the patients' ability to retain and understand the information given on the patient information sheet

2.2 *Exclusion Criteria*

1. Acute or chronic liver failure as determined from the patient's medical history and preoperative liver function tests
2. Baseline INR >1.5

2.3 Data collection

Participants were given a Patient Information Sheet (PIS) prior to surgery and enrolled in the study towards the end of their inpatient stay after they had recovered. The following data were then collected for each participant: demographics, type of surgery, cardio-pulmonary bypass (CPB) time, cross clamp-time, urea and electrolytes (U&Es), C-reactive protein (CRP), liver function tests (LFTs), International Normalised Ratio (INR), left ventricular ejection fraction (LVEF), concurrent medication prescribed, medication history, warfarin dose, indication and target INR. Warfarin dose index (WDI) was used as an outcome measure for warfarin sensitivity (Equation 1, [11]). The WDI is a well-established measure of sensitivity during both

warfarin initiation, and maintenance stages. The index normalizes the patient's clotting time (international normalized ratio [INR]) at day 4 following commencement of warfarin loading, to dose mean dose over the preceding 3 days.

Equation 1: WDI=INR (day 4*)/mean warfarin dose for preceding 3 days

* Post warfarin loading

2.4 Statistical power calculation

Sample size was calculated using the 'pwr' package in R (v3.2.1). For a final linear regression model with between 3-5 predictor variables, a sample of 35-42 patients is required to detect a large effect (F^2=0.35) with α=0.05 and β-1=0.80. For the same number of predictors (3-5) and an F^2=0.15 (medium effect) a sample size of 77-91 patients is required. We anticipated that our predictors would have a medium to large effect and so our target sample size was set to 35-50.

2.5 Statistical model

We built a linear regression model using the $\log_{10}$ of the WDI (log WDI) as our dependent variable, and factors hypothesized to alter warfarin sensitivity as our predictor variables. To determine which of the predictor variables collected should be included in our first iteration of the model we performed a series of correlations between these variables and log WDI. A Pearson Correlation was used for continuous variables that 1) demonstrate a normal distribution and 2) have no significant outliers [14-15]. For variables with a significant ($p<0.05$) Shapiro-Wilk test, or where there are extreme outliers in the sample, a Spearman Rank test was performed [15, 17]. For dichotomous predictor variables a Point-Biserial Correlation was performed after assessing normality and homogeneity of variance [14, 17]. Correlation coefficients are reported as r (Pearson's), ρ (Spearman's) and ρ_{pb} (Pearson's Point Biseral). Variables with a p value of $\leq$0.15 were then added to a linear regression model with

log WDI as the dependent variable. A significance level of $p < 0.05$ was accepted as statistically significant.

In describing continuous data with a normal distribution, mean ± standard deviations were used. For continuous data that was not normally distributed the median and interquartile ranges (IQR) is presented. Our final model was tested for the following assumptions of linear regression: independence of errors, collinearity, normal distribution of errors, linearity and heteroscedascity [13-21]. The British Society of Echocardiography Guidelines were used to categorise LVEF into groups [22].

Receiver operating characteristics curves, area under the receiver operator curves (AUROC), and sensitivity and specificity values were calculated using Graphpad Prism 6.0. Youden's index was calculated as: (sensitivity + specificity)-1. The AUROC and Youden's index were used to determine an appropriate cut-off value for log WDI to predict INR >4 during inpatient stay with maximum sensitivity and specificity.

Data analysis was conducted with SPSS version 22.0, Graphpad Prism 6.0, and R.

3. Results

Out of 55 patients admitted for cardiac surgery and initiated on warfarin during the study period, 41 patients were eligible for inclusion in the study. 35 of these patients had a complete dataset and were included in the final model (Figure 1). A breakdown of baseline demographic details is found in Table 1. Patients received post-operative warfarin for a range of indications including atrial fibrillation, mechanical mitral valve replacement, and mitral valve repair (Table 2). Of the 35 patients included in the final model, 31 were admitted for valve related surgery, and 4 for non-valve related surgery. Non-valve related surgery included coronary artery bypass graft (CABG), atrial ablation, and surgical treatment of atrial myoxoma and left atrial appendage occlusion.

3.1 Dosing and INR Ranges

Warfarin was started a median of 1 day after surgery (IQR = 1 - 3, range 0 - 18 days) and took a median of 5 days to reach the therapeutic range (IQR 4 - 7 days, range 3 - 21 days). Over the first 3 days of loading a median dose of 4 mg daily was used (IQR 3 – 5 mg). The median cumulative dose to achieve therapeutic range was 20 mg, (IQR 13.0 - 27.5 mg).

Fifteen (37%) patients had an INR value which exceeded the patient’s target therapeutic range for a median of 2.5 days (IQR 2 – 4.5 days, range 1 - 6 days) and of these, 12 (80%) patients had an INR > 4.0. One patient had vitamin K administered to reverse an INR of 7.5. During the study 10 (24%) patients had a total of 39 doses omitted due to the INR exceeding the therapeutic range. Discharge was delayed in four patients (10%) due to the INR being below the therapeutic range and one patient had a delayed discharge due to the INR being too high. Comparing valve and non-valve related surgery patients, 9/31 in the valve related surgery group, and 3/4 in the

non-valve related surgery group developed and INR >4 during loading with warfarin post-surgery.

3.2 Bivariate Correlation

To identify variables to enter in the first iteration of our model we performed a series of statistical correlation tests between log WDI and predictor variables (supplementary material). From these correlations we identified left ventricular ejection fraction (LVEF), CPB, cross-clamp time, baseline INR, and the co-administration of amiodarone and omeprazole as potential predictors. Other factors that have previously been associated with warfarin sensitivity, such as age, gender and weight were not significantly correlated with log WDI in this sample (ρ=0.019, p=0.907 age; r_{pb}=0.056, p=0.728 gender; r=-0.068, p=0.676 weight) and therefore were not included in the model.

3.3 Linear regression

Initially the predictors identified were added to the linear regression model as single variables. As single predictors of sensitivity LVEF, cross clamp-time, CPB time and the addition of amiodarone (n=20/41) all had statistically significant changes in the F-ratio, F (1,33) = 15.87, p = 0.00035, F (1,39) = 4.817, p = 0.034, F (1,39) = 4.665, p = 0.037 and F (1,39) = 4.743, p = 0.036 respectively. As a single predictor LVEF accounted for 32.5% of variability in the model (R^2 = 0.325, adjusted R^2 = 0.304, n=35, Figure 2) and when combined with cross-clamp time the model accounted for 41% of the variance ((R^2 = 0.41, adjusted R^2 = 0.373, n=35). The combination of LVEF and length of cross-clamp time provided the best fit of the data (Table 3). The addition of amiodarone (F change = 1.307, p = 0.261), or CPB time (F change = 2.858, p = 0.101) to LVEF did not significantly improve the model. The equation for our final model is shown in equation 2, in which $E[LogWDI_i]$ is the expected values of $LogWDI_i$.

Equation 2: $E[LogWDI_i] = 0.026 + (-0.011 \times LVEF_i) + (0.002 \times clamptime_i)$.

3.4 Model Assumptions

Independence of residuals was confirmed with a Durban Watson test = 2.607. There was a small correlation between LVEF and cross-clamp time (r = .130) but assessment of collinearity was acceptable (VIF = 1.017). There was a normal distribution of the residuals as confirmed with a frequency histogram and a P-P plot. From visual inspection of a plot of standardised predicted values against standardised residuals there was no evidence of non-linearity or heteroscedascity. To detect outliers, the standardised residuals were set at ± 3 (z-score = 2.56), which all were below this range. The leverage value calculated was 0.086 and 2 cases had values greater than twice this value but the Cooks distances conformed to the accepted criteria so none of the data points would exert a high influence over the regression line.

3.5 Clinical Predictors

Left Ventricular Ejection Fraction (LVEF): 18 (51%) patients had good LVEF, 12 (34%) mild LVEF, 2 (6%) moderate LVEF and 3 (9%) poor LVEF. Log WDI was statistically significantly different amongst the groups (p = 0.033, n=35, Kruskal-Wallis).

3.6 Using the model to predict patients who develop INR >4 during stay

Using a patient's LVEF and cross-clamp time to predict log WDI may be of benefit to clinicians who are initiating warfarin, as it could, for example, be used to calculate the mean daily loading dose required to reach a target INR by day 4. This may not however be practical in a busy ward situation, and may introduce a focal point for medication error due to the multi-step nature of the calculation required to determine a loading dose. It may therefore be more useful to use the model to categorise patients as either high-risk, or low-risk; those individuals deemed high risk should then be loaded more cautiously with warfarin. To use the model in this way, we must first identify a 'cut-off' value in the 'predicted' log WDI above which there is high

sensitivity and specificity for detecting high-risk individuals. High-risk individuals in this case were considered those patients' who had developed an INR ≥4 during their inpatient stay. From our dataset we categorised patients according to whether they had developed an INR ≥4, and then calculated their 'predicted' log WDI using equation 2. This allowed us to construct a Receiver Operating Characteristics (ROC) curve to determine an appropriate cut-off value (Figure 3).

From our study, 12/35 patients had an INR of ≥4 during their inpatient stay. We identified a predicted log WDI cut-off value of -0.380 from our ROC curve (area under ROC = 0.7 (0.5-0.9), Figure 2). Using this cut-off value, we correctly identified, retrospectively, 9/12 patients who went on to develop a peak INR >4 during their inpatient stay (sensitivity 75%), and 17/23 patients with a peak INR <4 during inpatient stay (specificity 70%). Youden's index, which is a measure of the accuracy of our model, was calculated as J=0.45, and the positive predictor, and negative predictor values as 56% and 85% respectively.

4 Discussion

This study aimed to build a model to predict warfarin sensitivity in patients undergoing cardiothoracic surgery, using a range of routinely available clinical variables. In doing so we discovered that compromised cardiac function and the time spent on clamp increased the risk of developing sensitivity to warfarin post-surgery.

During the study, 37% of patients exceeded their target INR range. Of these, 29% had an INR > 4.0. For this population, these results are comparable with other studies looking at warfarin response after cardiac surgery, where between 38% and 48.8% of patients exceeded the therapeutic range [3, 5] and 25% patients had an INR ≥4.0 in the induction period [4]. Whilst there is no current guideline for dosing patients after surgery in the UK, the range of dosing used was consistent for the majority of patients over the first 3 days of loading, with a median of 4 mg daily (IQR 3 – 5 mg). Whilst other studies have suggested dosing all patients at lower doses [7], or applying a dosing algorithm to reduce the risk of high INRs during this period, this could result in delayed discharges due to sub therapeutic INRs. Therefore, a targeted, individualized approach to dosing would be advantageous, in terms of the patient experience, safety, and healthcare associated costs.

Of the factors hypothesized to be associated with increasing warfarin sensitivity, LVEF had a large effect size (r=0.57) and a statistically significant negative correlation associated with increased response to warfarin. CPB time, amiodarone and baseline INR were also found to have statistically significant positive correlations with the outcome measure, all with medium effect sizes. However, when added to our regression model, they did not increase the explanatory power of LVEF in predicting warfarin sensitivity. This study was not powered to assess this further.

4.1 Heart Failure

The negative relationship between LVEF and warfarin sensitivity is perhaps counterintuitive: warfarin is a low extraction drug, and elimination is not considered to be dependent upon hepatic blood flow [23], which is compromised in heart failure (a low LVEF). However, there are reports of an association between heart failure and increased response to warfarin in the literature, although some of these studies are older and problematic. For example, some used prothrombin time rather than INR [24] as a measure of warfarin efficacy, the parameters of which can vary between laboratories.

There are also conflicting findings between whether dose requirements are altered because of decompensated heart failure, or if the effect also manifests for stable heart failure [24]. A small study (n = 63) looking for factors affecting the maintenance dose in Hong Kong Chinese patients, found that chronic heart failure (n = 6) negatively correlated with warfarin dosage requirement ($r = -0.26$, $p = 0.025$) [25]. Doecke et al. (1991) also found that stable chronic heart failure was associated with increased response to warfarin during initiation [26].

Del Campo *et al* (2015) found warfarin sensitivity (WDI) to be significantly increased during exacerbations of heart failure and chronic obstructive pulmonary disease (COPD) when compared to a periods of disease stability [27]. The heart failure group had significantly greater sensitivity at admission compared to the COPD and control groups but no difference in sensitivity between the groups during periods of disease stability. This would indicate a transient change, relating to the exacerbation, which supports the theory relating to increased sensitivity for decompensated disease. Significantly more patients presented with INR ≥ 4 in NYHA class 3 and 4 compared to NYHA class 1 and 2 (41% vs. 7% respectively $p = 0.028$), indicating increased sensitivity with worsening function as found in this study.

Theories relating to proposed mechanisms for increased response in heart failure exacerbations relate to either the pharmacodynamic effect on clotting factor synthesis, or proposed pharmacokinetic mechanisms of reduced warfarin metabolism or clearance. As the liver is the site of synthesis for vitamin K dependent clotting factors, a decrease in synthesis due to hepatic congestion has been suggested [24].

4.2 Cardiopulmonary Bypass Time, Cross-clamp Time and Warfarin Sensitivity

Cardiopulmonary bypass is the use of an extracorporeal circuit to maintain circulation to the body during cardiothoracic surgery [28]. A cross-clamp is placed across the aorta to isolate the coronary circulation and can, in some circumstances lead to hypoxic damage of the myocardium, although various techniques are used to mitigate this [28]. Increasing length of cross-clamp time and CPB time were both found to be significantly correlated with increasing warfarin sensitivity and may be related to ensuing damage. However, other studies in this patient group did not find any relationship between CPB times in either of their cohorts when looking at warfarin sensitivity [11, 14], but may be related to differences in surgical procedures or patient demographics.

Both prolonged CPB and cross-clamp time are associated with increased morbidity and mortality following cardio-thoracic surgery. There is evidence that during the period of the cross-clamp, myocardial ischemia induces a systemic inflammatory response syndrome (SIRS) [29]. Pro-inflammatory cytokines, including interleukin 6 (IL-6), tumour necrosis factor α (TNF- α), interleukin 1 (IL-1) and endotoxin are released as part of the SIRS response, thought to result from the exposure of blood to the artificial surface of the bypass circuit [29-30]. Cytokines, such as IL-1, IL-6, TNF α and interferon have all been shown to have an effect on drug metabolism [31]. Production of cytokines, which may be responsible for the down regulation of individual CYP450 isoforms has been proposed as a mechanism for significant decreases in CYP450 related drug metabolism in critically ill patients with SIRS [32-33]. Peak

CRP was investigated in this study as a marker of inflammation but did not significantly correlate with log WDI, having a small effect size. As IL-6 seems to be implicated in both drug metabolism and the systemic inflammatory response from CPB this would appear to be a more useful indicator of this effect and worth investigating in the future.

4.3 Amiodarone

Amiodarone was the only interacting drug which correlated with warfarin sensitivity in this study, however, it failed to reach significance when included in our model. One possible reason for this could be the temporal trajectory over which the interaction occurs. If we were to conduct the study over a longer period for example, we may find this predictor plays a more prominent role in our model.

4.4 Limitations

A patient's response to warfarin therapy can be affected by various factors, including diet (vitamin K intake), genotype, and co-prescribed interacting drugs. Whilst we included major interacting drugs in our model, we did not collect data on genotype, or diet. Doing so may have improved our model. However, with respect to genotype, this is a factor which is not routinely screened for in the UK, and its inclusion in this model may have meant that using it as a risk prediction, or dosing tool would not be practical.

One further limitation includes the small sample size, and use of a single site for recruitment. Despite the small numbers of patients, out study was powered to identify predictor variables that had a medium, and hence clinically important effect size. Nevertheless, further research is required to confirm these preliminary findings, and validate our model in a more diverse patient population.

5. Conclusion

In this study, we found that 37% of patients had an INR above their therapeutic range and 29% had an INR ≥4.0, which can lead to patient harm and delay discharge from hospital. We identified two clinical markers that contributed to increased postoperative sensitivity to warfarin in patients that had undergone a range of valve related and non-valve related cardiac surgery. These were LVEF and length of cross-clamp time. By adding these to a linear regression model, they accounted for 41% of the variance in response to warfarin in the initial loading period in this cohort. Application of a log WDI cut-off value of -0.380 was able to successfully identify 75% of patients with and INR ≥4. It should be noted however that this is a single centre study, and further research is required to confirm these findings in a more diverse patient population, and rule out the influence of confounders. But, once validated, our model could be used to predict patients that are sensitive to warfarin following cardiothoracic surgery, and provide guidance of a suitable loading dose to achieve a target INR. This could reduce the risk of over anticoagulation in the early postoperative stages and lead to significant improvements in the dosing of this population.

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Declaration of interest

We confirm that there are no actual or potential conflicts of financial interest with any of the authors, or the authors' respective institutions.

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Figure 1. Differences between warfarin sensitivity (log WDI) and categories of left ventricular ejection fraction (LVEF) for patients undergoing cardiothoracic surgery and participating in the study (n = 41). The category of LVEF was assigned according to the British Society of Echocardiography Guidelines [19]: Good = ≥ 55%, mild = 45 - 54%, moderate = 36 - 44% and poor = ≤ 35%. Outliers are denoted by circular dots, indicating 1.5 times the box length and extreme outliers are denoted by * indicating 3 times the box length. Kruskal-Wallis test, * $p < 0.05$.

Figure 2. Scatter plots demonstrating the relationship between the two variables: Left Ventricular Ejection Fraction (LVEF, $R^2=0.32$, $p<0.001$) and Cross Clamp Time ($R^2=0.013$, $p<0.05$), and warfarin sensitivity (logWDI).

Figure 3. Receiver operating characteristics (ROC) curve showing the sensitivity and 1-specificity values for a range of predicted log WDI cut-off values. The area under the ROC was found to be 0.70 ($p=0.05$).

Table 1. Characteristics of participants initiated on warfarin after cardiothoracic surgery who consented to participate in the study (n = 41). One patient was an emergency admission so a pre-operative weight was not documented (in this case the first weight after surgery was used). Data are presented as the mean ± standard deviation unless otherwise stated.

Characteristic	Descriptive Statistic
Age (years)	Median = 65 IQR = 56 - 71 (range = 28 - 85)
Gender n (%)	Male = 31 (76%) Female = 10 (24%)
Weight (kg) (n = 40)	Mean = 81 ± 19.4 (Range = 47 - 128)

Table 2. Indication for warfarin after cardiothoracic surgery for patients participating in the study (n = 41).

Indication for Warfarin Therapy	n (%)
Mechanical Mitral Valve	10 (24.4)
Mechanical Aortic Valve	5 (12.2)
Tissue Mitral Valve	4 (9.8)
Mitral Valve Repair	11 (26.8)
Atrial Fibrillation	10 (24.4)
Left Ventricular Thrombus	1 (2.4)

Table 3. Linear regression model of predictors of log WDI with 95% confidence intervals reported in parentheses. Confidence intervals and standard errors (SE) based on 1000 bootstrap samples. Model 1 contains LVEF and Model 2 contains LVEF and length of cross-clamp time. R^2=0.33 for model 1 and delta R^2=0.085 for Model 2 (p=0.040). SE=Standard error of the mean; CI=95% confidence interval

Model	Coefficients ((95% CI)	SE	P value
1. Constant	0.308 (- 0.071, 0.428)	0.092	0.069
LVEF	- 0.012 (- 0.15, - 0.008)	0.002	0.000352
2. Constant	0.026 (- 0.468, 0.425)	0.217	0.901
LVEF	- 0.011 (- 0.015, - 0.004)	0.003	0.000352
Cross-clamp time	0.002 (0.0001, 0.005)	0.001	0.040