# Do we need ongoing monitoring of the intensity of anticoagulation with heparin for chronic hemodialysis?

**A quality initiative of the Division of Nephrology Eastern Health**

By

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# ABSTRACT

Background: Heparin is the standard anticoagulation used to prevent clotting in the extracorporeal circuit during hemodialysis. Its anticoagulation effect can be measured by the activated clotting time (ACT), to achieve 1.5–2 times the baseline value to prevent clotting or bleeding during hemodialysis. However, it is unknown whether changing ACT monitoring policy in chronic hemodialysis patients, from routine monthly ACT monitoring to ACT measurement in response to clinical events, will increase the risk of clotting and bleeding events.

Methods: To evaluate, *in chronic hemodialysis patients on a stable heparin dose,* whether a change in practice, from routine monthly ACT monitoring (Phase I) to one in which ACTs are only measured for initial dose assignment or in response to clinical indications (Phase II), will significantly increase the incidence of patients' bleeding or clotting events, 109 patients in our hemodialysis unit were followed and evaluated for 8 months in a quality initiative study using a before-and-after design. Clotting event was defined as visible signs of clot formation in the bottom of the dialyzer, coagulated dialyzer, or changing the circuit due to clotting. Overt bleeding documented by clinical examination or diagnostic investigations within 4 hours from hemodialysis session, doubling homeostasis time in patients with AVF; not secondary to fistula-related issues,

unexplained fall in hemoglobin ≥ 20 g/L within a month, or the requirement for blood transfusion due to bleeding were defined as a bleeding event.

Results: The mean ACT in phase I was higher than phase II ($P$ =0.003), but >50% of ACTs were below target. Although heparin doses were changed more often (Incident rate ratio (IRR) 9.11; 95% CI: 2.78-29.92, $P$ =0.000), and more effectively achieving ACT target during phase I compared with phase II (IRR 189.5; 95% CI: 25.36-1415.2, $P$ =0.000), the *incident rate ratio* for all clotting events occurred during phase I was unexpectedly and significantly higher (IRR 1.4; 95% CI: 1.01-1.97, $P$ =0.041) than phase II. For unclear reasons, the risk of any clotting event occurring during phase I was higher than phase II (Odd Ratio; OR 1.87; 95% CI: 1.03-3.39, $P$ =0.04). This could not be explained merely by the low frequency and effectiveness of heparin dose changes, which occurred in less than 10% of clotting events, and were effective achieving ACT target in only 50% of above cases. Although heparin doses were changed more often when serious clotting (type 2 or 3) occurred during phase I compared with phase II, heparin change was not statistically significant (OR 3.12; 95% CI: 0.62-15.8, $P$ =0.17), nor was it effective in achieving ACT target (OR 2; 95% CI: 0.08-51.6, $P$ =0.68).

Bleeding events occurred 6% less often during phase I compared with phase II. However, this was not statistically significant (P =0.84), although the risk for any bleeding event stayed the same during both phases (OR 1; 95% CI: o.53-1.9, $P$ =1).

Conclusions: Routine monthly ACT monitoring in adult chronic hemodialysis patients did not improve clinical outcomes reducing clotting and bleeding events compared with measuring ACTs only for the initial dose assignment or in response to clinical indications. However, as practiced locally, this could be due to the limited physician response to ACTs that were not at target.

To more thoroughly address the question of whether routine ACT monitoring is necessary, the best approach in a future randomized trial would include strictly standardized heparin dose-adjustment protocols to be used routinely by hemodialysis nurses to reduce the potential for bias due to physician response variability.

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## List of Symbols, Nomenclature or Abbreviations

ACT: Activated Clotting Time

AKI: Acute Kidney Injury

aPTT: Activated Partial Thromboplastin Time

ASN: American Society of Nephrology

AT-III: AntiThrombin III

AVF: ArteriVenous Fistula

CBC: Complete Blood Count

95% CI: 95% Confident Interval

CJASN: Clinical Journal of American Society of Nephrology

CVC: Central Venous Catheter

ER: Emergency Room

ESRD: End Stage Renal Disease

HD: HemoDialysis

Hgb: Hemoglobin

HIC: the Human Investigations Committee

IRR: Incident Rate Ratio

IU/Kg: International Unit per Kilogram

IU/Kg/Hr: International Unit per Kilogram per Hour

JASN: Journal of American Society of Nephrology

KI: Kidney Internal Journal

NDT: Nephrology Dialysis Transplant Journal

OR: Odds Ratio

PVD: Peripheral Vascular Disease

RCT: Randomized Controlled Trial

RPAC: The Research Proposals Approval Committee

TAT: Thrombin - AntiThrombin Complex

URR: Urea Reduction Ratio

WBPTT: Whole Blood Activated Partial Thromboplastin Time (WBPTT)

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# INTRODUCTION

Hemodialysis is an important mode of therapy in the treatment of patients with acute kidney injury (AKI) and end stage renal disease (ESRD). While blood is exposed to dialyzer membranes during hemodialysis, platelets adhere to the artificial surface, resulting in activation of the coagulation cascade and platelets (1). As a result of this activation, blood clotting in the dialyzer and dialysis machine circuit may occur. Dialyzer clotting may lead to decreased efficiency of treatment and loss of blood by the patient (2). Hypercoagulability may be present in hemodialysis patients secondary to predialysis elevated levels of coagulation proteins such as thrombomodulin and thrombin–antithrombin (TAT) complex (3, 4). *Therefore, to prevent clotting in the extracorporeal circuit during hemodialysis, anticoagulation is usually required. Furthermore, anticoagulation monitoring during hemodialysis may be indicated to reduce the risk of clotting and bleeding events.*

Unfractionated heparin is a mixture of glycosaminoglycans, with molecular weight between 3 and 30 kilo Daltons (kDa) that indirectly inhibits thrombin (5,6). One-third of unfractionated heparin molecules randomly contain a pentasaccharide sequence that binds to antithrombin III (AT-III), converting AT-III to a rapid inactivator of thrombin, factor Xa and other active coagulation factors, thus inhibiting the clotting cascade and preventing clotting (5,6). The anticoagulant effect of unfractionated heparin can be

measured by plasma-based activated partial thromboplastin time (aPTT), which measures the increased time taken for clot formation under controlled conditions (6). This anticoagulant effect of unfractionated heparin can also be measured by faster, bedside methods such as the whole blood activated partial thromboplastin time (WBPTT) (7) and the whole blood activated clotting time (ACT) (8). A rise in the WBPTT or ACT to 1.5–2 times the baseline value is usually acceptable to provide sufficient anticoagulation with unfractionated heparin (7, 8).

**Use of heparin is the standard of practice for anticoagulation during hemodialysis in most countries**; it is relatively inexpensive and most hemodialysis machines are equipped with a heparin infusion pump (6). We presently use heparin for anti-coagulation during dialysis. When initiating a patient on dialysis, a dose of heparin is prescribed and the effect on ACT is measured. Once an individualized patient dose has been determined to get the patient to the target ACT, the same dose is given for all subsequent dialyses. Anticoagulation with heparin is routinely performed with a loading dose (approximately 15-70 IU/kg) given through the venous port; three to five minutes prior to hemodialysis; followed by a continuous infusion (500-1500 IU/hr) (6, 9-13). To achieve an adequate anticoagulation without increasing the risk of bleeding, heparin infusion is generally stopped at the end of hemodialysis session unless the patient has an AV fistula, in which case, heparin infusion is usually stopped 30-60 minutes prior to the end of hemodialysis to limit bleeding on needle removal (14). Complicated mathematical

modeling can predict the required heparin dose during hemodialysis to reduce the risk of bleeding, but those models are inconvenient and not widely used (15, 16).

Other potential anticoagulation agents that can be used during hemodialysis to prevent clotting in the extracorporeal circuit during hemodialysis are low molecular weight heparin, citrate, prostacyclin, and recombinant hirudin anticoagulation.

Low molecular weight heparin (LMWH), like unfractionated heparin, inactivates clotting factor Xa, though it has a lesser effect on thrombin since most of the LMW heparins do not contain enough saccharide units to bind to thrombin and antithrombin III (AT-III). LMW heparins have been proposed to result in less thrombocytopenia and bleeding than unfractionated heparin (17,18), although there is extensive cross reactivity (> 90%) between the LMWH and unfractionated heparin in terms of thrombocytopenia and hypercoagulable state once a patient develops heparin-induced thrombocytopenia (HIT).

Although the cost of LMWH varies across countries, LMW heparins are still expensive in North America and have not been associated with less hemodialysis-related bleeding, thrombosis, or other complications compared with unfractionated heparin (17,18). Furthermore, monitoring LMWH with the activated partial thromboplastin time (aPTT) is

not accurate, and usually requires the measurement of anti-factor Xa levels, which is more expensive and less available (19,20).

The regional citrate anticoagulation regimen has been adopted in many hemodialysis units as an alternative method of anticoagulation in patients on chronic hemodialysis, especially when heparin use is contraindicated (21). The regional citrate anticoagulation regimen involves the continuous infusion of isosmotic trisodium citrate solution into the arterial side of the dialyzer (21). Trisodium citrate binds to patient's plasma calcium, inducing a decrease in the patient's free plasma calcium concentration, inhibiting the progression of the coagulation cascade. The citrate infusion rate is adjusted to keep the ACT above 200 seconds in the arterial limb.

Later, the citrate-calcium complex is removed across the dialyzer and the regional anticoagulation is reversed by the infusion of 5% Calcium citrate solution into the venous return line at adjusted rates according to the patient's plasma calcium concentration (22).

Although trials have showed lower bleeding incidence rates associated with the regional citrate anticoagulation compared with the standard heparin protocols (23,24), the regional citrate anticoagulation has been associated with major electrolyte abnormalities (hypocalcemia, hypercalcemia, or hypernatremia) and metabolic alkalosis that limited its use in patients on chronic hemodialysis.

The Citric acid-based dialysate (*Citrasate* ®) results in reduced clotting in no-heparin dialysis, by lowering patient's serum calcium enough to interfere with the clotting cascade without inducing symptomatic hypocalcemia or metabolic alkalosis (25,26). However, a small but significant change in the patient's serum calcium is a major complication of citrate dialysate. More trials are required to identify the safety and effectiveness of the use of citrate dialysate in chronic hemodialysis patients.

The arachidonic acid metabolite prostacyclin is a vasodilator and inhibitor of platelet aggregation. Prostacyclin regional anticoagulation involves a continuous infusion of prostacyclin into the dialyzer circuit during hemodialysis to prevent platelet aggregation and clotting (27). Side effects include headache, lightheadedness and facial flushing. However, its use during chronic hemodialysis has been limited by its expense as well as its side effects including headache, facial flushing, and most importantly hypotension due to vasodilation (28).

Hirudin inhibits thrombin by forming a noncovalent complex. Recombinant hirudin (lepirudin) has been used in hemodialysis patients as a single bolus at the beginning of hemodialysis or as a continuous infusion (29,30). However, due to its prolonged half-time in hemodialysis patients, its use has been limited (29,30).

**Although heparin has been widely used during hemodialysis as an anticoagulant,** and although studies have shown an improvement in dialysis efficiency (2) associated with the anticoagulation effect of heparin, **there is no standardized approach to heparin dosing or monitoring during hemodialysis** (6). Furthermore, searching the available literature could not identify an evidence-based protocol recommending ACT-guided heparin monitoring and dosing during chronic hemodialysis. Consequently, a quality initiative study was required to test whether an increased risk of clotting or bleeding would follow the change in ACT monitoring policies.

From a clinical practice approach, the majority of hemodialysis units in North America approve the continuous infusion regimen of unfractionated heparin during hemodialysis in patients with end stage renal disease and no contraindication for heparin. This regimen is generally delivered; as mentioned above; as a bolus followed by continuous infusion (6, 9-13). A prolongation of the aPTT, WBPTT, or ACT to 150% of their pre-dialysis values is recommended to provide sufficient anticoagulation without increasing the risk of bleeding (7, 8). ACTs are readout by automated machines in the dialysis unit, which are faster and more favorable than the other two tests (5). Some dialysis units, ours currently included, routinely measure ACTs on all patients on a monthly basis. This is done even in the absence of any indication of a clinical problem with bleeding or clotting. Minor adjustments to the heparin dose are sometimes made once the ACT results are reviewed. It is not clear that this leads to any improvement in patient outcomes, but the whole

process of measuring ACTs routinely is resource and staff time intensive. In contrast to our practice, many other hemodialysis units (e.g. The Ottawa Hospital, Ottawa, Ontario, Canada) do not routinely measure ACTs again on patients for whom a suitable dose of heparin has been identified and who are not showing any indication of either bleeding or clotting problems. However, there are no available studies or evidence to support the latter practice.

On the other hand, heparinization during hemodialysis has been associated with multiple hemorrhagic complications (such as subdural hematoma (31), retroperitoneal (32) and pleural (33) hemorrhage) in hemodialysis patients that could be complicated by death in 3-5% of cases (34, 35). Additionally clotting can diminish the efficiency of dialysis and lead to patient blood loss (2). Therefore, both bleeding and clotting have negative effects on patients and have cost impacts for the health system. Accordingly it is important to try to get the best balance between the risk for bleeding and clotting while using anticoagulants for hemodialysis.

**Aim of Study:**

The purpose of this Quality Improvement Exercise was to evaluate, in chronic hemodialysis patients on a stable dose of heparin, whether a change in practice from routine monthly monitoring of ACTs to one in which ACTs were only measured for

initial dose assignment or in response to clinical indications, will lead to any significant increase in patients' bleeding or clotting events. Furthermore, if no such safety concerns are identified, the plan would be to save or reassign resources by discontinuing our current practice of routine monthly ACT monitoring.

# LITERATURE REVIEW

Although heparin has been widely used during hemodialysis as an anticoagulant, and although studies have shown an improvement in dialysis efficiency (?) associated with the anticoagulation effect of heparin, there is no standardized approach to heparin monitoring and dosing in chronic hemodialysis patients on a stable heparin dose (6).

Searching the current available literature *using the following synonymous terms* (renal failure, end stage renal disease, ESRD, chronic hemodialysis, renal replacement therapy, anticoagulation, heparin, unfractionated heparin, monitoring and activated clotting time; ACT), *using the following sources* (The Cochrane Library, MEDLINE/PubMed/MeSH, Uptodate, ASN (American Society of Nephrology), Journals (JASN, CJASN, KI, NDT, etc), Textbooks, Experts opinion, and google.com), *looking at* (Randomized Controlled Trials, Systematic Review, Meta-analysis, practice guideline, and clinical trials) *in the light of the following limits* (English language, adult, age $\geq$ 19 year, end stage renal disease, chronic hemodialysis, and human model); could not identify any randomized controlled trial (RCT), systematic review, meta-analysis, or clinical trial that investigates ACT- guided heparin monitoring and dosing during chronic hemodialysis.

Multiple practices are currently used to dose unfractionated heparin for chronic hemodialysis. Heparin can be delivered during chronic hemodialysis as a continuous or intermittent bolus (6, 9-13). Continuous administration provides a predialysis loading dose, followed by a constant infusion of heparin during hemodialysis. Intermittent administration consists of one or more bolus doses (6,9-13).

Depending on the pharmacodynamics of unfractionated heparin, the continuous administration of heparin during chronic hemodialysis, as described above, provides a more uniform level of anticoagulation than the intermittent administration (9). However, due to the wide variability in the pharmacodynamics of unfractionated heparin from one patient to another, the use of the same heparin dose for all patients during chronic hemodialysis will result in excessive or inadequate anticoagulation (6,9). Subsequently, to provide excellent control of anticoagulation and to determine heparin dosing in hemodialysis patients, multiple clotting times (WBPTT or ACT) and careful dose adjustments are required (16), especially at the initiation of hemodialysis to establish the target heparin dose. An increase in the WBPTT or ACT to 1.5–2 times the baseline value is generally thought to provide adequate anticoagulation with unfractionated heparin (6). However, the same type of assay may provide different results depending on the measurement machine and the activating standard used (6). The above practice is also expensive, labor intensive, and unsuitable to busy hemodialysis units.

Complicated mathematical modeling, which requires the use of a computer-controlled heparin infusion pump, can predict the required heparin dose during hemodialysis to reduce the risk of bleeding, but those models are inconvenient and not widely used (15, 16).

Given the difficulties outlined above, there is no standardized approach to heparin monitoring and dosing in chronic hemodialysis nor there are evidence-based protocols, recommendations, or guidelines to recommend routine monthly clotting times (ACT) in chronic hemodialysis patients to monitor heparin dosing in order to reduce major heparin-related complications. From a clinical practice approach, some dialysis units in North America, ours currently included, routinely measure ACTs on all patients on a monthly basis, even in the absence of any clinical indication of bleeding or clotting. Minor adjustments to the heparin dose are sometimes made once the ACT results are reviewed. However, it is not clear that this leads to any improvement in patient's outcomes. In contrast to our practice, many other hemodialysis units do not routinely measure ACTs again on patients for whom a suitable dose of heparin has been identified and who are not showing any indication of either bleeding or clotting problems. However, as reported above, there are no available studies or evidence to support either practices over the other at this time.

# METHODS

This evaluation was done in our hemodialysis unit at the Waterford Hospital, in St. John's, Newfoundland and Labrador, in Canada, after our research proposal was approved by the Human Investigations Committee (*HIC # 09.111*) and the Research Proposals Approval Committee (RPAC) of Eastern Health. This hemodialysis unit provides hemodialysis to 100-120 stable ambulatory adult patients, six days a week, in three daily shifts and is geographically suitable for collection of the data required for this evaluation. Since both practices (routine monthly ACT monitoring versus ACT monitoring as indicated) have been adopted by several dialysis units in North America, and since this evaluation was considered a quality improvement exercise, *we proposed not to request an individual patient consent.* We planned the evaluation as *a before-and-after design*. In the first four months (Phase I), we continued our current practice of monthly monitoring of ACTs while collecting data on bleeding and clotting events. In the subsequent four months (Phase II), we changed our practice to that of measuring ACTs for clinical indications only while collecting data on bleeding and clotting events when these occurred. *We informed all staff and patients of the change at the time.*

All patients in our hemodialysis unit on established doses of heparin during hemodialysis were enrolled in this study, unless they had contraindication to heparin. Patients not receiving heparin for any reason were excluded. For the first four months (Phase I), all

patients received monthly ACT and heparin dose was supposed to be adjusted by the Nephrologist covering our hemodialysis unit depending on ACT values and as per our current protocol (Appendix A & B). For the following four months (Phase II), no patients had monthly routine ACTs. ACTs were *only* done if clinically indicated. In the event of a clinical problem, heparin dose was only adjusted, by the Nephrologist covering the hemodialysis unit, depending on a stat or scheduled ACT.

The dialysis nurses were instructed as to what constitutes a bleeding or clotting episode that they should note and record in patient's record (*Please refer to primary and secondary endpoints' definition below*). Throughout the eight months of the evaluation, clotting and bleeding events were evaluated and recorded in the patients' written and electronic dialysis charts, by the hemodialysis nurses as a part of their routine intra- and post-hemodialysis evaluation. At the end of the evaluation, patients' results and data were reviewed, collected, and analyzed by Dr. Shamseddin.

Meanwhile, to ensure the completeness and accuracy of the data recording, ongoing education to the nursing staff was provided to correctly identify, collect, and record primary and secondary end points. Periodic checks were done by Dr. Shamseddin to secure identifying and recording of all events. Identifying and recording events as a part of routine intra- and post-hemodialysis evaluation of hemodialysis by the nurses, was the most dependable means available to capture all primary and secondary events especially

the ones occurring during or shortly after hemodialysis sessions prior to patients departing the hemodialysis unit.

There was no specific budget for this study. The cost of hemodialysis, heparin, and routine monthly ACTs were all part of our standard current practice. Recording the clinical bleeding and clotting events was also part of our standard practice. Data retrieval and analysis were completed by Drs. Shamseddin and Barrett.

At all times, patient confidentiality was respected and protected as per Human Investigations Committee's (HIC) rules and protocol. Patients' data was not stored with identifiers attached. Study code numbers were assigned.

**Study Population:**

All adult patients with end stage renal disease (ESRD) receiving heparin anticoagulation during their chronic hemodialysis at established heparin doses at the Waterford Hospital, in St. John's, Newfoundland and Labrador, in Canada were enrolled in this study. None of them had contraindication to heparin nor had expected kidney function recovery within six months of the time of enrollment. Patients not receiving heparin for any reason were excluded.

**Study protocol:**

During the first four months of the study (Phase I), heparin was administered as per our usual practice and doses were expected to be adjusted depending on the monthly routine ACT values by the Nephrologist covering our hemodialysis unit as per our protocols (Appendix A & B). During the second four months of the trial (Phase II), there was no ACT-guided heparin monitoring; unless clotting or bleeding occurred; and heparin was delivered at a fixed dose similar to the last bolus and maintenance doses delivered at the last HD session at the end of the first four months. If clotting or bleeding events occurred at any point during the second 4 months, heparin doses were expected to be adjusted by the Nephrologist covering the hemodialysis unit depending on a stat or a scheduled ACT value as per our protocols (Appendix A & B).

Patients acted as their own controls and we tried to minimize the confounding factors during the period of the study by using whenever possible the same dialysis prescription throughout. Furthermore, since a few patients did not finish the study, as they were transplanted, transferred to different centers, or died before the end of the study, those patients did not have the full study length of exposure (*exposure time)*. Consequently, those patients could affect the study event rates over time. So, to accommodate for the primary events occurring during a particular length of observation, divided by time of

exposure, **Poisson regression with offset variable analysis** was used to calculate event rates as events per unit time, allowing the observation window to vary for each time unit.

Prior to the entry in the study, the last available monthly work up results including complete blood count (CBC), ACT, serum electrolytes, creatinine, urea, urea reduction ratio (URR), calcium, albumin, phosphate and liver function tests were collected as a baseline. During the study routine monthly work up including the above tests were recorded as per our dialysis unit protocol. Baseline and regular coagulation profiles (PT and INR) were also collected for those patients receiving warfarin (Coumadin). Extra blood work up was ordered and followed up only as clinically indicated.

**Primary endpoints:**

1. *Dialyzer clotting*; defined as any of the following:

The scale was based on visual inspection of the dialyzer and blood lines during and at the end of each session. The severity of the clotting event was classified as:

1. Visible signs of clot or fibrin formation in the bottom of the dialyzer

2. Coagulated filter
3. Circuit change required due to clotting

2. *Bleeding*; defined as any of the following;

1. Overt bleeding documented by clinical examination within 4 hours from hemodialysis session
2. Overt bleeding documented by diagnostic investigations within 4 hours from hemodialysis session
3. Doubling or more in the fistula needle site homeostasis time in patients with AVF; not secondary to fistula-related issues (No stenosis or high pressure)
4. Unexplained fall in hemoglobin $\geq$ 20 g/L within a month
5. Requirement for blood (PRBCs) transfusion due to bleed

**Secondary endpoints:**

1. *Urea clearance*; measured by monthly urea reduction ratio (URR)

**Study Data**

As a part of a routine intra- and post-hemodialysis evaluation carried out at each hemodialysis session by our hemodialysis nurses, the study primary endpoints including clotting and bleeding events, were reported by our dialysis nurses in details, recorded, and stored in our unit and hospital computer (MEDitech) system. Patient's paper and computer charts including Emergency Room (ER) records were also reviewed by Dr. Shamseddin to document those events that might happen either in our dialysis unit or later during ER visits or hospital admissions during the period of our study (8 months) with special attention given to the association between the occurrence of the clotting or bleeding event and the hemodialysis session initiation. Secondary endpoints as well as other laboratory parameters were obtained and collected completely by Dr. Shamseddin, from our monthly routine blood work up recorded in our MEDitech computer system. Dialysis machine pressure alarms and values, which were automatically downloaded to the MEDitech system, as well as all other relevant patients' data were also reviewed and collected by Dr. Shamseddin.

Primary endpoints events (clotting and bleeding) were reported as dichotomous dependent variables during the first and the second phases of the study. Event was reported as occurred or did not occur (Occurred = Yes = 1, Did not occur = No = 0). Furthermore, events were categorized further depending on the severity of the event using

a predefined scoring scale (*Please refer to primary endpoints*), and were reported as polychotomous or dummy dependent variables, when options included more than two possibilities. Secondary endpoint parameters including urea reduction ratio and hemoglobin were reported as continuous variables. The date of the last follow up, since some patients were transplanted, transferred to other hemodialysis units, or died, were reported as date variables.

Other patients' data including demographic characteristics such as age, hemoglobin levels, and urea reduction ratio (URR) were reported as continuous variables while gender, etiology of end stage renal disease, co-morbidities, and the administration of anti-platelet drugs, anticoagulation drugs, and heparin were reported as dichotomous and polychotomous variables when options included more than two possibilities. Data related to whether heparin was used or not, whether the dose was changed post events or not, whether the dose was effective in reaching therapeutic target or not, were reported as dichotomous variables.

Data was saved encrypted in Microsoft® Excel® sheet and was stored without identifiers attached. Study code numbers were assigned and patient confidentiality was respected and protected as per Human Investigations Committee's (HIC) rules and protocol. A copy of above data was only available to Drs. Barrett and Shamseddin.

At the end of the study, data was analyzed by Dr. Shamseddin using IBM® SPSS Statistics version 20. Since patients acted as their own controls in the second phase and as primary endpoints were dichotomous variables, results were analyzed using two paired groups statistical tests including; paired t test, a McNemar test, logistic regression, and Poisson regression as appropriate, to compare the safety, clotting, and bleeding incidence rates between the monthly ACT-guided heparin (Phase I) and no routine ACT periods (Phase II). Poisson regression was used to compare the differences between the **counts** of clotting, bleeding, and the number of heparin dose changes between phase I and II. To compensate for any intrapersonal factors affecting the occurrence of any clotting or bleeding events, Logistic regression was used to compare between events whether they occurred or not, regardless the count of events.

Further analyses were used to compare between different types of clotting and bleeding events that occurred during phase I and II. Effective heparin dose changes achieving ACT target after clotting and bleeding events were also compared between phase I and II.

**Sample size estimation:**

On average over 100 patients each receive three hemodialysis sessions per week in our dialysis unit. Prior to this evaluation, we completed a retrospective review of a sample of records under the then current monthly ACT-guided heparin monitoring protocol to estimate the number of bleeding and clotting events we might expect. We found two clotting events in a 20-patient sample over a 6-month period; both events required dialyzer and circuit change (2 clotting events per 20 patients per 6 months). So, over a 3-month period, and in a 100-patient sample instead of 20 patients, we expected a total of 5 clotting events. Now, in the absence of data and in order to plan our study, we assumed that bleeding events would occur at the same rate as clotting events, although the assumption was unfounded. Consequently and in the absence of any intrapersonal risk factors for bleeding or clotting events; the total clotting and bleeding events in a 100-patient sample over a 3-month period would be 10 events or in other words 10% of patients might develop a clotting or bleeding event.

As the relevant risk of bleeding or clotting is linked in time to dialysis treatments, we could convert this expected event rate to 10 per 3600 dialysis sessions (100 patients * 36 dialysis sessions each in three months). We recognized that this event rate might be an underestimate, as staff was likely not routinely recording all relevant events in the charts in the past.

Since the purpose of this study was to ensure that our change in practice was not unsafe, we considered an increase in the overall bleeding and clotting event rate of 10/3600 dialyses to be too large to justify not routinely monitoring the ACT. Depending on above, a sample size of 3600 dialysis treatments or in other words 100 patients on chronic hemodialysis three times weekly followed over three months, would yield a 95% confidence interval width of 0.02-0.04% around such a difference in rates. This level of precision was judged sufficient for the proposed evaluation. Furthermore, and in order to achieve enough events during this evaluation, we extended the observation period to four months, before and after changing our current practice from the monthly monitoring of ACTs to that of measuring ACTs for clinical indications only.

# RESULTS

After obtaining the approval of the Human Investigations Committee and the Research Proposals Approval Committee of Eastern Health, 109 ambulatory adult patients with end stage renal disease (ESRD) receiving heparin anticoagulation during their chronic hemodialysis (HD) at established doses of heparin at the Waterford Hospital were enrolled in our study on August 01, 2009.

## Descriptive Analysis:

Table 1 shows the results of the demographics and baseline characteristics of all patients. The average age of enrolled patients was 61.4 ± 15.9 years and 59% of participants were males (Table 1). Diabetes, hypertension, and glomerulonephritis were the most common etiologies of ESRD similar to other hemodialysis populations in North America (Table 1). Hypertension and other comorbidities such as Diabetes, coronary artery disease, and peripheral vascular disease were associated with ESRD in 82%, 44%, 40%, and 31% of patients, respectively (Table 1). Only one third of patients had arteriovenous fistula (AVF) while the other 70% had hemodialysis line (Table 1). Less than 50% of participants were receiving chronic Aspirin (43%) while very few were on clopidogrel (Plavix) and warfarin (Coumadin), 14% and 6%, respectively (Table 1).

| Table 1: Patient's Demographic Characteristics | |
|---|---|
| ***N*** **= 109** | Mean ± SD |
| **Age (Year)** | 61.40 ± 15.99 |
| **Gender – Male (%)** | 64 (59%) |
| **Etiology of ESRD (%)** | |
| **Unknown** | 7 (6.4%) |
| **DM** | 33 (30.2%) |
| **HTN** | 12 (11%) |
| **GN** | 18 (16.5%) |
| **PCKD** | 7 (6.4%) |
| **Vasculitis** | 3 (2.8%) |
| **Renovascular** | 14 (12.8%) |
| **RCC** | 3 (2.8%) |
| **Other** | 12 (11%) |
| **Comorbidities** | |
| **DM** | 44% |
| **HTN** | 82% |
| **Cancer** | 22% |
| **CAD** | 40% |
| **PVD** | 31% |
| **HD Access – CVC** | 76 (70%) |
| **HD Access – AVF** | 33 (30%) |
| **ASA** | 43% |
| **Plavix** | 14% |
| **Coumadin** | 6% |

Table 2 shows the reasons for loss to follow up and the number of follow up months of all patients who did not finish the study. Four patients received kidney transplantation while the other six patients died prior to the end of the study. The mean follow up during phase I was 3.82 ± 0.76 months compared with 3.7 ± 1.0 during phase II.

**Table 2: Loss of Follow Up and Mean Follow Up**

| Patient | Loss of Follow up Etiology | Number of Follow up Months |
|---|---|---|
| 4 | Kidney Transplantation | 2 |
| 10 | Kidney Transplantation | 4 |
| 49 | Death | 6 |
| 58 | Death | 5 |
| 62 | Death | 4 |
| 64 | Death | 2 |
| 80 | Death | 2 |
| 84 | Death | 5 |
| 91 | Kidney Transplantation | 7 |
| 106 | Kidney Transplantation | 3 |
| **Mean Follow Up of All Patients - Months (mean±SD)** | | |
| **Phase I** | | 3.82 ± 0.76 |
| **Phase II** | | 3.7 ± 1.0 |

During the first four months of our study (*Phase I*; August - November 2009), monthly routine ACTs were done as a part of our current practice and heparin doses were expected

to be adjusted by the Nephrologist covering our hemodialysis unit to achieve an ACT target of 150-200, as per our protocol (Appendix A & B). ACTs were expected to be rechecked after each heparin dose change to achieve above ACT target as per our protocol (Appendix A & B).

During phase I, more than 50% of routine ACTs were below target (ACT < 150), however, heparin doses were changed only in < 10% of cases in general (Table 3, Figure 1).

**Table 3: Routine Monthly ACT and Heparin Dose Changes**

| Count (%) | N | Routine ACT <150 | Heparin Changed | Post Heparin Change ACT | | |
|---|---|---|---|---|---|---|
| | | | | > 150 | <150 | Unknown |
| **Month 1** | 109 | 63 (57.8%) | 35 (55.56%) | 18 (51.43%) | 7 (20%) | 8 (22.9%) |
| **Month 2** | 108 | 63 (58.33%) | 2 (3.17%) | 0 | 0 | 0 |
| **Month 3** | 105 | 54 (51.43%) | 6 (11.11%) | 3 (50%) | 2 (33.37%) | 1 (16.67%) |
| **Month 4** | 104 | 51 (49.04%) | 4 (7.84%) | 3 (75%) | 1 (25%) | 0 |

Furthermore, in cases where ACTs were low and heparin doses were changed, an effective ACT target > 150 was only attained in 50% of cases (Table 3, Figure 1). During

the first month of the study, more than half of the ACT values (57.8%) were below a target of ACT > 150 (Table 3). Heparin doses during that specific month were adjusted in 55.56% of cases, however, dose changes were effective, achieving a target ACT of > 150, only in 51.43% of cases (Table 3), while 20% of cases failed to achieve ACT target > 150, or ACTs were never rechecked after changing heparin doses (23% of cases).

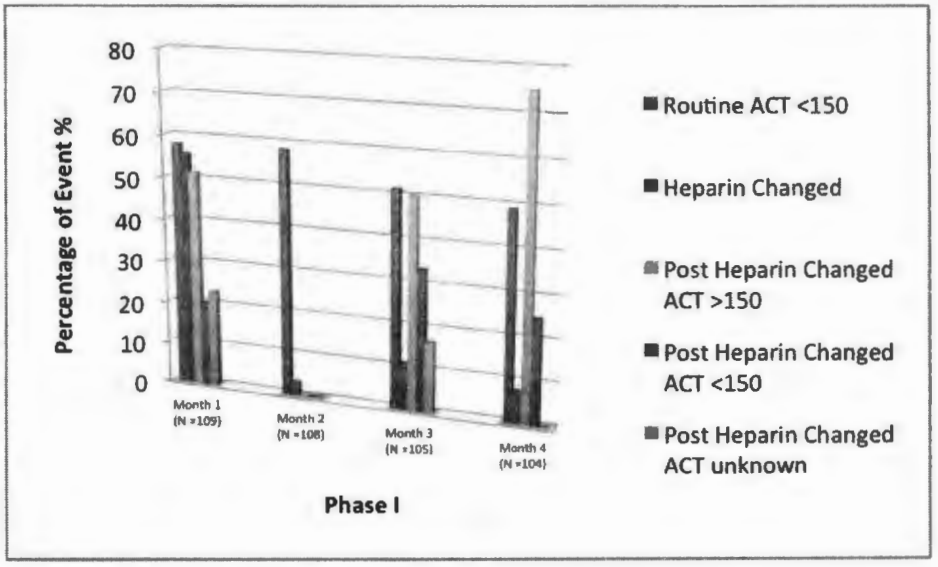


**Figure 1: Subtherapeutic Routine ACT and Heparin Dose Changes during Phase I**

The above findings showed that routine monthly ACT-directed heparin dose adjustment and monitoring in chronic HD patients was not very consistent. However, as practiced locally, this could be due to the Nephrologist's response to the ACTs.

***Clotting event*** was clearly defined and classified based on visual inspection of the dialyzer and hemodialysis circuit lines, to be done routinely by the HD nurse during and at the end of each HD session. The severity of each clotting event was evaluated by the HD nurse and scaled as defined above as 1, 2, or 3 (*Please see primary endpoints*), then was recorded regularly by our HD nurses in the patient electronic chart using our hospital computer (MEDitech) system at the end of each HD session as a part of a routine assessment to be done by our HD nurses during and at the end our each HD session. The above protocol secured detecting, capturing, and saving all clotting events, including minor clotting events, into our MEDitech system without missing any clotting-related data.

There was a total of 87 clotting events during phase I compared with only 58 clotting events during phase II.

**Table 4: Clotting Events During Phase I & II**

| Clotting Type | 1 | 2 | 3 | Total Events |
|---|---|---|---|---|
| **Phase I** | 62 | 23 | 2 | 87 |
| **Phase II** | 41 | 16 | 1 | 58 |

Those events were further categorized depending on the clotting type (Table 4, Figure 2). All clotting types occurred more often during phase I compared with phase II (Table 4).

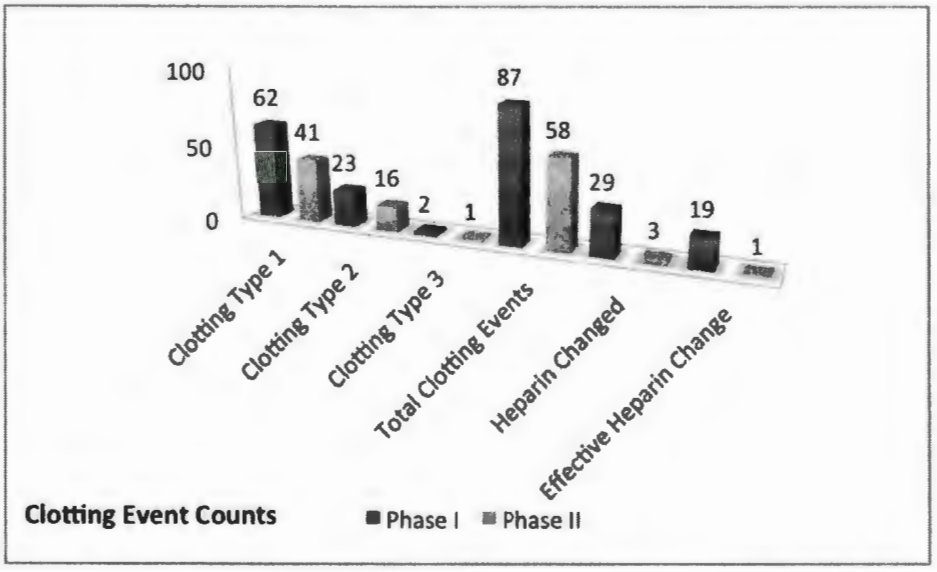


**Figure 2: Clotting Event Counts**

The heparin dose was changed following only one third (29/87) of all clotting events during phase I. Furthermore, heparin dose change was effective in achieving an ACT target of > 150 only in 19 events out of these 29 cases (Table 5).

**Table 5: Total Clotting Events and Heparin Dose Changes**

| | Total | Heparin changed (%) | Effective Change (ACT > 150) |
|---|---|---|---|
| **Phase I** | 87 | 29 (33.3) | 19 (65.5) |
| **Phase II** | 58 | 3 (5) | 1 |

Alternatively, heparin dose was changed following only 5% of all clotting events that occurred during phase II and heparin dose change was effective, achieving ACT target of > 150 after changing heparin dose, in only 1 of those 3 cases (Table 5).

Since clotting events type 2 and 3, compared with type 1, were more clinically important as serious clinical complications of clotting, we further categorized clotting events during phase I and II, to either type 1 events or type 2 and/or 3 events. Subsequently, we compared events occurrence, heparin dose changes after clotting occurrence, and whether heparin dose change was effective in achieving an ACT target > 150 post heparin dose change (Table 6).

The data show that the heparin dose was changed more often and the dose change was more effective during phase I compared with phase II (Table 6). Heparin dose was changed after clotting events in almost one third of all type 1 clotting events and in 40% of all type 2 and 3 clotting events during phase I (Table 6). Furthermore, heparin dose change was more effective, achieving an ACT target > 150 post heparin dose change, during phase I compared with phase II, especially after clotting events type 2 and 3 (Table 6).

| Table 6: Clotting Event Types and Heparin Dose Changes | | | |
|---|---|---|---|
| **Clotting Events during Phase I** | | | |
| | Total | Heparin changed (%) | Effective Change (%) |
| **Type 1** | 62 | 19 (30.6) | 12 (63.2) |
| **Type 2 or 3** | 25 | 10 (40) | 7 (70) |
| **Clotting Events during Phase II** | | | |
| | Total | Heparin changed (%) | Effective Change (%) |
| **Type 1** | 41 | 1 (2.4%) | 0 |
| **Type 2 or 3** | 17 | 2 (12%) | 1 |

On the other hand, ***bleeding event*** was clearly defined and scaled as defined above as 1, 2, 3, 4, or 5 (*Please see primary endpoints*). However, due to the nature and definition of bleeding events, which could occur at any point within the first 4 hours from HD session initiation up until a month post HD session, detecting and capturing all bleeding events was much harder compared with clotting events which were noted and recorded routinely as mentioned above in our hospital computer (MEDitech) system. Patient's electronic and paper records were reviewed by Dr. Shamseddin to identify any bleeding events prior to saving those events encrypted in a Microsoft® Excel® sheet. Consequently, although missing bleeding-related data could not be completely averted, we believe that little data were missed. However, if further studies were required in the future, the definition of

bleeding events and the methods of capturing and recording bleeding events has to be respecified to avoid missing any data.

There was a total of 28 bleeding events during phase I compared with 32 bleeding events during phase II (Table 7). Those bleeding events were further categorized depending on a pre-defined scoring system into 1 to 5 bleeding types (Table 7).

**Table 7: Bleeding Events During Phase I & II**

| Bleeding Type | 1 | 2 | 3 | 4 | 5 | Total |
|---|---|---|---|---|---|---|
| **Phase I** | 2 | 0 | 14 | 6 | 6 | 28 |
| **Phase II** | 0 | 0 | 20 | 9 | 3 | 32 |

Bleeding events type 1 (*Defined as overt bleeding documented by clinical examination within 4 hours from hemodialysis session*) were identified only in two cases during phase I (Table 7). While type 2 bleeding events (*Defined as overt bleeding documented by diagnostic investigations within 4 hours from hemodialysis session*) were not identified in any cases in either phase (Table 7). Bleeding events type 3, 4, and 5 (*Please refer to primary endpoints*), occurred more often in both phases at different rates (Table 7).

Heparin doses were not frequently changed after bleeding events, as you might have been expected (Table 8). Out of all bleeding events during phase I, heparin doses were changed only after 4 bleeding events. However, dose changes were effective, achieving a target ACT of 150 to 200 post heparin dose change, in all cases (Table 8). Moreover, heparin dose was changed only after three bleeding events occurred during phase II (Table 8). However, since ACTs were not remeasured after heparin dose changes following those bleeding events in phase II, heparin dose changes could not be evaluated as to whether they were effective, achieving a target ACT of 150 to 200, or not (Table 8).

**Table 8: Bleeding Events and Heparin Dose Changes**

| | All Bleeding Events | Heparin Changed (%) | Effective Change ACT > 150 (%) |
|---|---|---|---|
| **Phase I** | 28 | 4 (14%) | 4 (100%) |
| **Phase II** | 32 | 3 (9%) | No Available ACT |

**Comparative Analysis:**

**Clotting Events:**

To identify whether the difference between the **counts** of ***clotting events*** occurring during phase I and II was statistically significant, and since clotting event counts have the **Poisson distribution** (36), we analyzed our study data using **Poisson Regression** (37, 38). ***Poisson distribution*** is a discrete probability distribution that expresses the probability of a given number of events occurring in a fixed interval of time, if these events occur with a known average rate and independently of the time since the last event (36). ***Poisson Regression*** is a form of regression analysis used for independent count data model (37, 38), which assumes that:

1. The dependent variable (*Y = clotting event)* has a Poisson distribution
2. The dependent variable is a count of independent events over time at risk
3. The logarithm of its expected value can be modeled by a linear combination of unknown parameters

Furthermore, the Poisson regression model rate ($\lambda$ = count of event/number of times event could have occurred), estimates the risk of the event occurring in a specific group of people during a specified period of time, known as ***exposure time*** (38). However, *when*

*the study duration is long enough and not all subjects are observed for the same length of time* (such as if patients were lost to follow up, died, or transferred out of the study); the risk of the event can be presented in Poisson regression as ***incident rate ratio (IRR)*** for the reference group (38, 39). Those incident rate ratios (IRRs) can be reported by the IBM® SPSS Statistics version 20 outputs (38, 39). IRRs are equal to the coefficients above exponentiated from the IBM® SPSS Statistics version 20 outputs (38, 39).

Using this approach, the incident rate for all clotting events that occurred during phase I was significantly higher (1.5 times) than that during phase II (Table 9, IRR 1.5; 95% CI: 1.08 - 1.09, $P = 0.017$).

**Table 9: Total Clotting Events per Phase (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -.631 | .1313 | -.888 | -.374 | 23.086 | 1 | .000 | .532 | .411 | .688 |
| [Phase=1] | .405 | .1695 | .073 | .738 | 5.721 | 1 | .017 | 1.500 | 1.076 | 2.091 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_Clotting_Event
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Furthermore, when we compared the counts of different types of clotting events that occurred during phase I and phase II, we found that all types of clotting events occurred surprisingly more often during phase I compared with phase II (Table 10, 11, 12); type 1

(1.5 X), type 2 (1.44 X), and type 3 (2 X). However, the incident rate ratio of clotting events type 1 was the only statistically significant rate ($P = 0.04$), while the incident rate ratio of clotting events type 2 ($P = 0.27$), and 3 ($P = 0.57$) were not statistically significant (Table 10, 11, 12).

**Table 10: Total Clotting Type 1 per Phase (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -.978 | .1562 | -1.284 | -.672 | 39.198 | 1 | .000 | .376 | .277 | .511 |
| [Phase=1] | .414 | .2013 | .019 | .808 | 4.221 | 1 | .040 | 1.512 | 1.019 | 2.244 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_Clotting_Type_One
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 11: Total Clotting Type 2 per Phase (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -1.919 | .2500 | -2.409 | -1.429 | 58.906 | 1 | .000 | .147 | .090 | .240 |
| [Phase=1] | .363 | .3255 | -.275 | 1.001 | 1.243 | 1 | .265 | 1.438 | .759 | 2.721 |
| [Phase=2] | 0[a] | . | . | | | . | | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_clotting_Type_Two
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 12: Total Clotting Type 3 per Phase (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -4.691 | 1.0000 | -6.651 | -2.731 | 22.009 | 1 | .000 | .009 | .001 | .065 |
| [Phase=1] | .693 | 1.2247 | -1.707 | 3.094 | .320 | 1 | .571 | 2.000 | .181 | 22.056 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_Clotting_Type_Three
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

In our study, a few patients did not finish the study, as they either had a kidney transplant (x 4 patients) or they died (x 6 patients) before the end of the study (Table 2).

Since the above 10 patients did not have the full study length of exposure (*exposure time*), those patients may consequently model clotting event rates in this study over time and falsely underestimate or overestimate results (40). So, to accommodate for the clotting events occurring during any particular length of observation during the study, divided by the time of exposure, **Poisson regression with offset variable analysis** was used to calculate clotting event rates as events per unit time, allowing the observation window to vary for each time unit (40).

| Table 2: Loss of Follow Up and Mean Follow Up | | |
|---|---|---|
| **Patient** | Loss of Follow up Etiology | Number of Follow up Months |
| **4** | Kidney Transplantation | 2 |
| **10** | Kidney Transplantation | 4 |
| **49** | Death | 6 |
| **58** | Death | 5 |
| **62** | Death | 4 |
| **64** | Death | 2 |
| **80** | Death | 2 |
| **84** | Death | 5 |
| **91** | Kidney Transplantation | 7 |
| **106** | Kidney Transplantation | 3 |
| **Mean Follow Up of All Patients - Months (mean±SD)** | | |
| **Phase I** | | 3.82 ± 0.76 |
| **Phase II** | | 3.7 ± 1.0 |

Using *offset variable analysis*, the incident rate ratio for all clotting events during phase I remained unexpectedly higher (1.41 times) than that during phase II and was statistically significant (Table 13, IRR 1.41; 95% CI: 1.01-1.97, $P = 0.041$).

**Table 13: Total Clotting Events per Phase (Poisson Regression - offset Variable)**

Parameter Estimates

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -4.542 | .1313 | -4.799 | -4.284 | 1196.447 | 1 | .000 | .011 | .008 | .014 |
| [Phase=1] | .346 | .1695 | .014 | .679 | 4.177 | 1 | .041 | 1.414 | 1.014 | 1.971 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total Clotting Event
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

All types of clotting events occurred more often during phase I compared with phase II (Table 14,15,16), type 1 (1.43 X), type 2 (1.36 X), and type 3 (1.89 X). However, none of the incident rates of clotting event types were statistically significant (Table 14, 15, 16), type 1 ($P = 0.08$), type 2 ($P = 0.35$), and type 3 ($P = 0.61$).

**Table 14: Total Clotting Events Type 1 per Phase (Poisson Regression - Offset Variable)**

Parameter Estimates

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -4.889 | .1562 | -5.195 | -4.583 | 979.883 | 1 | .000 | .008 | .006 | .010 |
| [Phase=1] | .355 | .2013 | -.040 | .749 | 3.102 | 1 | .078 | 1.426 | .961 | 2.115 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_Clotting_Type_One
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 15: Total Clotting Events Type 2 per Phase (Poisson Regression - Offset Variable)**

Parameter Estimates

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -5.830 | .2500 | -6.320 | -5.340 | 543.767 | 1 | .000 | .003 | .002 | .005 |
| [Phase=1] | .304 | .3255 | -.334 | .942 | .871 | 1 | .351 | 1.355 | .716 | 2.565 |
| [Phase=2] | 0[a] | . | . | . | | | . | 1 | . | |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_clotting_Type_Two
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 16: Total Clotting Events Type 3 per Phase (Poisson Regression - Offset Variable)**

Parameter Estimates

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | 8.602 | 1.0000 | -10.562 | -6.642 | 73.999 | 1 | .000 | .000 | .000 | .001 |
| [Phase=1] | .634 | 1.2247 | -1.766 | 3.035 | .268 | 1 | .605 | 1.885 | .171 | 20.792 |
| [Phase=2] | 0[a] | . | . | . | | | . | 1 | . | |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total Clotting Type Three
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

While clotting events did not occur in some patients, clotting occurred more often in specific patients than others due to theoretical intrapersonal diathesis. However, the risk of clotting in those patients with higher clotting event counts, was not affecting outcomes over a short period of time, since events in those patients occurred at different intervals. Sometime, two events occurred in a row, then no event occurred for a variable length of time, followed by another event, for example.

In the setting of above findings and since the occurrence of clotting event is a dependent *categorical* variable (Clotting occurred; Yes = 1 or No = 0), to evaluate intrapersonal effects on clotting events, we compare the risk of any clotting occurrence versus not occurring between phase I and II, using binary Logistic regression. ***Binary Logistic Regression*** is a type of regression analysis used for predicting the outcome of a categorical dependent variable based on one or more predictor variables. It measures the relationship between a categorical dependent variable and usually a continuous or categorical independent variable (or several), by converting the dependent variable to probability scores and providing the odds ratio (Exp (B)) for each of the dependent variables (41,42).

An odds ratio (OR) measures the association between an exposure and an outcome and represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome happening in the absence of the same exposure (42,43). Odds ratios compare the relative odds of the occurrence of the outcome of interest (*e.g. clotting or bleeding events*), given exposure to the variable of interest (*e.g. exposure to monitored heparin on hemodialysis versus exposure to unmonitored heparin on hemodialysis*). The odds ratio (OR) can also determine whether a particular exposure (*e.g. exposure to monitored heparin on hemodialysis versus exposure to unmonitored heparin on hemodialysis*), is a risk factor for a particular outcome (*e.g. clotting or bleeding events*), and compares the implication of various risk factors for that outcome (43).

| | |
|---|---|
| OR = 1 | Exposure does not affect odds of outcome |
| OR > 1 | Exposure associated with higher odds of outcome |
| OR < 1 | Exposure associated with lower odds of outcome |

When a logistic regression is calculated, the regression coefficient (B) is the estimated increase in the log odds of the *outcome per unit increase* in the value of the *exposure* (43). In other words, the exponential function of the regression coefficient [Exp (B)] is the odds ratio associated with a one-unit increase in the exposure (42,43). The 95% confidence interval (CI) estimates the precision of the OR. A wide CI indicates a low level of precision of the OR, whereas a narrow CI indicates a higher precision of the OR (43). The 95% CI is often used as an alternate for the presence of statistical significance if it does not overlap the null (e.g. OR = 1) value (43). Otherwise, it would be unsuitable to explain an OR with 95% CI that crosses the null value as indicating evidence for lack of association between the exposure and outcome (43).

The Odds Ratio (OR) of any clotting event phase I was significantly higher (OR = 1.87) compared with phase II (Table 17, OR = Exp (B) 1.87; 95% CI: 1.03-3.39, $P = 0.04$).

**Table 17: Any Clotting per Patient per Phase (Binary Logistic Regression)**

Parameter Estimates

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -1.212 | .2278 | -1.658 | -.765 | 28.298 | 1 | .000 | .298 | .190 | .465 |
| [Phase=1] | .627 | .3030 | .033 | 1.221 | 4.281 | 1 | .039 | 1.872 | 1.034 | 3.390 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Any_Clotting_per_Patient_per-Phase
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Given on the above findings and since the majority of patients finished the study, we concluded that both the incident rate ratio and the Odds ratio of any clotting event in phase I was significantly higher than those in phase II. These findings were surprisingly unexpected, as prior to this study, we expected more events to occur in phase II since heparin doses were not monitored and adjusted appropriately during this phase compared with phase I. To verify whether the higher incident rate and risk of clotting events observed during phase I was due to a misplaced comfort on the part of the Nephrologists that the heparin dose was routinely monitored as well as the less than expected response of the Nephrologists to change heparin dose and to follow up on ACT results to adjust heparin doses appropriately, we compared whether heparin dose was changed more often in phase I versus phase II, using Poisson regression without and with offset variable analysis (*since 10 patients left the study before the end of the study as mentioned above*).

Heparin dose was changed following 29 clotting events out of 87 events that occurred in phase I compared to 3/58 events in phase II (Table 5).

| Table 5: Total Clotting Events and Heparin Dose Changes | | | |
|---|---|---|---|
| | Total | Heparin changed (%) | Effective Change (ACT > 150) |
| **Phase I** | 87 | 29 (33.3) | 19 (65.5) |
| **Phase II** | 58 | 3 (5) | 1 |

As expected, heparin doses were changed significantly more often (9 X) when clotting occurred in phase I compared with phase II (Table 18, IRR 9.67; 95% CI: 2.95-31.73, $P$ = 0.000), even when we evaluated our data using offset variable analysis since 10 patients left the study before the end of the study (Table 19, IRR 9.11; 95% CI: 2.78-29.92, $P$ = 0.000).

**Table 18: Incident Rate Ratio of Heparin Dose Change Post Clotting Events (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -3.593 | .5774 | -4.724 | -2.461 | 38.723 | 1 | .000 | .028 | .009 | .085 |
| [Phase=1] | 2.269 | .6065 | 1.080 | 3.457 | 13.993 | 1 | .000 | 9.667 | 2.945 | 31.733 |
| [Phase=2] | 0[a] | | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: totalclottingonheparin_heparinChanged
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 19: Incident Rate Ratio of Heparin Dose Change Post Clotting Events (Poisson Regression - Offset Variable)**

Parameter Estimates

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -7.504 | .5774 | -8.635 | -6.372 | 168.916 | 1 | .000 | .001 | .000 | .002 |
| [Phase=1] | 2.210 | .6065 | 1.021 | 3.398 | 13.275 | 1 | .000 | 9.113 | 2.776 | 29.915 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: totalclottingonheparin_heparinChanged
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Furthermore, to compare whether heparin dose change was more effective (*Defined as ACT value post heparin dose change achieved a target ACT > 150*) in phase I versus phase II, we analyzed our data using Poisson regression without and with offset variable analysis. Heparin dose change was effective in 19 clotting events out of 29 events where heparin dose was changed in phase I compared with 1/3 cases in phase II (Table 5). Heparin dose change was significantly more effective when heparin changed in phase I compared with phase II (Table 20, IRR 207.1; 95% CI: 27.73-1547.02, P =0.000), even with offset variable analysis (Table 21, IRR 189.45; 95% CI: 25.36-1415.2, P =0.000).

**Table 20: Incident Rate Ratio of Effective Heparin Dose Change Post Clotting Events (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -4.691 | 1.0000 | -6.651 | -2.731 | 22.009 | 1 | .000 | .009 | .001 | .065 |
| [Phase=1] | 5.333 | 1.0260 | 3.322 | 7.344 | 27.021 | 1 | .000 | 207.100 | 27.725 | 1547.015 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: totalclottingonheparin_heparinChanged_Effectivechange
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Table 21: Incident Rate Ratio of Effective Heparin Dose Change Post Clotting Events (Poisson Regression - Offset Variable)

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -8.602 | 1.0000 | -10.562 | -6.642 | 73.999 | 1 | .000 | .000 | .000 | .001 |
| [Phase=1] | 5.244 | 1.0260 | 3.233 | 7.255 | 26.126 | 1 | .000 | 189.454 | 25.362 | 1415.202 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: totalclottingonheparin_heparinChanged_EFFECTIVEchange
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

To extend above findings into different types of clotting events, we repeated our analysis combining clotting events type 1 separately from type 2 and/or 3 events and we compared those findings between phase I and II (Table 6). There was 19 clotting events type 1 out of 62 events where heparin was changed in phase I and change was effective in 12/19 events. While in phase II, heparin dose was changed only in 1 event out of 41 clotting events type 1 and change was not effective (Table 6). On the other hand, there were 10

clotting events type 2 or 3 out of 25 events where heparin was changed in phase I and change was effective in 7/10 events. In phase II, heparin dose was changed only in 2 events out of 17 clotting events type 2 or 3 and change was effective only in 1/2 events (Table 6).

Heparin dose was changed significantly more often when clotting events type 1 occurred in phase I compared with phase II, $P = 0.04$ (Table 22) and $P = 0.005$ (Table 23).

**Table 22: Incident Rate Ratio of Heparin Dose Change Post Clotting Events Type 1 (Poisson Regression)**

**Parameter Estimates**

| | | | 95% Wald Confidence Interval | | Hypothesis Test | | | | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | B | Std. Error | Lower | Upper | Wald Chi-Square | df | Sig. | Exp(B) | Lower | Upper |
| (Intercept) | -4.691 | 1.0000 | -6.651 | 2.731 | 22.009 | 1 | .000 | .009 | .001 | .065 |
| [Phase=1] | 2.944 | 1.0260 | .934 | 4.955 | 8.236 | 1 | .004 | 19.000 | 2.544 | 141.928 |
| [Phase=2] | 0[a] | | | | | | | 1 | | |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: totalclottingonheparin_type#1_heparinChanged
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Table 23: Incident Rate Ratio of Heparin Dose Change Post Clotting Events Type 1 (Poisson Regression - Offset Variable)

**Parameter Estimates**

| | | | 95% Wald Confidence Interval | | Hypothesis Test | | | | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Parameter | B | Std. Error | Lower | Upper | Wald Chi-Square | df | Sig. | Exp(B) | Lower | Upper |
| (Intercept) | -8.602 | 1.0000 | -10.562 | -6.642 | 73.999 | 1 | .000 | .000 | .000 | .001 |
| [Phase=1] | 2.885 | 1.0260 | .875 | 4.896 | 7.909 | 1 | .005 | 17.911 | 2.398 | 133.795 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: totalclottingonheparin_type#1_heparinChanged
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

The dose change was also significantly more effective when heparin changed in phase I compared with phase II, $P = 0.000$ (Table 24, 25). However, there were not enough clotting events during phase II where heparin was changed and none where the change was effective (Table 6), which could maximize the difference between phase II and I.

**Table 24: Incident Rate Ratio of effective Heparin Dose Change Post Clotting Events Type 1 (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -28.335 | .2887 | -28.900 | -27.769 | 9634.264 | 1 | .000 | 4.948E-013 | 2.810E-013 | 8.712E-013 |
| [Phase=1] | 28.740[a] | . | . | . | . | . | . | 3.032E+12 | .000 | .000 |
| [Phase=2] | 0[b] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[c] | | | | | | | | | |

Dependent Variable: totalclottingonheparin_type#1_heparinchange_EFFECTIVE
Model: (Intercept), Phase

a. Hessian matrix singularity is caused by this parameter. The parameter estimate at the last iteration is displayed.

b. Set to zero because this parameter is redundant.

c. Fixed at the displayed value.

**Table 25: Incident Rate Ratio of effective Heparin Dose Change Post Clotting Events Type 1 (Poisson Regression - Offset Variable)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -31.335 | .2887 | -31.901 | -30.769 | 11782.683 | 1 | .000 | 000 | .000 | .000 |
| [Phase=1] | 27.741[a] | . | . | . | . | . | . | 1.116E+12 | .000 | .000 |
| [Phase=2] | 0[b] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[c] | | | | | | | | | |

Dependent Variable: totalclottingonheparin_type#1_heparinchange_EFFECTIVE
Model: (Intercept), Phase, offset = Months_of_FU

a. Hessian matrix singularity is caused by this parameter. The parameter estimate at the last iteration is displayed.

b. Set to zero because this parameter is redundant.

c. Fixed at the displayed value.

Moreover, heparin dose was changed significantly more often if clotting events type 2 or 3 occurred in phase I compared with phase II, $P = 0.04$ (Table 26, 27), but the dose change was not significantly more effective when heparin changed in phase I compared with phase II, $P = 0.43$ (Table 28, 29).

**Table 26: Incident Rate Ratio of Heparin Dose Change Post Clotting Events Type 2 or 3 (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | 3.998 | .7071 | 5.384 | 2.612 | 31.971 | 1 | .000 | .018 | .005 | .073 |
| [Phase=1] | 1.609 | .7746 | .091 | 3.128 | 4.317 | 1 | .038 | 5.000 | 1.096 | 22.820 |
| [Phase=2] | 0[a] | | | | | | | 1 | | |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: totalclottinqonheparin_type#2or3_heparinchanged
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 27: Incident Rate Ratio of Heparin Dose Change Post Clotting Events Type 2 or 3 (Poisson Regression - Offset Variable)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | 7.909 | .7071 | 9.295 | 6.523 | 125.109 | 1 | .000 | .000 | .000 | .001 |
| [Phase=1] | 1.550 | .7746 | .032 | 3.069 | 4.006 | 1 | .045 | 4.713 | 1.033 | 21.512 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: totalclottinqonheparin_type#2or3_heparinchanged
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 28: Incident Rate Ratio of Effective Heparin Dose Change Post Clotting Events Type 2 or 3 (Poisson Regression)**

Parameter Estimates

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -.693 | 1.0000 | -2.653 | 1.267 | .480 | 1 | .488 | .500 | .070 | 3.550 |
| [Phase=1] | .847 | 1.0690 | -1.248 | 2.943 | .628 | 1 | .428 | 2.333 | .287 | 18.965 |
| [Phase=2] | 0[a] | | . | . | | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: totalclottingonheparin_type#2or3_heparinchanged_EFFECTIVE
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 29: Incident Rate Ratio of Effective Heparin Dose Change Post Clotting Events Type 2 or 3 (Poisson Regression – Offset Variable)**

Parameter Estimates

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -4.693 | 1.0000 | -6.653 | -2.733 | 22.026 | 1 | .000 | .009 | .001 | .065 |
| [Phase=1] | .847 | 1.0690 | -1.248 | 2.943 | .628 | 1 | .428 | 2.333 | .287 | 18.965 |
| [Phase=2] | 0[a] | | . | . | | . | . | 1 | . | |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: totalclottingonheparin_type#2or3_heparinchanged_EFFECTIVE
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

To measure the association between clotting events and heparin dose change during phase I and II as well as the association between heparin dose change and effective heparin change, we ran logistic regression analysis using any clotting event occurrence, regardless of the type or count of events, during phase I and II. The Odds ratio of changing heparin during phase I compared with phase II was OR = 6.1; 95% CI: 1.72-21.52, $P = 0.005$ (Table 30), and the OR of effective heparin dose change in phase I compared with phase II was significantly higher (Table 31, OR 180; $P = 0.000$).

**Table 30: Odds Ratio of Heparin Dose Change if Any Clotting Occurred (Binary Logistic Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig | | Lower | Upper |
| (Intercept) | -3.565 | .5855 | -4.712 | -2.417 | 37.075 | 1 | .000 | .028 | .009 | .089 |
| [Phase=1] | 1.805 | .6450 | .541 | 3.069 | 7.830 | 1 | .005 | 6.079 | 1.717 | 21.520 |
| [Phase=2] | 0[a] | . | . | . | | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: ifanyclottingonheparin_heparinchanged
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 31: Odds Ratio of Effective Heparin Dose Change If Any Clotting Occurred (Binary Logistic Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig | | Lower | Upper |
| (Intercept) | -4.682 | 1.0046 | -6.651 | -2.713 | 21.721 | 1 | .000 | .009 | .001 | .066 |
| [Phase=1] | 5.193 | 1.1296 | 2.979 | 7.407 | 21.135 | 1 | .000 | 180.000 | 19.669 | 1647.264 |
| [Phase=2] | 0[a] | . | . | . | | . | | 1 | | |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: ifanyclottingonheparin_heparinchanged EFFECTIVE change
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Furthermore, and as clotting events type 2 and 3 are more clinically considerable and important from a morbidity point of view, we repeated above analysis using only any clotting events type 2 or 3 during phase I versus phase II. The Odds ratio of changing heparin dose during phase I compared with phase II for any clotting events type 2 or 3 was still higher but not statistically significant OR = 3.12; 95% CI: 0.62-15.8, $P = 0.17$ (Table 32), and the OR of effective heparin dose change in phase I compared with phase II for any clotting events type 2 or 3 was also higher but not statistically significant (Table 33, OR 2; 95% CI: 0.08-51.6, $P = 0.68$). However, since the $P$ values were insignificant

and the 95% CIs were wide, we might have lacked power to pick up on a clinically meaningful difference.

**Table 32: Odds Ratio of Heparin Dose Change If Any Clotting Type 2 or 3 Occurred (Binary Logistic Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | 3.980 | .7137 | 5.378 | 2.581 | 31.095 | 1 | .000 | .019 | .005 | .076 |
| [Phase=1] | 1.137 | .8281 | -.486 | 2.760 | 1.884 | 1 | .170 | 3.117 | .615 | 15.795 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: ifanyclottingtype2or3_onheparin_heparinchanged
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Table 33: Odds Ratio of Effective Heparin Dose Change If Any Clotting Type 2 or 3 Occurred (Binary Logistic Regression)

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | 1.110E-016 | 1.4142 | -2.772 | 2.772 | .000 | 1 | 1.000 | 1.000 | .063 | 15.988 |
| [Phase=1] | .693 | 1.6583 | -2.557 | 3.943 | .175 | 1 | .676 | 2.000 | .078 | 51.593 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: ifanyclottingtype2or3_onheparin_heparinchanged_EFFECTIVE
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

***In conclusion***, changing heparin dose after any clotting events during phase I was significantly more likely to happen compared with phase II, but change was not significantly successful especially after more serious clotting events such as type 2 and 3,

even in phase I when initially we thought that routine monthly ACT monitoring would reduce the occurrence of clotting events and guarantee effective heparin dose change, achieving ACT target above 150, when change occurred.

In order to predict the likelihood of any clotting events occurrence during phase I, we built a multivariable Logistic regression model using any clotting event occurrence as a dichotomous dependent variable while using age, gender (Male =1), HD line (CVC =1), peripheral vascular disease (PVD coexistence =1), cancer (coexistence =1), Aspirin (intake = 1), Plavix (intake = 1), and Coumadin (intake = 1) as covariate independent variables (Table 34).

**Table 34: Multivariate Analysis – Odds Ratio of Any Clotting per Phase I (Logistic Regression Model)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -1.009 | .9084 | -2.790 | .771 | 1.234 | 1 | .267 | .365 | .061 | 2.163 |
| Age | .002 | .0135 | -.024 | .029 | .030 | 1 | .862 | 1.002 | .976 | 1.029 |
| Gender | .150 | .4356 | -.704 | 1.003 | .118 | 1 | .731 | 1.161 | .495 | 2.727 |
| HD_access | .621 | .4525 | -.266 | 1.508 | 1.885 | 1 | .170 | 1.861 | .767 | 4.519 |
| Comorb_PVD | -.369 | .4850 | -1.320 | .581 | .580 | 1 | .446 | .691 | .267 | 1.788 |
| Comorb_Cancer | -.600 | .5332 | -1.646 | .445 | 1.268 | 1 | .260 | .549 | .193 | 1.560 |
| ASA | .576 | .4455 | -.298 | 1.449 | 1.669 | 1 | .196 | 1.778 | .743 | 4.258 |
| Plavix | .212 | .6102 | -.984 | 1.408 | .121 | 1 | .728 | 1.236 | .374 | 4.087 |
| Coumadin | -1.009 | 1.1418 | -3.247 | 1.229 | .780 | 1 | .377 | .365 | .039 | 3.419 |
| (Scale) | 1[a] | | | | | | | | | |

Dependent Variable: Anyclotting_phase1
Model: (Intercept), Age, Gender, HD_access, Comorb_PVD, Comorb_Cancer, ASA, Plavix, Coumadin

a. Fixed at the displayed value.

**Hosmer and Lemeshow Test**

| Step | Chi-square | df | Sig. |
|---|---|---|---|
| 1 | 8.321 | 8 | .403 |

Although the Hosmer-Lemeshow Goodness of Fit Test (42) indicated support for our model since *P* value was higher than 0.05 ($P = 0.4$), none of the independent variables (Table 34) could predict the risk of clotting occurrence during phase I (*P* values were not statistically significant). Moreover, in a similar model trying to predict the likelihood of any clotting events type 2 or 3, we were unable to identify any independent variable that could predict the occurrence of clotting events type 2 or 3 (Table 35), although the Goodness of model fit (42) was appropriate ($P = 0.19$).

**Table 35: Multivariate Analysis – Odds Ratio of Any Clotting Type 2 or 3 per Phase I (Logistic Regression Model)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -3.183 | 1.2794 | -5.691 | -.675 | 6.190 | 1 | .013 | .041 | .003 | .509 |
| Age | .006 | .0180 | -.029 | .041 | .120 | 1 | .729 | 1.006 | .971 | 1.042 |
| Gender | 1.030 | .6230 | -.191 | 2.251 | 2.733 | 1 | .098 | 2.801 | .826 | 9.497 |
| HD_access | 1.040 | .5929 | -.122 | 2.202 | 3.079 | 1 | .079 | 2.830 | .885 | 9.047 |
| Comorb_PVD | -.624 | .6593 | -1.917 | .668 | .897 | 1 | .344 | .536 | .147 | 1.950 |
| Comorb_Cancer | -1.491 | .8725 | -3.201 | .219 | 2.919 | 1 | .088 | .225 | .041 | 1.245 |
| ASA | .841 | .5912 | -.318 | 1.999 | 2.021 | 1 | .155 | 2.318 | .727 | 7.384 |
| Plavix | 1.001 | .7540 | -.477 | 2.478 | 1.761 | 1 | .185 | 2.720 | .620 | 11.923 |
| Coumadin | .327 | 1.2254 | -2.074 | 2.729 | .071 | 1 | .789 | 1.387 | .126 | 15.317 |
| (Scale) | 1[a] | | | | | | | | | |

Dependent Variable: Anyclotting_type2or3_phaeI
Model: (Intercept), Age, Gender, HD_access, Comorb_PVD, Comorb_Cancer, ASA, Plavix, Coumadin

a. Fixed at the displayed value.

**Hosmer and Lemeshow Test**

| Step | Chi-square | df | Sig. |
|---|---|---|---|
| 1 | 11.212 | 8 | .190 |

Due to a complex interaction between phases that will require complicated statistical analysis restricted by the limited data that we had, and after consulting with one of our Biostaticians, Dr. Bingshu E. Chen from the Cancer Research Institute at Queen's University, we could not build a multivariate logistic model that will combine both phases of the study to identify the independent variables that would be able to predict the occurrence of clotting.

Consequently, we repeated above Logistic regression models to predict the likelihood of any clotting events and any type 2 or 3 events occurrence during phase II (Table 36, 37). The use of CVC line as a HD line was associated with a significant risk of any clotting events as well as type 2 or 3 events during phase II (OR 4.27; 95% CI: 1.5-12.13, $P$ = 0.006). Hosmer-Lemeshow Goodness of Fit Test indicated support for the models (42) since $P$ values were higher than 0.05 ($P$ = 0.999).

Table 36: Multivariate Analysis – Odds Ratio of Any Clotting per Phase II (Logistic Regression Model)

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi Square | df | Sig. | | Lower | Upper |
| (Intercept) | -2.523 | 1.1444 | -4.766 | -.280 | 4.860 | 1 | .027 | 080 | 009 | .756 |
| Age | .000 | .0169 | -.033 | .033 | .000 | 1 | .991 | 1.000 | .967 | 1.034 |
| Gender | .701 | .5358 | -.349 | 1.751 | 1.713 | 1 | .191 | 2.016 | .705 | 5.763 |
| HD_access | 1.451 | .5329 | .407 | 2.495 | 7.415 | 1 | .006 | 4.267 | 1.502 | 12.127 |
| Comorb_PVD | .375 | .5817 | -.765 | 1.515 | .416 | 1 | .519 | 1.456 | .465 | 4.551 |
| Comorb_Cancer | .698 | .5808 | -.441 | 1.836 | 1.444 | 1 | .230 | 2.009 | .644 | 6.273 |
| ASA | -.451 | .5547 | -1.538 | .636 | .661 | 1 | .416 | .637 | .215 | 1.889 |
| Plavix | .833 | .6511 | -.443 | 2.110 | 1.639 | 1 | .201 | 2.301 | 642 | 8.244 |
| Coumadin | 1.191 | .9799 | -.729 | 3.112 | 1.478 | 1 | .224 | 3.291 | .482 | 22.461 |
| (Scale) | 1[a] | | | | | | | | | |

Dependent Variable: Anyclotting_phaseII
Model: (Intercept), Age, Gender, HD_access, Comorb_PVD, Comorb_Cancer, ASA, Plavix, Coumadin

a. Fixed at the displayed value.

**Hosmer and Lemeshow Test**

| Step | Chi-square | df | Sig. |
|---|---|---|---|
| 1 | .942 | 8 | .999 |

Table 37: Multivariate Analysis – Odds Ratio of Any Clotting Type 2 or 3 per Phase II (Logistic Regression Model)

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -2.523 | 1.1444 | -4.766 | -.280 | 4.860 | 1 | .027 | .080 | .009 | .756 |
| Age | .000 | .0169 | -.033 | .033 | .000 | 1 | .991 | 1.000 | .967 | 1.034 |
| Gender | .701 | .5358 | -.349 | 1.751 | 1.713 | 1 | .191 | 2.016 | .705 | 5.763 |
| HD_access | 1.451 | .5329 | .407 | 2.495 | 7.415 | 1 | .006 | 4.267 | 1.502 | 12.127 |
| Comorb_PVD | .375 | .5817 | -.765 | 1.515 | .416 | 1 | .519 | 1.456 | .465 | 4.551 |
| Comorb_Cancer | .698 | .5808 | -.441 | 1.836 | 1.444 | 1 | .230 | 2.009 | .644 | 6.273 |
| ASA | -.451 | .5547 | -1.538 | .636 | .661 | 1 | .416 | .637 | .215 | 1.889 |
| Plavix | .833 | .6511 | -.443 | 2.110 | 1.639 | 1 | .201 | 2.301 | .642 | 8.244 |
| Coumadin | 1.191 | .9799 | -.729 | 3.112 | 1.478 | 1 | .224 | 3.291 | .482 | 22.461 |
| (Scale) | 1[a] | | | | | | | | | |

Dependent Variable: anyclotting_type2or3_phaseII
Model: (Intercept), Age, Gender, HD_access, Comorb_PVD, Comorb_Cancer, ASA, Plavix, Coumadin

a. Fixed at the displayed value.

**Hosmer and Lemeshow Test**

| Step | Chi-square | df | Sig. |
|---|---|---|---|
| 1 | .942 | 8 | .999 |

**Bleeding Events:**

Similar to clotting events and since bleeding event counts have the **Poisson distribution**, and in order to identify whether the difference between bleeding event counts between phase I and II was statistically significant, we analyzed our data using **Poisson Regression** (*Please refer to page 34 for further details about Poisson Regression and incident rate ratio*).

There was a total of 28 bleeding events during phase I compared with 32 events during phase II (Table 7). Those events were further categorized depending on the bleeding type (Table 7). Bleeding events type 2 (*Defined as overt bleeding documented by diagnostic investigations within 4 hours from hemodialysis session*) were not identified in either phase (0 events) while two type 1 bleeding events (*Defined as overt bleeding documented by clinical examination within 4 hours from hemodialysis session*) were identified only during phase I since no type 1 and no such bleeds occurred during phase II (Table 7).

| Table 7: Bleeding Events During Phase I & II | | | | | | |
|---|---|---|---|---|---|---|
| **Bleeding Type** | 1 | 2 | 3 | 4 | 5 | Total |
| **Phase I** | 2 | 0 | 14 | 6 | 6 | 28 |
| **Phase II** | 0 | 0 | 20 | 9 | 3 | 32 |

The incident rate ratio for all bleeding events during phase I was 12% lower than during phase II but was not statistically significant (Table 38, IRR 0.88; 95% CI: 0.53-1.45, $P$ = 0.61).

**Table 38: Total Bleeding Events per Phase (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -1.226 | .1768 | -1.572 | -.879 | 48.068 | 1 | .000 | .294 | .208 | .415 |
| [Phase=1] | -.134 | .2588 | -.641 | .374 | .266 | 1 | .606 | .875 | .527 | 1.453 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_Bleeding_Events
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Since bleeding events type 1 and 2 did not occur during phase I and II (Table 7), we only compare the incident rate of bleeding event types 3, 4, and 5 that occurred during phase I and phase II. Bleeding events type 3 and 4 occurred less frequently during phase I compared with phase II, 30% and 33% less for type 3 and 4, respectively during phase I

(Table 39, 40), while type 5 occurred more frequently during phase I (2 X) compared with II (Table 41). However, none of the incident rate ratios of those bleeding event types were statistically significantly different across phases (Table 39, 40, 41), type 3 ($P = 0.31$), type 4 ($P = 0.44$), and type 5 ($P = 0.33$).

**Table 39: Total Bleeding Events Type 3 per Phase (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -1.696 | .2236 | -2.134 | -1.257 | 57.502 | 1 | .000 | .183 | .118 | .284 |
| [Phase=1] | -.357 | .3485 | -1.040 | .326 | 1.048 | 1 | .306 | .700 | .354 | 1.386 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_bleeding_Type_Three_per_Phase
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 40: Total Bleeding Events Type 4 per Phase (Poisson Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -2.494 | .3333 | -3.147 | -1.841 | 55.986 | 1 | .000 | .083 | .043 | .159 |
| [Phase=1] | -.405 | .5270 | -1.438 | .628 | .592 | 1 | .442 | .667 | .237 | 1.873 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_bleeding_type_four_per_pt_phase#1
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 41: Total Bleeding Events Type 5 per Phase (Poisson Regression)**

Parameter Estimates

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig | | Lower | Upper |
| (Intercept) | -3.593 | .5774 | -4.724 | -2.461 | 38.723 | 1 | .000 | .028 | .009 | .085 |
| [Phase=1] | .693 | .7071 | .693 | 2.079 | .961 | 1 | .327 | 2.000 | .500 | 7.997 |
| [Phase=2] | 0[a] | . | | | | | | 1 | | |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_bleeding_Type_Five_per_Phase
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Moreover, since a few patients did not finish the study, as they were transplanted (x 4 patients) or died (x 6 patients) before the end of the study (Table 2), those patients did not have the full study length of exposure. Consequently, those patients who did not complete the study may model bleeding event rates in this study over time. To accommodate for the bleeding events occurring to a particular length of observation, divided by time of exposure, **Poisson regression with offset variable analysis** was used to calculate event rates as events per unit time, allowing the observation window to vary for each time unit (40).

Using *offset variable analysis*, there was no difference of the incident rate ratio of all bleeding events occurring during phase I compared with phase II (Table 42, IRR 0.94; 95% CI: 0.54-1.66, $P = 0.84$).

**Table 42: Total Bleeding Events per Phase (Poisson Regression - Offset Variable)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -5.424 | .2041 | -5.824 | -5.024 | 706.137 | 1 | .000 | .004 | .003 | .007 |
| [Phase=1] | -.059 | .2887 | -.625 | .507 | .042 | 1 | .838 | .943 | .535 | 1.660 |
| [Phase=2] | 0[a] | . | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Any_Bleedin_per_Patient_per-Phase
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

Bleeding events type 3 and 4 occurred less frequently during phase I compared with phase II, 30% and 37% less for type 3 and 4, respectively during phase I (Table 43, 44), while type 5 occurred more frequently during phase I (1.9 X) compared with II (Table 45). However, none of the incident rates of those bleeding event types were statistically significantly different across phases (Table 43, 44, 45), type 3 ($P = 0.23$), type 4 ($P = 0.38$), and type 5 ($P = 0.37$).

**Table 43: Total Bleeding Events Type 3 per Phase (Poisson Regression - Offset Variable)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi Square | df | Sig. | | Lower | Upper |
| (Intercept) | -5.607 | .2236 | -6.045 | -5.168 | 628.670 | 1 | .000 | .004 | .002 | .006 |
| [Phase=1] | -.416 | .3485 | -1.099 | .267 | 1.423 | 1 | .233 | .660 | .333 | 1.306 |
| [Phase=2] | 0[a] | | | | | | | 1 | | |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_bleeding_Type_Three_per_Phase
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 44: Total Bleeding Events Type 4 per Phase (Poisson Regression - Offset Variable)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -6.405 | .3333 | -7.058 | -5.752 | 369.224 | 1 | .000 | .002 | .001 | .003 |
| [Phase=1] | .464 | .5270 | -.569 | 1.497 | .777 | 1 | .378 | 1.590 | .566 | 4.466 |
| [Phase=2] | 0[a] | | | | | | | 1 | | |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_bleeding_type_four_per_pt_phase#1
Model: (Intercept), Phase, offset = Months_of_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

**Table 45: Total Bleeding Events Type 5 per Phase (Poisson Regression - Offset Variable)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -7.504 | .5774 | -8.635 | -6.372 | 168.916 | 1 | .000 | .001 | .000 | .002 |
| [Phase=1] | .634 | .7071 | -.752 | 2.020 | .804 | 1 | .370 | 1.885 | .472 | 7.539 |
| [Phase=2] | 0[a] | | . | . | . | . | . | 1 | . | . |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Total_bleeding_Type_Five_per_Phase
Model: (Intercept), Phase, offset = Months_OF_FU

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

To evaluate the intrapersonal effects on bleeding events and in order to identify whether the difference between bleeding event occurrence, as a dependent categorical variable (Bleeding occurred; Yes = 1 or No = 0), between phase I and II was statistically significant, we analyzed our data using **Binary Logistic Regression** (*Please refer to page 41 for further details about Binary Logistic Regression, Odds Ratio and the interpretation of the width of 95% confidence interval*).

The Odds Ratio (OR) of any bleeding event to occur in either phases was similar (Table 46, OR 1; 95% CI: 0.53-1.9, $P = 1$).

**Table 46: Any Bleeding Events Phase I versus II (Logistic Regression)**

**Parameter Estimates**

| Parameter | B | Std. Error | 95% Wald Confidence Interval | | Hypothesis Test | | | Exp(B) | 95% Wald Confidence Interval for Exp(B) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Lower | Upper | Wald Chi-Square | df | Sig. | | Lower | Upper |
| (Intercept) | -1.265 | .2312 | -1.718 | -.812 | 29.930 | 1 | .000 | .282 | .179 | .444 |
| [Phase=1] | .000 | .3269 | -.641 | .641 | .000 | 1 | 1.000 | 1.000 | .527 | 1.898 |
| [Phase=2] | 0[a] | | | | | | | 1 | | |
| (Scale) | 1[b] | | | | | | | | | |

Dependent Variable: Any_Bleedin_per_Patient_per-Phase
Model: (Intercept), Phase

a. Set to zero because this parameter is redundant.

b. Fixed at the displayed value.

So, although all bleeding events occurred less frequently during phase I compared with phase II; 12% using Poisson regression (IRR 0.88) and 6% using Poisson regression with Offset variable analysis (IRR 0.94), differences were not statistically significant.

Furthermore, since there was only 4 bleeding events during phase I, where heparin doses were changed and were effective (ACT post heparin dose change achieved *a target ACT of 150 to 200*), and only 3 events occurred during phase II, where heparin was changed without available post heparin dose change ACTs (Table 8), we did not statistically analyze our limited data to compare whether heparin dose was changed more often in phase I versus phase II.

| Table 8: Bleeding Events and Heparin Doses Changes | | | |
|---|---|---|---|
| | All Bleeding Events | Heparin Changed (%) | Effective Change ACT > 150 (%) |
| **Phase I** | 28 | 4 (14%) | 4 (100%) |
| **Phase II** | 32 | 3 (9%) | No Available ACT |

**Secondary Endpoints:**

Since ACT, URR, and hemoglobin are continuous variables and since we have only one group of patients followed over the two phases of the study (*two different conditions*), we compared the mean of above variables of the two phases of the study analyzing our data using a Paired-samples t-test, assuming that the study sample was randomly selected from the hemodialysis population, study measurements observed were independent of one another and normally distributed with equal variances (42). With our large sample size ($n = 109, > 30$), violation of the last assumption was unlikely to cause any serious problems (43).

With a 2-tailed significance level of 0.05 ($\propto = 0.05$) and a degree of freedom of 108 ($n = 109 - 1 = 108$), the mean baseline ACT in phase I (152.8 ± 18.7) was significantly higher than the baseline in phase II (139.9 ± 43.7), t (108) = 2.99, $P = 0.003$ (Table 47). The mean decrease in ACT was 12.79 with a 95% CI: 4.31-21.28 in phase II compared with phase I (Table 47). However, this statistically significant difference of 12.8 seconds in ACT is not clinically relevant.

**Table 47: Paired Samples t-Test - ACT**

**Paired Samples Statistics**

| | | Mean | N | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|
| Pair 1 | meanACT_phaseI | 152.758440 | 109 | 18.7438605 | 1.7953362 |
| | meanACT_phaseII | 139.964679 | 109 | 43.7170065 | 4.1873298 |

**Paired Samples Correlations**

| | | N | Correlation | Sig. |
|---|---|---|---|---|
| Pair 1 | meanACT_phaseI & meanACT_phaseII | 109 | .161 | .094 |

**Paired Samples Test**

| | | Paired Differences | | | | | t | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | Std. Deviation | Std. Error Mean | 95% Confidence Interval of the Difference Lower | Upper | | | |
| Pair 1 | meanACT_phaseI - meanACT_phaseII | 12.7937615 | 44.7005593 | 4.2815371 | 4.3070122 | 21.2805107 | 2.988 | 108 | .003 |

To evaluate the effect of monthly routine ACT monitoring (intervention) on this difference, we calculate the intervention effect size for paired-sample t-test (known as ***Eta squared***) recommended by Cohen 1988 as the most commonly used effect statistics (42).

$$\textbf{Eta squared} = t^2 + [t^2 + (N-1)]$$

Where t is the t-test value and N is the sample size (109 in our study)

Depending on Cohen 1988 guideline (42) the intervention effect size on the dependent variable will be small if Eta squared was 0.01, moderate if Eta squared was 0.06, and large if Eta squared was 0.14.

Eta squared was 0.08, reflecting a moderate effect of routine monthly ACT monitoring on the difference of the mean ACT between phase I and II *(In other words, there was a difference in the mean ACT between phase I and II which could be secondary to routine monthly ACT monitoring).*

Repeating above analysis, the mean URR in phase I (70.50 ± 6.96) was significantly higher than phase II (66.16 ± 19.90), t (108) = 2.43, $P = 0.017$ (Table 48). The mean decrease in URR was 4.35 with a 95% CI: 0.8-7.9 (Table 48).

**Table 48: Paired Samples t-Test - URR**

**Paired Samples Statistics**

| | | Mean | N | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|
| Pair 1 | meanURR_phaseI | 70.5046 | 109 | 6.96118 | .66676 |
| | meanURR_phasII | 66.1568 | 109 | 19.89952 | 1.90603 |

**Paired Samples Correlations**

| | | N | Correlation | Sig. |
|---|---|---|---|---|
| Pair 1 | meanURR_phaseI & meanURR_phasII | 109 | .340 | .000 |

**Paired Samples Test**

| | | Paired Differences | | | | | t | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | Std. Deviation | Std. Error Mean | 95% Confidence Interval of the Difference | | | | |
| | | | | | Lower | Upper | | | |
| Pair 1 | meanURR_phaseI - meanURR_phaseII | 4.34780 | 18.71188 | 1.79227 | .79520 | 7.90040 | 2.426 | 108 | .017 |

Eta squared was 0.05 reflecting a small to moderate difference in the mean URR between phase I and II, however, this difference was not *necessarily* due to ACT monitoring.

Finally, the mean hemoglobin (Hgb) in phase I (114.11 ± 10.18) was significantly higher than phase II (105.6 ± 29.51), t (108) = 2.98, $P = 0.004$ (Table 49). The mean decrease in Hgb was 8.53 with a 95% CI: 2.85-14.21 (Table 49).

**Table 49: Paired Samples t-Test - Hemoglobin**

**Paired Samples Statistics**

| | | Mean | N | Std. Deviation | Std. Error Mean |
|---|---|---|---|---|---|
| Pair 1 | meanHGB_phaseI | 114.1116 | 109 | 10.18452 | .97550 |
| | meanHGB_phaseII | 105.5803 | 109 | 29.50928 | 2.82648 |

**Paired Samples Correlations**

| | | N | Correlation | Sig. |
|---|---|---|---|---|
| Pair 1 | meanHGB_phaseI & meanHGB_phaseII | 109 | .130 | .177 |

**Paired Samples Test**

| | | Paired Differences | | | | | t | df | Sig. (2-tailed) |
|---|---|---|---|---|---|---|---|---|---|
| | | Mean | Std. Deviation | Std. Error Mean | 95% Confidence Interval of the Difference | | | | |
| | | | | | Lower | Upper | | | |
| Pair 1 | meanHGB_phaseI - meanHGB_phaseII | 8.53128 | 29.93610 | 2.86736 | 2.84768 | 14.21489 | 2.975 | 108 | .004 |

Eta squared was 0.08 reflecting a moderate difference in the mean hemoglobin between phase I and II. However, the difference in the mean of hemoglobin, between phase I and II, could not be necessarily attributed to ACT monitoring.

## DISCUSSION AND CONCLUSION

After obtaining the ethical approval from the Human Investigations Committee and the Research Proposals Approval Committee (RPAC) of Eastern Health, a total of 109 adult chronic hemodialysis patients receiving heparin anticoagulation during their chronic hemodialysis, at established heparin doses at our hemodialysis unit, were enrolled and followed in our study, which represent a Quality Improvement Exercise, with a before-and-after design.

During the first four months of the study (Phase I), all patients received heparin as per our usual practice and heparin doses were expected to be adjusted, depending on the monthly routine ACT values, by the Nephrologist covering our hemodialysis unit as per our protocols (Appendix A & B). During the second four months of the study (Phase II), patients received heparin at a fixed dose, similar to the last bolus and maintenance doses delivered at the last HD session at the end of phase I. ACT-guided heparin dose monitoring was not done routinely during phase II; unless clotting or bleeding events occurred. If clotting or bleeding occurred at any point during phase II, heparin doses were expected to be adjusted by the Nephrologist covering the hemodialysis unit depending on a stat or a scheduled ACT value as per our protocols (Appendix A & B).

Patients' demographics and baseline characteristics were similar to chronic hemodialysis population in North America from age, gender, etiology of ESRD, and comorbidities points of view, as it was shown in table 1. Average age was 61.40 ± 15.99 years and almost 60% of patients were males. Diabetes and hypertension were the most common etiology of ESRD and both diabetes and hypertension were existed as comorbidities in most patients, as it was shown in table 1. Two third of the patients had dialysis lines, which is mildly higher than recommended. However, this high rate of dialysis line in our patients was mainly due to patients' personal preferences.

The majority of enrolled patients completed the study. However, ten patients did not finish the study since six patients died and the other four received kidney transplantation before the end of the study. The average follow up of patients during phase I was 3.82 ± 0.76 months compared with 3.7 ± 1.0 months during phase II.

As it was expected, the mean ACT in phase I was significantly ($P = 0.003$) higher (152.8 ± 18.7) than phase II (139.9 ± 43.7), and heparin doses were changed more often and more effectively achieving ACT target during phase I compared with phase II. However, more than 50% of routine ACTs during phase I, were below target (ACT < 150), and heparin doses were unexpectedly changed *only* in less than 10% of these cases. Furthermore, heparin dose changes were unpredictably effective, attaining ACT target *only* in 50% of those cases where ACTs were low and heparin doses were changed.

Although the mean ACT level during phase I was significantly higher than phase II, and although heparin doses were changed more often and more effectively during phase I, all clotting events occurred unexpectedly and significantly more often during phase I compared with phase II. Even after compensating for the exposure time, using Poisson regression with offset variable analysis since a few patients did not finish the study, the incident rate ratio of all clotting events during phase I remained unexpectedly 41% significantly higher than in phase II ($P = 0.041$). This could be explained by the high prevalence of low monthly routine ACT values (ACT < 150) found in more than 50% of patients during phase I, combined with the low frequency of changing heparin doses (in less than 10% of those with low ACT during phase I), and finally by the low rate of effective heparin dose changes achieving a target ACT above 150, which occurred only in 50% of the above cases during phase I. However, and although the above proposed mechanisms could be accountable for the high Odds ratio (OR = 1.87, $P = 0.04$) of any clotting event that could occur during phase I compare with phase II, they could not be the predominant contributors to clotting, since low ACT values were also observed in phase II with minimal effective heparin dose changes.

Moreover, even when more serious clotting events occurred (clotting events type 2 and 3), heparin dose change was not significantly more often or more successful during phase I compared with phase II.

As practiced locally, this could be due to doctors' responses to the ACTs. In our hemodialysis unit, doctors rotated on a monthly basis. In the first month of the study, more than half of the ACT values (57.8%) were below a target of ACT > 150. The doctor covering the hemodialysis unit during that month made a lot of heparin dose changes depending on routine ACT values. Even then, heparin dose changes, during that month, were surprisingly adjusted *only* in 55.6% of low ACT cases, and dose changes were effective, achieving a target ACT of > 150, *only* in 51.4% of those cases. During the following three months of the study, and although ACT was low at < 150 in more than 50% of routine ACT values, other doctors arbitrarily made very little changes, adjusting heparin doses in less than 10% of low ACT cases (3.2%, 11.1% and 7.8% during the 2$^{nd}$, 3$^{rd}$ and 4$^{th}$ month of the study). The above differences in the physicians' practices lead one to speculate that this might be due to the physicians' sense that tinkering with the heparin dose made little difference in their experiences. It might also attest to the challenge of regularly changing heparin doses to achieve targets in middle size to large hemodialysis units due to workload and other unstudied risk factors. However, a multicenter randomized trial or a large multicenter retrospective chart review study will be required to externally validate above finding before we can generalize our local doctors' response to ACT values, to the general Nephrology population. Furthermore, in future studies it would be advisable to have standardized heparin dose-adjustment protocols used routinely by hemodialysis nurses when either routine ACTs or event driven ACT values suggest a heparin dose adjustment. Doing so would reduce the

potential for bias due to physician variability in response to ACT data, especially in an open label study.

In a multivariate analysis, we could not identify any significant specific risk factors that will increase the risk of clotting events, except for *the use of hemodialysis CVC lines,* which *was associated with a significant risk of any clotting events as well as type 2 and 3 clotting events during phase II but not phase I.* With good multivariate models fit since the Hosmer-Lemeshow Goodness of Fit Test *P* values were above 0.05 ($P = 0.999$), the above finding further supports the proved benefits of arteriovenous fistula (AVF) compared with hemodialysis CVC line in chronic hemodialysis patients. Such a finding provides another rationale to encourage patients to accept AVF creation as an optimal dialysis access in chronic hemodialysis.

The above findings related to clotting events were surprising and unexpected since we expected more clotting events to occur during phase II compared with phase I. Whether this resulted from doctors' response to ACT values and heparin dose changes in phase I, a failure to note and record some clotting events especially in phase II, the low number of clotting events, or other factors; was not very clear.

However, we believe that since detecting and recording all clotting events as a routine part of nurses' assessment during and at the end of each hemodialysis session as well as

ongoing education and encouragement of the hemodialysis unit's nurses, done periodically by Dr. Shamseddin during the study, minimizes the risk of missing clotting events during the study.

Furthermore, prior to the study, we expected to have 5 clotting events per 100 patients over three months or 5 clotting events per 3,600 hemodialysis sessions. If these numbers were correct, the expected number of clotting events in our actual study, which had 109 patients followed for 4 months, would be 7 clotting events per 109 patients or 7 clotting events per 5,232 hemodialysis sessions. Our study showed a total of 87 clotting events in phase I and 58 clotting events in phase II, both numbers were much higher than what we expected prior to our study. This is in line with our pre-study assumption that routine documentation of clotting events prior to the study would fail to capture all events. Furthermore, it also suggests that although the missing of clotting-related data could not be completely prevented in our study, data capture was definitely more complete during the study. It also indicates that diagnosing and recording clotting events in patients' records is feasible and should be a part of a routine assessment by hemodialysis nurses to be done during and at the end of each hemodialysis sessions. Furthermore, we believe that the recording system we invented and incorporated in our hospital computer (MEDitech) system was effective in capturing the majority of clotting events. However, if further studies were required in the future, the methods of capturing and recording clotting events has to be evaluated to avoid missing any data.

On the other hand, we identified a total of 28 bleeding events during phase I and 32 events during phase II. Those events were further categorized depending on a specific definition into 5 different bleeding types (table 7). The incident rate ratio of all bleeding events during phase I, was 12% lower than phase II. However, this was not statistically significant and when we compensate for the exposure time, using Poisson regression with offset variable analysis, there was no significant difference in bleeding events comparing phase I with II.

This was confirmed further by analyzing our data using logistic regression, which provided an Odds ratio of 1. This Odds ratio as well as the insignificant *P* value and the 95% confidence interval, containing the value of 1, confirmed that there was no significant difference in bleeding events comparing phase II with phase I. However, since the *P* values were insignificant and the 95% CIs were wide, we might have lacked power to pick up on a clinically meaningful difference.

Furthermore, since there were only 4 bleeding events during phase I, following which heparin doses were effectively changed (*ACT post heparin dose change achieved a target ACT of 150 to 200*), and only 3 events during phase II, following which heparin doses were changed, but changes were unknown to be effective since ACTs were not available (Table 8), we did not analyze our limited data to compare whether heparin dose was changed more often in phase I versus phase II.

The above findings related to bleeding events were surprising since we expected more bleeding events to occur during phase II compared with phase I. Whether this resulted from doctors' response to ACT values and heparin dose changes, missed bleeding events, the low number of bleeding events, or other factors; was not very clear.

However, prior to the study, we expected to have 5 bleeding events per 100 patients over three months or 5 bleeding events per 3,600 hemodialysis sessions. If these numbers were correct, the expected number of bleeding events in our actual study, which had 109 patients followed for 4 months, would be 7 bleeding events per 109 patients or 7 clotting events per 5,232 hemodialysis sessions. Our study showed a total of 28 bleeding events in phase I and 32 bleeding events in phase II, both numbers were much higher than what we expected prior to our study. This is in line with our pre-study assumption that routine documentation of bleeding events prior to the study would fail to capture all events.

Furthermore, it also suggests that although the missing of bleeding-related data could not be completely prevented in our study, data capture was definitely more complete during the study. It also indicates that diagnosing and recording bleeding events in patients' records is feasible and should be a part of a routine assessment by hemodialysis nurses to be done during and at the end of each hemodialysis sessions. Moreover, we believe that the recording system we invented and incorporated in our hospital computer (MEDitech) system was effective in capturing the majority of bleeding events. However, if further

studies were required in the future, the methods of capturing and recording bleeding events has to be evaluated to avoid missing any data.

Regarding the secondary end points, we found that the mean urea reduction ratios (URR) and hemoglobin (Hgb) levels during phase I were significantly higher compared with phase II. However, the differences could not be clearly linked to higher and more effective ACT levels during phase I compared with phase II since the Eta squared were 0.05 (small to moderate effect of ACT on URR), and 0.08 (moderate effect of ACT on Hgb) and the study design is open to many confounders affecting these outcomes.

**Strengths:**

Our study was the first and the only study that evaluated the effect of routine monthly ACT monitoring on major clinical events (clotting and bleeding) as well as laboratory parameters (clearance – URR and Hgb) in an ambulatory adult chronic hemodialysis population on an established heparin dose. It is a prospective study with a before-and-after design. The sample size, the primary endpoint events occurred during the study, and the follow up were large and long enough to achieve our estimated power as reported above. The loss to follow up was less than 10% and offset variable analysis was used to compensate for the exposure time.

**Limitations:**

Generalizability may be affected by the single center nature of the study. However, our hemodialysis unit provided dialysis to stable ambulatory adult chronic hemodialysis patients, in a suitable geographical location reflecting typical characteristics of a North American hemodialysis population. This suggests that the findings might apply to other North American hemodialysis units, although multicenter trials are still required to confirm our findings.

Furthermore, due to the design of our study, an observational study with before-and-after design and the absence of blinding since patients were informed that ACTs will not routinely measured during the second phase, *information bias* could not be completely avoided. *Reporting and data abstract biases* were the main types of information bias we faced in our study, while the *recall bias* was not important in the study since *patients did not have to recall exposure to heparin or primary and secondary end points,* as those were observed, diagnosed, and recorded prospectively and mainly by our hemodialysis nurses. Furthermore, since patients acted as their own controls and had the same exposure to heparin although ACTs were not routinely done during the second phase, selection bias was not considered. Likewise, although the open label nature of our study could be subject to a potential bias favoring the monthly routine ACTs monitoring, our study analysis indicated that the efficacy effects of monthly ACTs monitoring was likely

not confounded by ascertainment bias since monitoring was not associated with better outcomes.

Primary end points, specifically clotting events, were clearly defined and classified based on visual inspections of the dialyzer and hemodialysis circuit lines, that were evaluated routinely by the hemodialysis nurses during and at the end of each HD session and recorded regularly in the patients' electronic chart using our hospital computer (MEDitech) system at the end of each HD session. Since nurses subjectively evaluated and scored events prior to recording them, reporting bias could not be avoided completely. However, since periodic education and encouragement to note and record event accurately were done by Dr. Shamseddin with our hemodialysis nurses during the study, we believe that the majority of events, including minor events, were diagnosed and recorded in patients' records. Moreover, the higher number of identified events that were observed during the study compared with those recorded prior to the study, confirmed that our developed protocol aided detection and recording the majority of events, reaching the stated study power. Alternatively, bleeding events were much more difficult to define and report, leaving a higher chance of missing data. A better definition of bleeding event and data collection would be required for future larger randomized controlled trials in the future. Furthermore, if our data are representative, in order to calculate sample size for future potential trials, it should be noted that clotting events were three times as frequent

as bleeding events, which is different from the assumption we made in planning this study.

***In conclusion,*** routine monthly ACT monitoring in adult chronic hemodialysis patients was not associated with a reduction in clotting and bleeding events compared with measuring ACTs only for initial dose assignment or in response to clinical indications.

Simultaneously, we believe that clotting and bleeding events in chronic hemodialysis patients in general are under diagnosed and unreported sufficiently in hemodialysis units. Defining those events clearly, noting and recording events as a part of a routine assessment that has to be done and documented regularly in patients' records, by the hemodialysis nurses during and at the end of each hemodialysis sessions, and ongoing education and encouragement of the hemodialysis nurses to observe, diagnose, and record events are required to enhance patients' care and management.

Furthermore, although routine monthly ACT monitoring did not reduce the incidence of clotting and bleeding events in chronic adult hemodialysis patients, tailoring the best care plan to manage those events and avoid furthers events should be discussed individually with the local Nephrologist until multicenter randomized trials are available to confirm and generalize our findings.

Developing better objective definitions of clotting and bleeding events as well as more practical recording systems and strict standardized heparin dose-adjusting protocols to be used routinely by hemodialysis nurses as a part of routine intra- and postdialytic patient-care assessment, have to precede before a future multicenter blinded randomized trial or a large multicenter retrospective chart review study, to externally validate our findings in order to improve generalizability and to reduce confounded physician response variability and biases. Expecting an incident rate of bleeding events at 1:3 clotting events instead of 1:1 ratio has to be considered to calculate future sample size. Meanwhile, adopting our invented hospital computer system to assess and record clotting events, including minor events, should be practical until a better system is available.

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# Appendix

Appendix A: Heparin – Full Intensity Protocol

Appendix B: Heparin – Low Intensity Protocol

# Appendix A

## Heparin – Full Intensity Protocol

| Policy Name: HEPARIN-FULL INTENSITY | **Clinical Practice** CLP –160 |
|---|---|
| **Issuing Authority** (sign & date) | **Norma Baker Interim Chief Operating Officer Adult & Acute Care ( St. John's)** |
| **Office of Administrative Responsibility** | Dialysis Unit |
| **Author** | Cathy Cake Clinical Educator/Dr.Brendan Barrett Nephrologist |
| **Level** | Two |
| **Original Approval Date** | March /09 |
| **Effective Date** | March /09 |
| **Review Date** | March /10 |
| **Revision Date(s)** | |

## Overview

Anticoagulation with unfractionated heparin is the usual way of preventing clotting in the extracorporeal system. Routine full dose heparin prescriptions are for patients at normal risk for bleeding.

## POLICY

- Hemodialysis patients either receive systemic heparin at full intensity, low intensity, or have heparin free dialysis.
- Full intensity heparinization is the usual treatment. This is usually achieved by administration of a heparin bolus dose 3-5 minutes prior to initiating dialysis followed by a continuous infusion.
- Low intensity heparinization, or heparin free therapy may be implemented by the RN for a given dialysis session on the basis of his/her pre dialysis assessment (refer to policy for Low

Intensity or Heparin- Free Dialysis).
The decision about what level of heparinization to use in subsequent dialysis sessions should be made in consultation with the nephrologist.

## Scope

Registered nurses working in Dialysis Units within Eastern Health upon completion of Hemodialysis orientation

## Purpose

To prevent or minimize clotting in the extracorpeal system, while also maintaining an acceptable risk of bleeding.

### Procedure

1. Assess for any bleeding or potential risk for bleeding.
2. Check patient's prescription for heparin if established and verify that this is appropriate to current bleeding risk. If so, follow this heparin prescription. Otherwise, follow the appropriate low intensity/heparin-free algorithm, either as ordered by the physician, or as judged appropriate to the current bleeding risk (see low intensity or heparin-free policy).
3. If bleeding risk is considered normal and there is not an existing prescription for full intensity heparin, please ask the responsible nephrologist for an appropriate initial heparin prescription, and then follow the assessment and dosing algorithm below.
4. If using the algorithm for the current dialysis session, measure baseline ACT prior to heparin bolus. Please see section B for further details.
5. Draw up bolus dose of heparin and attach to arterial

needle.

6. Instill bolus dose 3-5 minutes prior to initiation of dialysis and once all dialysis needles have been successfully placed.

7. Start continuous heparin infusion with initiation of dialysis.

8. Heparin infusion rates are monitored, at least once per hour, during the dialysis treatment as part of the normal routine monitoring.

9. The extracorporeal circuit is assessed at the same times for any visible signs of fibrin/clot formation.

10. Discontinue infusion one hour prior to the discontinuation of dialysis unless otherwise ordered.

11. During the rinseback procedure the extracorporeal circuit is assessed for any visible signs of clotting/fibrin formation.

12. Record hemostasis time in patient's chart and notify nephrologist if prolonged.

**Procedure for patients with hemodialysis catheters**

Procedure is as above with the following exceptions:

a) Follow catheter opening policy for administration of heparin bolus

b) Continue heparin infusion until discontinuation of dialysis

**Heparinization during dialysis for patients already receiving heparin or low-molecular weight heparin IV or SC.**

If the patient is receiving an IV unfractionated heparin infusion or SC unfractionated heparin at therapeutic doses, no additional heparin will be required for dialysis. The protocol for

monitoring and adjusting the heparin as already ordered should be followed.

If the patient is being treated with therapeutic doses of low-molecular weight heparin (IV or SC), no additional heparin will be required for dialysis. The protocol for monitoring and adjusting the low-molecular weight heparin as already ordered should be followed.

If the patient is receiving low dose prophylactic unfractionated or low-molecular weight heparin S/C, continue with the usual dialysis heparin orders.

**Section B: Determining the initial dose for full dose heparin therapy (see Flowsheet).**

1. Measure the baseline ACT pre dialysis. When access being used is a fistula or graft, draw the baseline sample directly from the fistula needle prior to flushing the needle with 0.9% NaCl. Normal range in uremic patients can be 68-132 seconds with a mean of 100 seconds.
2. 1.5 to 2.0 times the patient's baseline number provides an ACT value range adequate for full intensity heparinization for the majority of dialysis patients.
3. Administer the ordered bolus dose of heparin. However, if the baseline ACT is greater than 150 further prolongation may be associated with bleeding and a bolus is not necessary. Omit the initial bolus of heparin in this case.
4. Turn on the hourly heparin infusion. If the baseline ACT is greater than 150, reduce the hourly rate to 500-1,000 units.
5. 15 minutes later, perform a 2$^{nd}$ ACT to determine the patient's response to the heparin bolus dose. The target is 150-250 seconds. Re-bolus with 500 – 1,000 units of heparin if the ACT is below the target range. If the ACT is > 300, reduce the infusion to 500 units per hour until the 60 minute ACT check.
6. At 60 minutes into the dialysis treatment take a 3rd ACT to determine the effect of the hourly rate. The target ACT is

150-250 seconds. Increase the hourly rate by 500- 1,000 units if the ACT is below the target range. Reduce the hourly rate by 500- 1,000 units if the ACT is above the target range. The hourly infusion rate will usually range from 500 units to 3,000 units depending on the patients' sensitivity to heparin.

7. At 120 minutes take a 4th ACT. The target ACT is 150-250 seconds. The heparin dose may again be adjusted. Increase the hourly rate by 500- 1,000 units if the ACT is below the target range. Reduce the hourly rate by 500- 1,000 units if the ACT is above the target range.
8. Note the time heparin will be stopped prior to the end of dialysis (usually 60 minutes for fistulae and grafts, end of dialysis session for catheters).
9. At 180 minutes into treatment, take a 5th ACT unless you plan to stop heparin within the next 60 minutes. The target ACT at this stage is 150-180 seconds (reflecting the bolus wearing off and the anticipated end of dialysis session). The heparin dose may again be adjusted. Increase the hourly rate by 500- 1,000 units if the ACT is below the target range. Reduce the hourly rate by 500- 1,000 units if the ACT is above the target range.
10. If hemostasis time was prolonged after needle removal in the last prior dialysis session or the system clotted out following heparin discontinuation, prior to discontinuing dialysis through either a fistula or AV graft on this occasion, take a final ACT to determine the effect of stopping the heparin infusion. The target ACT is 100-120 seconds.
11. Document the clearance of the dialyzer and drip chambers. A reduced blood flow and/or multiple alarm situations can affect the condition of the dialyzer.
12. Document the time for needle sites to stop bleeding. Acceptable time is ≤ 10 minutes.
13. In planning for second and subsequent dialyses using this protocol, consider the adjustments that had to be made during prior sessions in choosing the bolus and first hourly infusion rate.
14. Complete at least 3 consecutive dialyses using this

protocol to determine the best bolus dose, hourly rate and stop time. If after 3 treatments, heparin dosage is still being adjusted, continue to do ACT testing until at least 1 treatment is completed without changing the heparin dose. After that this protocol does not need to be followed unless clinical indications arise.

If clinical indications of problems arise (e.g. clots noted in dialyzer or blood lines, or signs of bleeding) while the patient is being treated with a previously established heparin dose, this protocol of ACT checks and heparin dose adjustments should again be followed while giving the patient's usual initial bolus and first hourly heparin dose, to determine whether further adjustments are now required.

**Guideline**

Normal intensity heparinization ACT range 150-250 sec
Low intensity heparinization ACT range 100-150 sec

**Supporting Documents** *(References, Industry Best Practice, Legislation, etc)*

Nephrology Nursing Standards of Practice and Guidelines for Care ANNA

Contemporary Nephrology Nursing: Principles and Practice, Second Edition-American Nephrology Nurses' Association 2006

**Linkages**

ACT CLP-150,Heparin-Low Intensity CLP-180,Heparin-free Dialysis CLP-190,Changing Dialyzer/Bloodlines TBS-010

**Key Words**

ACT anticoagulation heparin system clotting

**Definitions & Acronyms**

| | |
|---|---|
| **ACT** | Activated clotting time |
| | |

**Policy History**

| | |
|---|---|
| **Policy Name** (if different) | |
| **Policy #** (if different) | |
| **Date(s) Revised** | |

## Hemodialysis Heparin Dosing Flowsheet- Full intensity heparin

Patient:_____

| | Date | | Date | | Date |
|---|---|---|---|---|---|
| **Time due** | **Pre ACT:_____** (Normal 68-132) | **Time due** | **Pre ACT:_____** (Normal 68-132) | **Time due** | **Pre ACT:_____** (Normal 68-132) |
| | Heparin bolus _____u Omit initial dose if >150 Hourly rate_____u/hr | | Heparin bolus _____u Omit initial dose if >150 Hourly rate_____u/hr | | Heparin bolus _____u Omit initial dose if >150 Hourly rate_____u/hr |

| | | | | | |
|---|---|---|---|---|---|
| | **15 Min ACT:**<br>_____<br>(Target 150-250)<br>If ACT< 150 give 500-1,000 u bolus<br>If ACT > 300, reduce infusion to 500 u/hr<br>**Action taken:** | | **15 Min ACT:**<br>_____<br>(Target 150-250)<br>If ACT< 150 give 500-1,000 u bolus<br>If ACT > 300, reduce infusion to 500 u/hr<br>**Action taken:** | | **15 Min ACT:**<br>_____<br>(Target 150-250)<br>If ACT< 150 give 500-1,000 u bolus<br>If ACT > 300, reduce infusion to 500 u/hr<br>**Action taken:** |
| | **60 Min ACT:**<br>_____<br>(Target 150-250)<br>if ACT<150- increase hourly rate by 500-1,000 u<br>if ACT >250 decrease hourly rate by 500-1,000 u<br>**Action taken:** | | **60 Min ACT:**<br>_____<br>(Target 150-250)<br>if ACT<150- increase hourly rate by 500-1,000 u<br>if ACT >250 decrease hourly rate by 500-1,000 u<br>**Action taken:** | | **60 Min ACT:**<br>_____<br>(Target 150-250)<br>if ACT<150- increase hourly rate by 500-1,000 u<br>if ACT >250 decrease hourly rate by 500-1,000 u<br>**Action taken:** |
| | **120 min ACT:**<br>_____<br>(Target 150-250)<br>if ACT<150- increase hourly rate by 500-1,000 u<br>if ACT >250 decrease hourly rate by 500-1,000 u<br>**Action taken:** | | **120 min ACT:**<br>_____<br>(Target 150-250)<br>if ACT<150- increase hourly rate by 500-1,000 u<br>if ACT >250 decrease hourly rate by 500-1,000 u<br>**Action taken:** | | **120 min ACT:**<br>_____<br>(Target 150-250)<br>if ACT<150- increase hourly rate by 500-1,000 u<br>if ACT >250 decrease hourly rate by 500-1,000 u<br>**Action taken:** |
| | **180 min ACT:**<br>_____<br>(normal 150-180)<br>if ACT<150- increase hourly rate by 500-1,000 u<br>if ACT >180 decrease hourly rate by 500- | | **180 min ACT:**<br>_____<br>(normal 150-180)<br>if ACT<150- increase hourly rate by 500-1,000 u<br>if ACT >180 decrease hourly rate by 500- | | **180 min ACT:**<br>_____<br>(normal 150-180)<br>if ACT<150- increase hourly rate by 500-1,000 u<br>if ACT >180 decrease hourly rate by 500- |

| | | | | | |
|---|---|---|---|---|---|
| | 1,000 u<br>**Action taken:** | | 1,000 u<br>**Action taken:** | | 1,000 u<br>**Action taken:** |
| | Heparin stop time:_____ | | Heparin stop time:_____ | | Heparin stop time:_____ |
| | **If fistula or graft** | | **If fistula or graft** | | **If fistula or graft** |
| | **ACT pre discontinuation:** ____ (Target 100-120) | | **ACT pre discontinuation:** ____ (Target 100-120) | | **ACT pre discontinuation:** ____ (Target 100-120) |
| | **Circuit clear?**<br>Art chamber_____ ____<br>Dialyzer_____ _____<br>Ven chamber_____ ___ | | **Circuit clear?**<br>Art chamber_____ ____<br>Dialyzer_____ _____<br>Ven chamber_____ ___ | | **Circuit clear?**<br>Art chamber_____ ____<br>Dialyzer_____ _____<br>Ven chamber_____ ___ |
| | Sites held x ____min<br>Art x ____min<br>Ven | | Sites held x ____min<br>Art x ____min<br>Ven | | Sites held x ____min<br>Art x ____min<br>Ven |
| | Plan for next treatment:<br>Bolus:_____u<br>Hourly rate:_____u/hr<br>Stop time:_____ | | Plan for next treatment:<br>Bolus:_____u<br>Hourly rate:_____u/hr<br>Stop time:_____ | | Plan for next treatment:<br>Bolus:_____u<br>Hourly rate:_____u/hr<br>Stop time:_____ |
| | Completed by:<br>_____<br>_____RN | | Completed by:<br>_____<br>_____RN | | Completed by:<br>_____<br>____RN |

Notes:

1) Please complete for 3 consecutive treatments or until one complete treatment without adjustments
2) Leave the worksheet in the Patient Chart
3) Target ACT values provided are for **Full intensity heparinization** only

# APPENDIX B

## Heparin Low Intensity Protocol

Eastern Health

Appendix B

| Policy Name: HEPARIN –LOW INTENSITY | Clinical Practice CLP–170 |
|---|---|
| **Issuing Authority** (sign & date) | **Norma Baker Interim Chief Operating Officer Adult & Acute Care ( St. John's)** |
| **Office of Administrative Responsibility** | Dialysis Unit |
| **Author** | Cathy Cake Clinical Educator ,Dr.Brendan Barrett Nephrologist |
| **Level** | Level two |
| **Original Approval Date** | March/ 09 |
| **Effective Date** | March /09 |
| **Review Date** | March /010 |
| **Revision Date(s)** | |

## Overview

Anticoagulation with heparin is the usual way of preventing clotting in the extracorpeal system. Routine full intensity heparin prescriptions are for patients at normal risk for bleeding, whereas dialysis with low intensity heparin or heparin free dialysis may be prescribed in those at higher risk for bleeding.

## POLICY

- Low intensity heparinization may be implemented by the RN for a given dialysis session on the basis of his/her pre dialysis assessment.
- The decision about what level of heparinization to use in subsequent dialysis sessions should be made in consultation with the nephrologists.

## Scope

Registered nurses working in Dialysis Units within Eastern Health upon completion of Hemodialysis orientation

## Purpose

To prevent or minimize clotting in the extracorporeal system, while also maintaining an acceptable risk of bleeding.

### Procedure

#### Procedure for patients with AV fistulas or grafts

1. Assess for any bleeding or potential risk for bleeding.
2. Check patient's prescription for heparin if established and verify that this is appropriate to current bleeding risk. If not, assess whether low-intensity heparin will be given as per this policy or heparin free dialysis is required. Heparin free dialysis is indicated in the following clinical situations:

- Active pericarditis.
- Recent surgery with bleeding complications.
- Recent surgery after which bleeding would be very dangerous such as vascular, cardiac, retinal, brain, and renal transplant.
- Severe coagulopathy (e.g. INR > 4 or PTT > 70 secs).
- Severe thrombocytopenia (plts < 30).
- Intracerebral hemorrhage, or suspected increased risk of intracerebral hemorrhage due to a recent head injury, or severe hypertension (>200/115mmHg), especially with patients exhibiting changes in neurological status.
- Any active bleeding not easily controlled prior to dialysis.
- Recent patient falls with associated hematomas.
- For dialysis within 24 hours of a new AV graft insertion or

revision, or insertion of a PD catheter.
- ❖ Dialysis within 4 hours of arterial puncture (e.g. for angiography).
- ❖ Known or suspected heparin Induced thrombocytopenia

3. Please consult with the responsible nephrologist if there is any concern or uncertainty about which heparin policy to apply. If the decision is to provide heparin free dialysis, please refer to the heparin free dialysis policy, otherwise continue as below.

4. If the patient already has an order for heparin intended to achieve full intensity ACT targets, reduce the bolus and infusion by 50%. If the patient does not have an existing order for a dose of heparin intended to achieve full intensity ACT targets, please ask the nephrologist to provide an initial order appropriate to low-intensity heparinization.

5. If using the algorithm for the current dialysis session, measure baseline ACT prior to heparin bolus. Please see section B for further details.

6. Draw up bolus dose of heparin and attach to arterial needle.

7. Instill bolus dose following cannulation of both needles 3-5 minutes prior to initiation of dialysis.

8. Start continuous heparin infusion with initiation of dialysis.

9. Heparin infusion rates are monitored, at least once per hour, during the dialysis treatment as part of the normal routine monitoring.

10. The extracorporeal circuit is assessed for any visible signs of fibrin/clot formation.

11. Discontinue infusion one hour prior to the

discontinuation of dialysis unless otherwise ordered.

12. During the rinseback procedure the extracorporeal circuit is assessed for any visible signs of clotting/fibrin formation.

13. Record hemostasis time in patient's chart and notify nephrologist if prolonged.

**Procedure for patients with hemodialysis catheters**

Procedure is as above with the following exceptions:

a) Follow catheter opening policy for administration of heparin bolus

b) Continue heparin infusion until discontinuation of dialysis

**Heparinization during dialysis for patients already receiving heparin or low-molecular weight heparin IV or SC.**

If the patient is receiving an IV unfractionated heparin infusion or SC unfractionated heparin at therapeutic doses, no additional heparin will be required for dialysis. The protocol for monitoring and adjusting the heparin as already ordered should be followed.

If the patient is being treated with therapeutic doses of low-molecular weight heparin (IV or SC), no additional heparin will be required for dialysis. The protocol for monitoring and adjusting the low-molecular weight heparin as already ordered should be followed.

If the patient is receiving low dose prophylactic unfractionated or low-molecular weight heparin S/C, continue with the usual dialysis heparin orders for low-intensity heparinization.

**Section B: Determining heparin requirements (see Flowsheet)**

1. Measure the baseline ACT pre dialysis. When access being

used is a fistula or graft, draw the baseline sample directly from the fistula needle prior to flushing the needle with 0.9% NaCl. Normal range in uremic patients can be 68-132 seconds with a mean of 100 seconds.

2. 1.0 to 1.5 times the patient's baseline number provides an ACT value range adequate for low intensity heparinization for the majority of dialysis patients.
3. Administer the ordered bolus dose of heparin. However, if the baseline ACT is greater than 100 further prolongation may be associated with bleeding and a bolus is not necessary. Omit the initial bolus of heparin in this case.
4. Turn on the hourly heparin infusion. If the baseline ACT is greater than 100, reduce the hourly rate to 300-500 units.
5. 15 minutes later, perform a 2nd ACT to determine the patient's response to the heparin bolus dose. This target should be within 100-150 seconds. Re-bolus with 500 – 1,000 units of heparin if the ACT is below the target range. If the ACT is > 200, reduce the infusion to 300 units per hour until the 60 minute ACT check.
6. At 60 minutes into the dialysis treatment take a 3rd ACT to determine the effect of the hourly rate. This target ACT should be within 100-150 seconds. Increase the hourly rate by 500- 1,000 units if the ACT is below the target range. Reduce the hourly rate by 500- 1,000 units if the ACT is above the target range. The hourly infusion rate will usually range from 300 units to 1,500 units depending on the patients' sensitivity to heparin and the heparin half-life.
7. At 120 minutes take a 4th ACT. The target ACT should be 100-150 seconds. The heparin dose may again be adjusted. Increase the hourly rate by 500- 1,000 units if the ACT is below the target range. Reduce the hourly rate by 500- 1,000 units if the ACT is above the target range.
8. Note the time heparin will be stopped prior to the end of dialysis (usually 60 minutes for fistulae and grafts, end of dialysis session for catheters).
9. At 180 minutes into treatment, take a 5th ACT unless you plan to stop heparin within the next 60 minutes. The target ACT at this stage is 100-130 seconds (reflecting the bolus wearing off and the anticipated end of dialysis session).

The heparin dose may again be adjusted. Increase the hourly rate by 500- 1,000 units if the ACT is below the target range. Reduce the hourly rate by 500- 1,000 units if the ACT is above the target range.

10. If hemostasis time was prolonged after needle removal in the last prior dialysis session or the system clotted out following heparin discontinuation, prior to discontinuing dialysis through either a fistula or AV graft on this occasion, take a final ACT to determine the effect of stopping the heparin infusion. The target ACT is 100-120 seconds.
11. Document the clearance of the dialyzer and drip chambers. A reduced blood flow and/or multiple alarm situations can affect the condition of the dialyzer.
12. Document the time for needle sites to stop bleeding. Acceptable time is ≤ 10 minutes.
13. In planning for second and subsequent dialyses using this protocol, consider the adjustments that had to be made during prior sessions in choosing the bolus and first hourly infusion rate.
14. Complete at least 3 consecutive dialyses using this protocol to determine the best bolus dose, hourly rate and stop time. If after 3 treatments, heparin dosage is still being adjusted, continue to do ACT testing until at least 1 treatment is completed without changing the heparin dose. After that this protocol does not need to be followed unless clinical indications arise.

If clinical indications of problems arise (e.g. clots noted in dialyzer or blood lines, or signs of bleeding) while the patient is being treated with a previously established heparin dose, this protocol of ACT checks and heparin dose adjustments should again be followed while giving the patient's usual initial bolus and first hourly heparin dose, to determine whether further adjustments are now required

**Guideline**

| | |
|---|---|
| Normal intensity heparinization ACT range | 150-250 sec |
| Low intensity heparinization ACT range | 100-150 sec |

**Supporting Documents** *(References, Industry Best Practice, Legislation, etc)*

Nephrology Nursing Standards of Practice and Guidelines for Care ANNA

Contemporary Nephrology Nursing: Principles and Practice, Second Edition-American Nephrology Nurses' Association 2006

**Linkages**

ACT CLP-150,Heparin-Full intensity CLP-160,Heparin-free Dialysis CLP-180,Changing Dialyzer/Bloodlines TBS-010

**Key Words**

ACT anticoagulation heparin system clotting

**Definitions & Acronyms**

| | |
|---|---|
| **ACT** | Activated Clotting Time |
| | |

**Policy History**

| | |
|---|---|
| **Policy Name** (if different) | |
| **Policy #** (if different) | |
| **Date(s) Revised** | |




**Appendix B**

## Not a Permanent Record

## Hemodialysis Heparin Kinetic Flowsheet- Low intensity heparin

**Patient:**_____

| Time due | **Date** Pre ACT:_____ (Normal 68-132) | Time due | **Date** Pre ACT._____ (Normal 68-132) | Time due | **Date** Pre ACT:_____ (Normal 68-132) |
|---|---|---|---|---|---|
| | Heparin bolus _____u<br>Omit initial dose if >100<br>Hourly rate_____u/hr | | Heparin bolus _____u<br>Omit initial dose if >100<br>Hourly rate_____u/hr | | Heparin bolus _____u<br>Omit initial dose if >100<br>Hourly rate_____u/hr |
| | **15 Min ACT:** _____<br>(Normal 100-150)<br>If ACT< 100 give 500-1,000 u bolus<br>If ACT > 200, reduce infusion to 300 u/hr<br>**Action taken:** | | **15 Min ACT:** _____<br>(Normal 100-150)<br>If ACT< 100 give 500-1,000 u bolus<br>If ACT > 200, reduce infusion to 300 u/hr<br>**Action taken:** | | **15 Min ACT:** _____<br>(Normal 100-150)<br>If ACT< 100 give 500-1,000 u bolus<br>If ACT > 200, reduce infusion to 300 u/hr<br>**Action taken:** |
| | **60 Min ACT:** _____<br>(Normal 100-150)<br>if ACT<100- increase hourly rate by 500-1,000 u<br>if ACT >150 decrease hourly rate by 500-1,000 u<br>**Action taken:** | | **60 Min ACT:** _____<br>(Normal 100-150)<br>if ACT<100- increase hourly rate by 500-1,000 u<br>if ACT >150 decrease hourly rate by 500-1,000 u<br>**Action taken:** | | **60 Min ACT:** _____<br>(Normal 100-150)<br>if ACT<100- increase hourly rate by 500-1,000 u<br>if ACT >150 decrease hourly rate by 500-1,000 u<br>**Action taken:** |
| | **120 min ACT:** _____<br>(normal 100-150)<br>if ACT<100- increase hourly rate by 500-1,000 u<br>if ACT >150 decrease hourly rate by 500-1,000 u<br>**Action taken:** | | **120 min ACT:** _____<br>(normal 100-150)<br>if ACT<100- increase hourly rate by 500-1,000 u<br>if ACT >150 decrease hourly rate by 500-1,000 u<br>**Action taken:** | | **120 min ACT:** _____<br>(normal 100-150)<br>if ACT<100- increase hourly rate by 500-1,000 u<br>if ACT >150 decrease hourly rate by 500-1,000 u<br>**Action taken:** |
| | **180 min ACT:** _____<br>(normal 100-130)<br>if ACT<100- increase hourly rate by 500-1,000 u<br>if ACT >150 decrease hourly rate by 500-1,000 u<br>**Action taken:** | | **180 min ACT:** _____<br>(normal 100-130)<br>if ACT<100- increase hourly rate by 500-1,000 u<br>if ACT >150 decrease hourly rate by 500-1,000 u<br>**Action taken:** | | **180 min ACT:** _____<br>(normal 100-130)<br>if ACT<100- increase hourly rate by 500-1,000 u<br>if ACT >150 decrease hourly rate by 500-1,000 u<br>**Action taken:** |
| | Heparin stop time:_____ | | Heparin stop time:_____ | | Heparin stop time._____ |

Eastern Health

POLICY NAME

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**Appendix B**

| | | | | | |
|---|---|---|---|---|---|
| | **If fistula or graft**<br>**ACT pre discontinuation:** ____<br>(target 100-120) | | **If fistula or graft**<br>**ACT pre discontinuation:** ____<br>(target 100-120) | | **If fistula or graft**<br>**ACT pre discontinuation:** ____<br>(target 100-120) |
| | **Circuit clear?**<br>Art chamber_____<br>Dialyzer_____<br>Ven chamber_____ | | **Circuit clear?**<br>Art chamber_____<br>Dialyzer_____<br>Ven chamber_____ | | **Circuit clear?**<br>Art chamber_____<br>Dialyzer_____<br>Ven chamber_____ |
| | Sites held x ____min Art<br>x ____min Ven | | Sites held x ____min Art<br>x ____min Ven | | Sites held x ____min Art<br>x ____min Ven |
| | Plan for next treatment:<br>Bolus:_____u<br>Hourly rate:_____u/hr<br>Stop time:_____ | | Plan for next treatment:<br>Bolus:_____u<br>Hourly rate:_____u/hr<br>Stop time:_____ | | Plan for next treatment:<br>Bolus:_____u<br>Hourly rate:_____u/hr<br>Stop time:_____ |
| | Completed by:<br>_____RN | | Completed by:<br>_____RN | | Completed by:<br>_____RN |

Notes:
1) Please complete for 3 consecutive treatments or until one complete treatment without adjustments
2) Leave the worksheet in the Patient Chart.
3) Normal values are provided and are for **Low intensity heparinization** only