Complications in abdominal surgery: Assessment, prediction and prevention
Slankamenac, Ksenija

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Chapter 5

Clinical Study Protocol

Does Terlipressin Improve Renal Outcome after Liver Surgery – A Double-Blinded Randomized Control Trial (TIROL-Trial)

Ksenija Slankamenac, Milo A. Puhan, Pierre-Alain Clavien

References


# STUDY SYNOPSIS

<table>
<thead>
<tr>
<th>Sponsor-Investigator</th>
<th>University Hospital of Zurich, Department of Visceral Surgery and Transplantation</th>
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<tbody>
<tr>
<td>Study Title:</td>
<td>Does Terlipressin Improve Renal Outcome after Liver Surgery – A Double-Blinded Randomized Control Trial (TIROL-Trial)</td>
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<tr>
<td>Short Title/Study ID:</td>
<td>TIROL-Trial</td>
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<td>Version 1 / 06.12.2012</td>
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<td>Clinical study phase III</td>
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<td>Methodology:</td>
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<td>Study Duration:</td>
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<td>Study Center(s):</td>
<td>Single-center</td>
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<tr>
<td>Investigator(s):</td>
<td>Prof. Dr. med. Pierre-Alain Clavien, PhD Klinikdirektor University Hospital of Zurich Department of Visceral Surgery and Transplantation Rämistrasse 100 8091 Zurich, Switzerland Tel: 044 255 33 00 Fax: 044 255 44 49 Email: <a href="mailto:clavien@access.uzh.ch">clavien@access.uzh.ch</a></td>
</tr>
</tbody>
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| Objective(s)/Outcome(s): | Primary endpoint:  
- serum creatinine peak level within 48 hours post-operative.  
Secondary endpoints:  
- renal function:  
  - the urinary output/24h will be measured from POD 0 to 3  
  - Daily measuring of NGAL in the urine from POD 0 – 3  
  - Glomerular filtration rate from POD 0 – 3  
  - Need for hemofiltration and/or hemodialysis from POD 0 to discharge  
- In-hospital morbidity after surgery:  
  - comprehensive complication index (CCI) from POD 0 to discharge  
  - Clavien-Dindo score (grade I to IVb) from POD 0 to discharge  
- liver function:  
  - serum levels of AST, ALT, bilirubin, Factor V, blood platelets, leukocytes and INR from POD 0-5  
- In-hospital mortality from POD 0 to discharge  
- Length of special care unit and length of hospital stay (days) |
| Number of Subjects:  | Total number: n=150 (75 for each group)                                           |
| **Diagnosis and Main Inclusion Criteria:** | We will enrol all patients undergoing an elective liver resection with a moderate to high risk for post-operative acute renal failure after liver surgery from the Department of Visceral and Transplantation Surgery of the University Hospital of Zurich. Based on those assumptions for the benefit-harm analysis we investigated that a benefit-harm balance is reached at a 12% risk for post-operative ARF. Translating this 12% risk for post-operative ARF on our recently developed and validated prediction score for ARF after liver surgery, patients will need five points or more in the pre-operative assessment of the predictors to be enrolled in the trial. |
| **Main Exclusion Criteria:** | - < 18 years  
- liver cirrhosis  
- coronary insufficiency with ST elevation or ST depression in the intra-operative ECG as signs of an acute coronary syndrome  
- pregnancy and breast feed |
| **Study Product, Dose, Route, Regimen:** | **Study drug:** terlipressin (Glypressin®) in combination with human albumin (Albumin Human Octapharma 20% ®, Octapharma)  
**Dose:** 0.5 mg terlipressin dissolved in 100 mL Ringer lactate solution intravenous during 30 minutes for all 4 hours (6x/day) for next 48 hours postoperatively. Additionally, once per day an intravenous infusion of human albumin (Albumin Human Octapharma 20% ®, Octapharma) at an initial dose of 1g/kg body weight at the first day, followed by 20g/day for the next 48 hours. |
| **Duration of administration:** | Single drug administration for 30 minutes, 6x/day, totally for 48 hours postoperatively |
| **Reference therapy, Dose, Route, Regimen:** | Control group will receive an intravenous administration of 100 mL Ringer lactate solution at the same flow rate and time points as the terlipressin patients (all 4 hours (6x/die), totally for 48 hours postoperatively. They will also receive 100 mL Ringer lactate solution once per day intravenously instead of human albumin for the first 48 hours postoperatively |
| **Study Schedule:** | Start July 2013 (planned)  
Duration: 5 years  
Anticipated End: July 2018 |
| **Statistical Methodology:** | Uni- and multivariate linear/logistic regression analysis. |
| **GCP Statement:** | This study will be conducted in compliance with the protocol, the current version of the Declaration of Helsinki, and ICH-GCP as well as all national legal and regulatory requirements. |
## STUDY SCHEDULE

<table>
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<tr>
<th>Study Periods</th>
<th>Screening</th>
<th>Treatment</th>
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<td>Day</td>
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<td><strong>Not study specific examinations</strong></td>
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<td>Adverse Events</td>
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<sup>1</sup> If not performed during the previous 6 months
INTRODUCTION

Acute renal failure (ARF) is a severe post-operative complication and strongly associated with mortality and increased costs\(^1\). The incidence of post-operative ARF after liver surgery is with 15% relatively high\(^4\). ARF is also associated with an increased length of hospital and intensive care unit stay\(^4\). More than a fourth of those patients (26.7%) with post-operative ARF after liver surgery need further treatment with hemofiltration\(^4\). In 5% of patients ARF is irreversible and patients develop chronic renal failure\(^4\). Therefore, effective treatment strategies are needed to reduce the incidence and severity of ARF after liver surgery and to prevent hemofiltration.

Today, the standard care treatment for patients with post-operative ARF is a combination in the management of volume/fluid, electrolytes, acid-based disorder, hypertension, uremia and nutritional intake\(^6\). Nephrotoxic medications such as e.g. aminoglycosides, contrast agent, nonsteroidal anti-inflammatory drugs are strictly avoided in case of post-operative ARF\(^8,9\). Additionally, in patients with kidney failure and advanced liver cirrhosis, a combination called hepatorenal syndrome type I, terlipressin in combination with human albumin significantly improves the renal function and survival\(^10-14\). The treatment mechanism of terlipressin in patients with hepatorenal syndrome type I is not fully understood\(^15-17\). Although terlipressin is sometimes used in clinical practice in selective patients of ARF after liver surgery when standard care treatment fails, there is no evidence for or against the preventive use of terlipressin in patients with ARF after liver surgery.

Whether or not to use terlipressin as preventive treatment strategy against ARF depends on its benefit harm balance. Although terlipressin is a potent vasoconstrictor and may be effective to prevent ARF, it is associated with minor and major adverse effects. Frequent but not life threatening side effects (1-10%) of terlipressin include skin pallor, water retention, headache, nausea, diarrhea, abdominal cramps, arterial hypertension and weakness of the legs\(^12,18,19\). The literature describes a wide range of life threatening (severe) adverse effects (9-22%) of terlipressin in patients with hepatorenal syndrome type I\(^12,18,19\) including cardiac arrhythmia, angina pectoris or myocardial infarction. Because of these potential severe harm effects of terlipressin patients receiving preventive terlipressin need to be carefully selected. In patients at low risk for ARF it is very likely that the harms caused by terlipressin outweigh its benefits. At moderate to high risk for ARF terlipressin may provide a net benefit. Therefore, our aim is to perform a double-blinded randomized controlled trial and to investigate for the first time if terlipressin improves the renal outcome in patients at moderate to high risk for ARF after liver surgery.

STUDY DESIGN

We aim to address whether terlipressin improves the renal outcome after liver surgery. Therefore we are planning to conduct a double-blinded randomized control trial. We will randomize patients undergoing any kind of liver surgery and being at increased moderate to high risk (defined below) for post-operative ARF into a control group receiving post-operative a placebo or into a group receiving...
post-operatively terlipressin in combination with human albumin as it is the standard treatment for hepatorenal syndrome type I.

**CONTROL GROUP:** Patients receiving a post-operative placebo to preserve the renal function

**TERLIPRESSIN GROUP:** Patients receiving a post-operative intravenous terlipressin treatment in combination with human albumin to preserve the renal function

**PARTICIPANTS RECRUITMENT**

**Inclusion criteria**

We will enrol all patients undergoing an elective liver resection with a moderate to high risk for post-operative ARF after liver surgery from the Department of Visceral and Transplantation Surgery of the University Hospital of Zurich. We will restrict the trial to patients at a certain risk because it is unlikely that terlipressin will provide more benefits than harms in patients at low risk. To formally explore the threshold for ARF risk above which to include patients we performed a formal benefit harm analysis based on data that are already available and based on some assumptions we had to make.

We used the Gail/National Cancer Institute (NCI) approach for the assessment of benefit and harm of terlipressin for primary prevention of ARF events after liver surgery. We selected the Gail/NCI approach because it considers multiple outcomes of varying importance and provides a single benefit and harm comparison estimate. However this approach requires data from additional sources on baseline risks and relative weights of outcomes that reflect their importance. It also considers competing risks such as mortality. We assumed a relative risk (RR) for ARF (benefit) for terlipressin vs placebo of 0.7, a RR for harm outcomes of 1.5, an incidence of post-operative ARF of 5-35% (benefit) and harm outcomes such as post-operative myocardial infarction (5%)\(^2\), stroke (1%)\(^2\) and mesenteric ischemia (<1%)\(^2\) (Table 1). The wide range for the incidence of post-operative ARF of 5-35% was chosen to find the threshold where terlipressin provides a net benefit. Based on those assumptions for the benefit-harm analysis we investigated that a benefit-harm balance is reached at a 12% risk for post-operative ARF (Table 1 & 2).

Translating this 12% risk for post-operative ARF on our recently developed and validated prediction score for ARF after liver surgery, patients will need five points or more in the pre-operative assessment of the predictors to be enrolled in the trial (Table 2 & 3).

**Exclusion criteria**

We will exclude patients with:

- < 18 years
- liver cirrhosis
- coronary insufficiency with ST elevation or ST depression in the intra-operative ECG as signs of
Recruitment

All consecutive patients planned for elective liver surgery and at risk for ARF (≥ 12% risk) will be assessed for study eligibility by the principal investigator and/or senior staff surgeons of the Department of Visceral and Transplantation Surgery of the University Hospital of Zurich. If patients are willing to participate, a physician will inform patients about the study orally and in written form. Patients who are willing to participate, fulfilling the inclusion/exclusion criteria and providing written informed consent will be randomly assigned after arrival on the special care unit to the control or the terlipressin group. All patient information and data will be anonymously reported (Figure 1).

INTERVENTION AND COMPARISON

Surgical procedure

The liver surgery will be performed exclusively by surgeons specialized in HPB surgery according to the international surgical standards for liver surgery. Usually, for the liver surgery, a low central venous pressure (CVP) from 0 to 5 mmHg is required to prevent a high intra-operative blood loss\textsuperscript{24-26}. But in case of increased co-morbidities such as pre-operative cardiac or renal insufficiency the CVP will be appropriately increased as it has been usually done in such cases. The parenchymal transections will be done with the Kelly clamp crushing technique and if necessary under the Pringle manoeuvre to decrease the blood loss too\textsuperscript{27-30}. The tourniquet technique around the portal triad will be used as the common Pringle manoeuvre technique\textsuperscript{26}.

Study start

After admission on the special care unit we will start with the drug application according to the randomization.

CONTROL GROUP: Patients receiving post-operative placebo (Ringer lactate solution) treatment to preserve the renal function

TERLIPRESSIN GROUP: Patients receiving a post-operative intravenous terlipressin treatment in association with human albumin to preserve the renal function

Study drug

The study drug will immediately start at admission to the special care unit. The patients will stay in the special care unit during the whole study drug administration of 48 hours after surgery. Patients in the terlipressin group will receive all 4 hours an intravenous administration of terlipressin (Glypressin®) at
a dose of 0.5 mg during 30 minutes. The terlipressin medication will be dissolved in 100 mL of Ringer lactate solution. The study drug (terlipressin) will be given for 2 days (48 hours). Patients of the terlipressin group will additionally receive once per day an intravenous infusion of human albumin (Albumin Human Octapharma 20% ®, Octapharma) at an initial dose of 1g/kg body weight at the first day, followed by 20g/day for the next 48 hours (Figure 1). See also the investigator’s brochure with the “Fachinformation des Arzneimittel-Kompendium der Schweiz” to terlipressin and human albumin.

Whereas patients in the placebo group will receive an intravenous administration of 100 mL Ringer lactate solution at the same flow rate and time points as the terlipressin patients. Additionally those controlled patients will also receive 100 mL Ringer lactate solution once per day intravenously instead of human albumin for the first 48 hours postoperatively (Figure 1).

Vital signs (blood pressure and heart rate) will be checked all 30 minutes after start of terlipressin for 2 hours (half-life of terlipressin is 53-55 min.). In the meantime when no terlipressin application is given the vital signs will be checked all two hours until the study endpoint. We will also check daily the ECG and perform daily neurological, abdominal and peripheral arterial examinations of all patients for 48 hours post-operatively.

Masking/Blinding against drugs

Terlipressin and human albumin (HA) should be made indistinguishable to guarantee the double-blinding in this trial and to minimize the risk of differential information bias for daily examinations.

Therefore the “Kantonsapotheke Zurich” (KAZ) will blind the human albumin, so that the infusion tubes will have identical appearance (e.g. color, taste, smell ect.) as the placebo tubes. The KAZ will label those tubes for patients in the control group as “TIROL trial HA: arm A” whereas the tubes for patients in the terlipressin group will be labeled as “TIROL trial HA: arm B”.

Terlipressin will not be blinded by the KAZ because terlipressin has to be administrated in a short infusion over 1 hour. Therefore the nurses will prepare each terlipressin infusion in neutral tubes on that
time point when it has to be given to the patient, because terlipressin in solution is not stable enough to be stored and prepared by the KAZ. The infusion tubes will have an identical appearance (e.g. color, taste, smell etc.) as the placebo tubes, so that it will not be determined for patients nor the responsible surgeons treating team from all services in which arm the patients is randomized and if he/she gets terlipressin or a placebo infusion. The nurses will label the neutral tubes by “TIROL Trial: arm A or arm B”. Neither patients nor the responsible surgeons treating team from all services will know that arm A is equal to the control group, and arm B means the terlipressin group. Those neutral tubes and infusions for the terlipressin administration will be offered from the KAZ. The data manager (KS) and/or responsible HPB-fellow will prescribe the right doses and administration time points of the study drug after randomization for the whole 48 hours period. In case of serious adverse events (SAE) (see definition in chapter 12.5.) the data manager (KS) and/or responsible HPB-fellow as well as the nurses will have the access to the subject’s code. They will open the blinding and inform if the SAE occurred due to the treatment.

Storage Conditions
Terlipressin has to be stored at 2 - 8°C in a carton box protected from the light in a refrigerator. The human albumin and Ringer lactate infusion has to be stored at room temperature (<25°C) also protected from the light. All medicaments (terlipressin, human albumin and Ringer lactate) are often used on the special care unit so that we do not have to install new refrigerators or stock. They will be stored in the preferred way in a limited access storage area under recommended storage conditions. The principal investigator will maintain accurate and adequate records including dates, lot number, quantities received and individual usage.

Study drug accountability
The principal investigator will maintain accurate and adequate records including dates, lot number, quantities received and individual usage. The data manager (KS) and/or responsible HPB-fellow will prescribe the right doses and administration time points of the study drug or placebo after randomization for the whole 48 hours period (please see also 4.2.1 and 4.2.2). They will make sure that the records are completed with the drug dose, patient, date of birth, date, time and individual removing drug from the central inventory. If study drug is administered, the worksheet should note the date, actual time that the drug was given and the refrigerator temperature. If the drug is not administered, even though a dose was prepared, then a note should record that drug was destroyed. This worksheet will be processed by the responsible nurses on the ICU/IMC, but daily checked and controlled by the data manager and/or responsible HPB fellow who are prescribing the study drug.
Early Withdrawal of Subjects

The patient will be advised that he/she is free to withdraw from the trial at any time. Also, the investigators may remove a patient if he/she feels this action is in the best interest of the patient.

Patient removal may occur as the result of an (severe) adverse event ((S)AE) that in the judgment of the investigator places an unacceptable consequence or risk for the patient. Notification of the discontinuation will be clearly documented on the patient’s case report form (CRF).

When and how to withdraw subjects

We will immediately stop the terlipressin in combination with human albumin administration (the medicaments can be stopped without further consequences) in case of complications such as an AE or even severe adverse event (SAE). Those patients will consequently receive the standard care treatment and will be continuously supervised by the principal and/or co-investigators. We will also report all SAE to the Swissmedic as well as independent ethic committee as it is describe in chapter 11.5.

Data collection of withdrawn subjects

We require the collection and maintenance of complete study data. This also includes information on subjects who withdraw from a clinical investigation, whether the subject decides to discontinue participation in the clinical trial or is discontinued by the investigators because the subject no longer qualifies under the protocol (e.g. due to a significant AE or failure to cooperate with study requirements). However, the withdrawal does not extend to the data already obtained during the time the subject was enrolled. Therefore we will collect all data collected up to the point of withdrawal and will be maintained in the database and included in subsequent analyses, as appropriate.

OUTCOME

Primary endpoint

Our primary endpoint will be the serum creatinine peak level within 48 hours post-operative.

Using our database of liver surgery the correlation between the post-operative serum creatinine peak level within 48 hours and the incidence of post-operative ARF is strong (Spearman’s rho r=0.59, p<0.001). The odds ratio for ARF is 2.18 per increase of post-operative serum creatinine of 10 µmol/L (95% confidence interval: 1.84-2.58, p<0.001) what also shows a significant association between ARF and the creatinine peak level. Therefore we believe that it is justified to use the serum creatinine peak level as the primary endpoint and surrogate for ARF.

Secondary endpoints

We will investigate several important secondary endpoints post-operatively. All laboratory examinations are daily and routinely performed in all liver resected patients from the first POD until
discharge. We will only examine routine lab values and therefore no additional costs will result for the patients. Below-mentioned parameters are secondary endpoints which we will be investigated in the analysis of the trial:

- Renal function:
  - the urinary output/24h will be measured from *POD 0 to 3*
  - Glomerular filtration rate from *POD 0 – 3*
  - Need for hemofiltration and/or hemodialysis (yes/no) from *POD 0 to discharge*

- In-hospital morbidity after surgery:
  - comprehensive complication index (CCI) from *POD 0 to discharge*
  - Clavien-Dindo score (grade I to IVb)\(^{31}\) from *POD 0 to discharge*

- Liver function:
  - serum levels of AST, ALT, bilirubin, Factor V, blood platelets, leukocytes and INR from *POD 0 to 5*

- In-hospital mortality from *POD 0 to discharge*

- Length of special care unit and length of hospital stay (days)

**SAMPLE SIZE CALCULATION**

Until now there is no study or trial investigating whether terlipressin is improving renal function after liver surgery. Therefore we looked at the literature for terlipressin treatment in hepatorenal syndromes type I. The literature showed a 30-58% reduction of the mean serum creatinine peak level in patients receiving a terlipressin treatment due to a hepatorenal syndrome type I\(^{12,19,32}\). Based on those results we assume a 30% difference in mean serum creatinine level between the treatment and control group and a standard deviation (SD) in patients with terlipressin that is smaller by about 20%, a power of 80% and a significance level of \(p\)-value \(\leq 0.05\). Based on the mean serum creatinine level of our patients after liver surgery observed earlier of 110 µmol/l (SD 70µmol/l) we will expect a mean serum creatinine level of the treatment group of 80 µmol/l (SD 55µmol/l). We will need 70 patients per group according to the sample size calculation. But we will increase the sample size to totally 150 patients due to an assumption of 5% protocol violation. Finally, we will enroll 75 patients per group in the trial.

In our center, we are performing about 55-60 liver surgeries per year with an increased risk for ARF (≥ 5 points in the ARF score). This will take three years to complete the trial.
**Multicenter Study**

To reduce the study period, we are planning to perform a multicentre trial. We are already in discussion with other interested liver centers worldwide but any contract is signed so far. As soon as the collaborative partners are signing the contracts, we will submit an amendment to the ethic committee of the Kanton Zürich.

**RANDOMIZATION**

Since we have a small to moderately sized trial we expect that simple randomization may no yield groups balanced in terms of confounders. Confounders for the association of treatment exposure and renal function are, based on the current literature and our knowledge, pre-existing chronic renal dysfunction, cardiovascular disease, diabetes, age, sex and increased pre-operative serum alanine-aminotransferase. Chronic renal failure is defined as a glomerular filtration rate of less than 60ml/min/1.73m$^2$ for all adults$^{33,34}$. Cardiovascular disease is defined as the presence of a coronary heart disease, previous coronary revascularization, cerebral arterial occlusive disease and/or peripheral vascular occlusive disease.

Therefore, we will use minimization, a dynamic way of randomization widely used in clinical trials for achieving a balance of prognostic factors and confounders across treatment groups and to ensure balance between groups with relatively small sample size. With the computer-based minimization, the allocation sequence will less be predictable and the allocation concealment is secured. The randomization will be performed by commonly used website (www.randomizer.at).

**BLINDING**

We will perform a *double blinded* study. Patients and the responsible surgeons treating team from all services (e.g. surgeons, ICU physicians, and residents) will be blinded to treatment allocation to minimize possible bias in patient management and in assessing outcomes. The procedure to get the drug indistinguishable and the guarantee of blinding are already described in chapter 4.2.2. In case of serious adverse events (SAE) (see definition in chapter 11.5.) we will open the blinding and inform if the SAE occurred due to the treatment.

**STATISTICS**

**Data management**

We will offer standardized and pilot-tested forms for the assessment of the baseline characteristics, intra-operative as well as post-operative parameters. We will also offer printed forms for the prescription of the drugs from POD 0 to 3. The data manager will store all documents in a safe and defined place. The
data will be entered in a central online database of our Clinical Trial Centre (SecuTrial) of the University Hospital of Zurich independently by two people and any discrepancy will be solved by consensus. The central online database will be anonymous and supervised by the data manager. The online database will have a central backup-server at the University Hospital of Zurich that regularly synchronizes with the online database (see also chapter 13).

Analytical Plan

We will perform an intention-to-treat (ITT) analysis so that all patients being intended to treat will also be analyzed in the statistics independently if the treatment procedure was per protocol or not. All patients will be analyzed according to that group which they were randomized for.

Statistical methods

Normality of distribution will be determined by the Kolmogorov-Smirnov test and quantile-quantile plots of dependent variables for all continuous variables.

In case of missing data we will use the multiple imputation technique. This process is performed multiple times (e.g. 10-20 times) so that we have multiple data sets which have to be combined to produce one overall analysis by standard procedures. This results in statistically valid inferences that properly reflect the uncertainty due to missing values.

We will use univariate linear regression analysis to test if the primary outcome (post-operative peak serum creatinine level) can significantly be reduced in the terlipressin compared to the control group. For the analysis of all secondary endpoints we will use the linear or logistic regression method. The main statistical analysis, we will adjust for baseline parameters that might not be well balanced between groups by randomization using multivariate linear or logistic regression analyses. We will conduct all analyses using STATA (version 12, Stata Corp., College Station, Texas).

Data Monitoring & Interim Analyses

We also plan to perform interim analysis. The interim analysis will take place strictly for safety, efficacy as well as sample size adjustment due to the fact that the sample size calculation based on another underlying disease. Due to the fact that terlipressin may still have a harmful effect despite of the benefit-harm analysis, we will perform the first interim analysis after randomizing the first five patients to the terlipressin group to increase the safety issues.

The interim analysis will be performed by an independent Data Monitoring Committee (DMC) (see also chapter 12.1). Our DMC will be comprised by the independent Clinical Trial Center of the University Hospital of Zurich. The DMC will be compromised by monitors who remain completely independent of the study investigators and have never received any honoraria from, or held stock in any of the manufacturers whose products are used in this trial. The DMC members will span the spectrum
from clinical experts with prior trial experience, a clinical trial methodologist, and a biostatistician. The specialist most experience in DMC work will chair the DMC. The DMC functions in an advisory rather than executive capacity and its duties are detailed in Table 4. When the DMC decide that a definitive answer to the trial question has been achieved (in terms of efficacy, safety, or futility) they will unblind the PI. These terms of reference and functions are derived from the principles established by the Data Monitoring Committees: Lessons, Ethics, Statistics (DAMOCLES) Study Group charter. They have been approved by the ethics committees and implemented successfully in several international multi-centre trials.

We plan to appropriately adjust the sample size according to the results of the interim analysis. This will show if our current sample size is over- or even underestimated and if we need an adjustment of our sample size. In case that we need an adjustment of the sample size we will submit an amendment of the study protocol to the independent ethic committee.

**STUDY PROCEDURES**

**Visits of Patients**

**Visit 1 (on the day of admission):**

On the day of admission eligible patients (according to the inclusion/exclusion criteria) will be asked about their interest in participating. Especially, a pregnancy test with the routine blood examination will be performed in female patients. In case of a positive test (pregnancy), the patient will be excluded of the trial. Furthermore, all female patients will receive the information and possibility to protect of a pregnancy for four months after surgery. If the female patient has not already used contraception, we will offer a mandatory hormonal contraception (birth control pill) with a combination with mechanical prevention for four months after surgery. In case of a male patient, no further contraception methods have to be performed for his wife. These additional costs for female patients will be paid by the Sponsor Investigator and not by the patients.

After receiving all information about the trial and signing the informed consent the demographic data, medical history and vital signs will be recorded. Physical examination will be carried out.

**Visit 2 (the day of surgery):**

Computer-based randomization into one of the two groups ((A) control versus (B) terlipressin group) will be directly performed at the admission to the special care unit after surgery by the principal investigator or Co-PIs in case that no new exclusion criteria occurred during the surgery.

The treatment will be started according to the group randomization on the special care unit. From that time point the primary and secondary variables will be continuously assessed. In those cases where the patient is still intubated post-operatively on the intensive care unit we have to give special attention on the fact that propofol in combination with terlipressin may cause a bradycardia (hear rate < 40/min) and has
to be immediately treated according to standard treatment procedures (e.g. administration of atropine). Physical examinations will be daily performed. (Severe) Adverse events will be noted. Concomitant therapies will be administered.

**Visit 3 (1 - 2 hours after surgery):**

The first blood examinations according to the primary and secondary variables will be immediately performed after admission on the special care unit (ca. 1 – 2 hours after surgery).

Prior to giving the human albumin, the form “Dokumentation chargenpflichtiger Blutprodukte” has to be completed by the nurses.

**Visits 4 - 6 (postoperative days 1 -3):**

Vital signs will be evaluated. Physical examinations will be daily performed. Primary and secondary variables will be assessed. (Severe) Adverse effects will be noted. Concomitant therapies will be administered.

Prior to giving the human albumin, the form “Dokumentation chargenpflichtiger Blutprodukte” has to be completed by the nurses.

**Visits 7 - discharge (postoperative days 4 to discharge):**

Vital signs will be evaluated. Physical examinations will be daily performed. Secondary variables among other things e.g. post-operative complications will be assessed. (Severe) Adverse effects will be noted. Concomitant therapy will be administered.

**Efficacy and Safety Variables**

**Primary Efficacy Variable**

The primary efficacy endpoint will be the *serum creatinine peak level within 48 hours post-operative*.

**Secondary Efficacy Variables**

- renal function:
  - the urinary output/24h will be measured from *POD 0 to 3*
  - Daily measuring of NGAL in the urine from *POD 0 - 3*
  - Glomerular filtration rate from *POD 0 – 3*
  - Need for hemofiltration and/or hemodialysis from *POD 0 to discharge*

- Inhospital morbidity after surgery:
  - comprehensive complication index (CCI) from *POD 0 to discharge*
  - Clavien-Dindo score (grade I to IVb)\(^{31}\) from *POD 0 to discharge*
• liver function:
  • serum levels of AST, ALT, bilirubin, Factor V, blood platelets, leukocytes and INR from POD 0 to 5

• Inhospital mortality from POD 0 to discharge

• Length of special care unit and hospital stay (days)

Safety Endpoints
The comprehensive complications index (submitted) will serve as safety endpoint for the safety assessment during the interim analysis.

Safety Variables
In case of the presence of any exclusion variables the patient will not be enrolled in the trial.

(Serious) Adverse Events

Definition of (Serious) Adverse Events

Adverse events (AE)
Adverse events (AEs) are defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal study product, whether or not related to the medicinal study product. An AE may also consist of a new disease, an exacerbation of a pre-existing illness or condition, a recurrence of an intermittent illness or condition, a set of related signs or symptoms, or a single sign or symptom.

AEs observed by the investigator and/or reported by the subject must be reported in the CRF during the entire study period, i.e. the period of time from the first (= signature of informed consent) to the last protocol-specific procedure regardless of the medicinal study product relation assessment.

For all AEs, sufficient information will be pursued and/or obtained so as to permit an adequate determination of the outcome of the event (i.e., whether the event should be classified as a serious adverse event (SAE) and an assessment of the causal relationship between the AE and the investigational drug or study treatment(s).

Whenever available, the underlying disease or condition for which a therapeutic or diagnostic procedure is required should be reported as the AE term.

Surgeries or other invasive procedures that had already been planned prior to the start of the study do not have to be documented as AEs. These planned procedures will be recorded in the CRF by the
investigator at the baseline visit. It is not important if the condition was known before enrolment, only if the procedure was planned before.

Pregnancy per se does not classify as an AE. However, AEs related to a pregnancy have to be reported like any other AEs. Pregnancy should be confirmed by a reliable laboratory test. In all studies not designed for pregnant subjects or successful conception the following applies: Pregnant subjects must be immediately withdrawn from the clinical study. All pregnancies occurring during the treatment phase of the study and within four months after discontinuation of study medication have to be reported to the Investigator-Sponsor within one working day of the investigational sites knowledge of the pregnancy. The Sponsor-Investigator will contact the attendant physician by phone during pregnancy and after the estimated date of delivery to enquire about course and outcome of the pregnancy. Course of the pregnancy and health status of the new born child have to be documented in database too.

**Serious adverse event (SAE)**

A SAE is any untoward medical occurrence that at any dose results in

- participant death
- life – threatening condition
- subject hospitalization or prolongation of current hospitalization
- persistent or significant disability/incapacity
- any important medical event and any event which, though not included in the above, may jeopardize the subject or may require intervention to prevent one of the outcomes listed above.

Any other medically important condition that may be not immediately life-threatening or results in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes, listed above, should also usually (i.e. based on medical and scientific judgment) be considered serious.

**Recording of (Serious) Adverse Events**

Clinical study subjects will be routinely questioned about AEs at study visits. The well-being of the subjects will be ascertained by neutral questioning ("How are you?"). The investigator is responsible for reporting all AEs occurring during the course of the study.

All observed or volunteered adverse drug events (serious or non-serious) and abnormal test findings, regardless of treatment group or suspected causal relationship to the investigational drug or study treatment(s) will be recorded in the CRF.

AEs or abnormal test findings felt to be associated with the study treatment(s) will be followed until the event (or its sequelae) or the abnormal test finding resolves or stabilizes at a level acceptable to the investigator.
An abnormal test finding will be classified as an AE if one or more of the following criteria will be met:

- The test finding is accompanied by clinical symptoms.
- The test finding necessitates additional diagnostic evaluation(s) or medical/surgical intervention; including significant additional concomitant drug treatment or other therapy
  Note: simply repeating a test finding, in the absence of any of the other listed criteria, does not constitute an AE.
- The test finding leads to a change in study dosing or discontinuation of subject participation in the clinical study.

All AEs, serious and non-serious, will be fully documented on the appropriate CRF. For each AE, the investigator will provide the onset, duration, intensity, treatment required, outcome and action taken with the investigational product.

The intensity of AEs will be assessed as being

- mild (hardly noticeable, negligible impairment of well-being),
- moderate (marked discomfort, but tolerable without immediate relief), or
- severe (overwhelming discomfort, calling for immediate relief).

The investigator will determine the relationship of the investigational drug to all AEs as defined on the Adverse Event Reporting Form.

**Assessment of (Serious) Adverse Events**

The investigator will promptly review documented AEs and abnormal test findings to determine if

- the abnormal test finding should be classified as an AE,
- if there is a reasonable possibility that the AE was caused by the investigational drug or study treatment(s), and
- if the AE meets the criteria for an SAE.

The assessment by the investigator with regard to the study drug relation is done according to the following definitions:

**Unlikely relation**

An AE

- whose temporal relationship to drug administration makes a causal relationship improbable and
- in which other drugs or chemicals or underlying disease provides plausible explanations.
Possible relation
An AE, which

- occurs within a reasonable time sequence to administration of the drug but
- could also be explained by concurrent disease or other drugs or chemicals.

Information on drug withdrawal may be lacking or unclear.

Likely relation
An AE, which

- occurs within a reasonable time sequence to administration of the drug,
- is unlikely to be attributed to concurrent disease or other drugs or chemicals, and
- follows a clinically reasonable response on withdrawal (de - challenge).

Re - challenge information is not required to fulfill this definition.

Certain relation
An AE, which

- occurs in a plausible time relationship to drug administration and
- can not be explained by concurrent disease or other drugs or chemicals.
- the response to withdrawal of the drug (de - challenge) should be clinically plausible. The event
  must be pharmacologically or phenomenon - logically definitive, with use of a satisfactory re -
  challenge procedure if necessary.

Reporting of Serious Adverse Events
The principal investigator is responsible for the SAE reporting to Swiss Medic and to the independent
ethic committee (IEC), respectively, according to the following details.

The principal investigator is responsible to report to the Swiss Medic for:

- Compliance with the regulatory requirements of Swiss Medic regarding prompt reporting of unexpeceted SAEs for which a causal relationship with the study drug or device cannot be ruled out.
- Reporting to Swiss Medic of fatal and life-threatening SAEs if evaluated as “suspected”, “unexpected” and “drug related” (SUSAR):
  - Without delay and no later than 7 calendar days following awareness that event
    meets criteria for a SUSAR;
  - Follow up information regarding the SUSAR within further 8 calendar days.
- Reporting to Swiss Medic of non-fatal and not life-threatening SAEs if evaluated as “suspected”, “unexpected” and “drug related” (SUSARs):
- *Promptly* and no later than *15 calendar days* following awareness that event meets criteria for a SUSAR.

- Sending yearly safety reports, starting one year after the date of notification to Swiss Medic. These reports should contain:
  - A concise critical summary of the safety profile of the drug studied as well as the safety issues that have arisen
  - A listing of all SUSARs that have occurred in Switzerland and at international level (if applicable)
  - Ideally all adverse drug reactions at international level.

The investigator is also responsible to report to the IEC for:

- Reporting to IEC any SAE which resulted in death:
  - Immediately, i.e. *within 24 hours*.

- Reporting to IEC of fatal and life-threatening SAEs if evaluated as “suspected”, “unexpected” and “drug related” (SUSAR):
  - *Without delay* and no later than *7 calendar days* following awareness that event meets criteria for a SUSAR;
  - Follow up information regarding the SUSAR within *further 8 calendar days*.

- Reporting to IEC of non-fatal and not life-threatening SAEs if evaluated as “suspected”, “unexpected” and “drug related” (SUSAR):
  - *Promptly* and no later than *15 calendar days* following awareness that event meets criteria for a SUSAR.

**Follow-up of (Serious) Adverse Events**

Subjects terminating the study (either regularly or prematurely) with

- reported ongoing SAE, or

- any ongoing AEs of laboratory values or of vital signs being beyond the alert limit will return for a follow-up investigation. This visit will take place *up to 30 days* after terminating the treatment period. Follow-up information on the outcome will be recorded on the respective AE page in the CRF. All other information has to be documented in the source documents. Source data has to be available upon request.

For any AEs the outcome “unknown” is not acceptable, except if attempts to collect the information have been made and documented. In case of subjects lost to follow-up, efforts should be made and documented to contact the subject to encourage him/her to continue study participation as scheduled. In case of minor AEs a telephone call to the subject may be acceptable.
All new SAE or pregnancies that the investigators will be notified of within 4 months after discontinuation of study medication have to be reported in appropriate report forms and in the CRF if required. However, if the termination visit takes place more than 4 months after the subject has discontinued study medication, the reporting time has to be extended until the termination visit.

Follow-up investigations may also be necessary according to the investigator’s medical judgment even if the subject has no AE at the end of the study. However, information related to these investigations does not have to be documented in the CRF but must be noted in the source documentation.

DATA QUALITY ASSURANCE

The Sponsor-Investigator is implementing and maintaining quality assurance and quality control systems with written SOPs and Working Instructions to ensure that trials are conducted and data are generated, documented (record), and reported in compliance with the protocol, GCP, and applicable regulatory requirement(s).

Monitoring and Audits will be conducted during the course of the study for quality assurance purposes.

Routine Monitoring

Regular monitoring visits at the investigator’s site prior to the start and during the course of the study will help to follow up the progress of the clinical study, to assure utmost accuracy of the data and to detect possible errors at an early time point. The Sponsor-Investigator organises professional independent monitoring for the study (see also chapter 9.4).

All original data including all patient files, progress notes and copies of laboratory and medical test results must be available for monitoring. The monitor will review all or a part of the CRF/eCRFs and written informed consents. The accuracy of the data will be verified by reviewing the above referenced documents. The investigator's site will collaborate with the Clinical Trials Center (CTC) of the University Hospital Zurich to ensure regular monitoring. According to the CTC’s Monitoring SOP the extent and nature of monitoring activities based on the objective and design of the study will be defined in a study specific Monitoring Plan.

Audits and Inspections

A quality assurance audit/inspection of this study may be conducted by the regulatory authority or IEC, respectively. The quality assurance auditor/inspector will have access to all medical records, the investigator's study related files and correspondence, and the informed consent documentation that is relevant to this clinical study.

The investigator will allow the people being responsible for the audit or the inspection to have access to the source data/documents and to answer any questions arising. All involved parties will keep the
patient data strictly confidential.

**Specification of Source Documents**

The following documents are considered source data, including but not limited to:

- SAE worksheets
- Nurse records, records of clinical coordinators, and
- Medical records from other department(s), or other hospital(s), or discharge letters and correspondence with other departments/hospitals, if subject visited any during the study period and the post study period.

Source data must be available at the site to document the existence of the study subjects and substantiate the integrity of study data collected. Source data must include the original documents relating to the study, as well as the medical treatment and medical history of the subject.

The following information (at least but not limited to) should be included in the source documents:

- Demographic data (age, sex)
- Inclusion and Exclusion Criteria details
- Participation in study and signed and dated Informed Consent Forms
- Visit dates
- Medical history and physical examination details
- Key efficacy and safety data (as specified in the protocol)
- AEs and concomitant medication
- Results of relevant examinations
- Laboratory printouts
- Dispensing and return of study drug details
- Reason for premature discontinuation
- Randomization number

**DATA HANDLING AND RECORD KEEPING**

The study will strictly follow the protocol. If any changes become necessary, they must be laid down in an amendment to the protocol. All amendments of the protocol must be signed by the Sponsor-Investigator and submitted to IEC and Swissmedic.

The investigators will use case report forms (CRF), one for each enrolled study participant, to be filled in with all relevant data pertaining to the subject during the study. All requested information in the CRF should be completed in a neat legible manner. Use of a black or blue ball pen is recommended to ensure clarity of reproduced copies in the CRF. All corrections in a CRF must be made in a way that does not obscure the original entry. The correct data must be inserted with the reason for the correction, dated
and initialed by the investigator. A declaration ensuring accuracy of data recorded in the case report forms must be signed by the investigator.

CRFs must be kept current to reflect subject status at each phase during the course of the trial. Subjects will not to be identified on the CRF by name. Appropriate coded identification (e.g. Subject Number) and subject initials will be reported on the CRF.

Documented medical histories and narrative statements relative to the subject's progress during the study will be maintained. These records will also include the following: originals or copies of laboratory and other medical test results (e.g. ECGs, etc.) which must be kept on file with the individual subject's CRF. The investigators assure to perform a complete and accurate documentation of the subject data in the CRF. The data manager will store all documents in a safe and defined place. The data will be entered in a central online database of our Clinical Trial Centre (SecuTrial) of the University Hospital of Zurich independently by two people and any discrepancy will be solved by consensus. The central online database will be anonymous and supervised by the data manager. The online database will have a central backup-server at the University Hospital of Zurich that regularly synchronizes with the online database. Essential documents shall be retained for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product (ICH GCP 4.9.5). However, these documents should be retained for at least 10 years after the regular end or a premature termination of the respective study (VKlin. Ar. 25).

The investigators are liable to treat the entire information related to the study and the compiled data strictly confidentially.

The investigators will arrange contracts with the hospital pharmacy regarding the payment of the additional costs for terlipressin and human albumin. Those additional costs will be paid by the Sponsor Investigator and not by patients. Additionally, the pre-operative pregnancy test and contraception for 4 months after surgery will be paid by the Sponsor Investigator and not by patients. Furthermore the ECG examination on POD 1 and 2 will be performed with our own ECG device by the HPB fellows and will not be paid by the patients.

**NOT study specific examinations = routine examinations:**

<table>
<thead>
<tr>
<th>Study Periods</th>
<th>Screening</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Day</td>
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<td>0</td>
</tr>
<tr>
<td>Demographics</td>
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<tr>
<td>Medical History</td>
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<td></td>
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<tr>
<td>Chest x-ray</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Physical Exam.</td>
<td>x</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>
Vital Signs | x | x | x | x | x
---|---|---|---|---|---
Laboratory Tests | x | x | x | x | x
Resting-ECG | x

### Study specific examinations:

<table>
<thead>
<tr>
<th>Study Periods</th>
<th>Screening</th>
<th>Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit 1</td>
<td>2 3</td>
<td>4-7</td>
<td>8 - discharge</td>
</tr>
<tr>
<td>Day -1 0 0</td>
<td>1-3</td>
<td>4 - discharge</td>
<td></td>
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<tr>
<td>Pregnancy Test</td>
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<td>x incl. POD 2</td>
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<tr>
<td>Resting-ECG</td>
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<tr>
<td>Contraception</td>
<td></td>
<td></td>
<td>For 4 months</td>
</tr>
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</table>

### CONFIDENTIALITY

The investigators are liable to treat the entire information related to the study and the compiled data strictly confidentially. Any passing-on of information to persons that are not directly involved in the study must be approved by the owner of the information.

Data generation, transmission, archiving and analysis of personal data within this study, strictly follows the current Swiss legal requirements for data protection. Prerequisite is the voluntary approval of the subject given by signing the informed consent prior start of participation of the clinical trial.

Individual subject medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited. Subject confidentiality will be further ensured by utilising subject identification code numbers to correspond to treatment data in the computer files.

Such medical information may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare, if the patient has given his/her written consent to do so.

Data generated as a result of this study are to be available for inspection on request by the monitors, by the IEC and the regulatory health authorities.

### INSURANCE

Insurance is covered by “Haftpflichtversicherung für den Kanton Zürich betreffend das UniversitätsSpital Zürich“ (Policy no.: 14.970.888).

Any damage developed in relation to study participation is covered by this insurance. So as not to forfeit their insurance cover, the subjects themselves must strictly follow the instructions of the study personal. Subjects must not be involved in any other medical treatment without permission of the
principal investigator (emergency excluded). Medical emergency treatment must be reported immediately to the investigator. The investigator must also be informed instantly, in the event of health problems or other damages during or after the course of study treatment.

The investigator will allow delegates of the insurance company to have access to the source data/documents as necessary to clarify a case of damage related to study participation. All involved parties will keep the patient data strictly confidential.

A copy of the insurance certificate will be placed in the Investigator’s Site File.

STUDY REGISTRATION

The study will be registered in the local trial registry of the University Hospital Zurich („Studienregister USZ“) and in the international ClinicalTrials.gov registry (clinicaltrials.gov).

PUBLICATION POLICY

After the statistical analysis of this trial the investigator will make every effort to publish the data in a peer-reviewed medical journal. Co-authors will be listed according to their contribution.

ETHICS

Independent Ethics Committee (IEC)

Before this study will be conducted, the protocol, the proposed subject information and consent form will be submitted to a properly constituted Independent Ethics Committee (IEC) in agreement with local legal requirements, for formal approval. Any amendments to the protocol, other than administrative ones, must also be approved by this committee.

The decision of the IEC concerning the conduct of the study will be made in written form to the PI before beginning of this study.

Ethical Conduct of the Study

The study will be carried out in accordance with principles enunciated in the current version of the Declaration of Helsinki, the guidelines of Good Clinical Practice (GCP) issued by ICH, and Swiss regulatory authority’s requirements.

Subject Information and Informed Consent

The investigators will explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits and any discomfort it may entail. Each subject must be informed that the participation in the study is voluntary and that he/she may withdraw from the study at any time, without any information of the causes and that the withdrawal of consent will
not affect his/her subsequent medical treatment.

The subject must be informed that his/her medical records may be examined by authorized individuals other than their treating physician.

All subjects for this study will receive a subject information sheet and a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study.

The subject information sheet and the consent form will be submitted with the protocol for review and approval by the IEC for the study. The formal consent of a subject, using the IEC-approved consent form, must be obtained before that subject is submitted to any study procedure.

Prior to subject participation in the study, informed consent will be obtained from each subject. The subject should read and consider the statement before signing and dating it, and should receive a copy of the signed document. The consent form must also be signed and dated by the investigator (or his designee) and it will be retained as part of the study records.
Table 1: Benefit-harm analysis of terlipressin

<table>
<thead>
<tr>
<th>Scenarios for different ARF risks</th>
<th>5%</th>
<th>6%</th>
<th>7%</th>
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<th>10%</th>
<th>11%</th>
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<th>33%</th>
<th>34%</th>
<th>35%</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR 0.6 on ARF</td>
<td>1.15</td>
<td>0.79</td>
<td>0.43</td>
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<tr>
<td>RR 0.7 on ARF</td>
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<td>1.40</td>
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<td>1.09</td>
<td>1.04</td>
<td>0.98</td>
<td>0.92</td>
<td>0.87</td>
<td>0.81</td>
<td>0.76</td>
<td>0.71</td>
<td>0.66</td>
<td>0.61</td>
<td>0.56</td>
</tr>
</tbody>
</table>

positive = harm > benefit
negative = benefit > harm
Table 2: Full risk score of ARF

<table>
<thead>
<tr>
<th>Full Risk Score (7 Predictors)</th>
<th>Risk of ARF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>4.1%</td>
</tr>
<tr>
<td>1</td>
<td>5.2%</td>
</tr>
<tr>
<td>2</td>
<td>6.4%</td>
</tr>
<tr>
<td>3</td>
<td>7.9%</td>
</tr>
<tr>
<td>4</td>
<td>9.8%</td>
</tr>
<tr>
<td>5</td>
<td>12.0%</td>
</tr>
<tr>
<td>6</td>
<td>14.7%</td>
</tr>
<tr>
<td>7</td>
<td>17.8%</td>
</tr>
<tr>
<td>8</td>
<td>21.4%</td>
</tr>
<tr>
<td>9</td>
<td>25.6%</td>
</tr>
<tr>
<td>10</td>
<td>30.2%</td>
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<tr>
<td>11</td>
<td>35.3%</td>
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<tr>
<td>12</td>
<td>40.7%</td>
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<tr>
<td>13</td>
<td>46.4%</td>
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<tr>
<td>14</td>
<td>52.1%</td>
</tr>
<tr>
<td>15</td>
<td>57.8%</td>
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<tr>
<td>16</td>
<td>63.3%</td>
</tr>
<tr>
<td>17</td>
<td>68.5%</td>
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<tr>
<td>18</td>
<td>73.2%</td>
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<tr>
<td>19</td>
<td>77.5%</td>
</tr>
<tr>
<td>20</td>
<td>81.3%</td>
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<tr>
<td>21</td>
<td>84.5%</td>
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<tr>
<td>22</td>
<td>87.3%</td>
</tr>
<tr>
<td>Predictor</td>
<td>Categories</td>
</tr>
<tr>
<td>-------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Diabetes</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>ALT</td>
<td>$\leq 35/50$ U/L $^\S$</td>
</tr>
<tr>
<td></td>
<td>$&gt;35/50$ U/L $^\S$</td>
</tr>
<tr>
<td>Age</td>
<td>&lt;60 yr</td>
</tr>
<tr>
<td></td>
<td>60–69 yr</td>
</tr>
<tr>
<td></td>
<td>$\geq 70$ yr</td>
</tr>
<tr>
<td>Bilirubin</td>
<td>$&lt;17$ µmol/L</td>
</tr>
<tr>
<td></td>
<td>$\geq 17$ µmol/L</td>
</tr>
<tr>
<td>Female</td>
<td>No</td>
</tr>
<tr>
<td></td>
<td>Yes</td>
</tr>
</tbody>
</table>
Table 4: Function of the Data Monitoring Committee (DMC)

The DMC will function in an advisory rather than executive capacity and its duties will include the following:

- Offering advice about the research protocol and proposals for data safety and monitoring, including statistical ‘warning rules’ for efficacy, safety and futility.

- Evaluating the progress of the trial, including periodic assessments of data quality and timeliness, participant recruitment, accrual and retention, clinician adherence to the trial protocol and progress toward and information and orderly completion of the study.

- Carrying out the rapid evaluation of serious unanticipated adverse events.

- Evaluating pre-planned interim analyses for efficacy, safety and the triggering of statistical warning rules. When the DMC decide that a definitive answer to the trial question has been achieved (in terms of efficacy, safety, or futility) they will unblind the principal investigator.
Eligible patients for liver surgery at day of admission at moderate to high risk for ARF

Enrolled patients after signing the informed consent one day before surgery

Liver surgery

Exclusion:
- chronic liver disease
- viral hepatitis
- coronary insufficiency
- pregnancy
- terlipressin intolerance
- acute renal failure score ≤6 points

Exclusion due to intra-operative ECG changes:
- ST elevation
- ST depression

Admission to special care unit: start with the study medication

Randomization

Control group: placebo with Ringer lactate solution for 48 hours postoperatively

Terlipressin group: terlipressin in admission with human albumin for 48 hours postoperatively

100mL Ringer lactate solution per 4hrs intravenously as control and Ringer lactate solution 100mL/day instead of human albumin on POD 0-2

Terlipressin 0.5mg/4hrs and human albumin 1 kg/Kg BW on POD 0, than 20g/d on POD 1-2

Figure 1: Flow chart