# Arterial perfusion with t-PA in donation after cardiac death (DCD) to reduce the incidence of non-anastomotic biliary strictures after orthotopic liver transplantation

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Prevention of NAS will result in less retransplantations due to NAS. This in turn will result in a shorter waiting list with less morbidity and more important less mortality while waiting for a donor liver. Patients will also be less often...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Hepatic and hepatobiliary disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON39319

**Source**
ToetsingOnline

**Brief title**
FLUSH

### Condition

- Hepatic and hepatobiliary disorders

**Synonym**
biliary strictures, narrowing of the bile ducts

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum
**Source(s) of monetary or material Support:** Boehringer Ingelheim,Fonds NutsOhra

## Intervention

**Keyword:** Arterial perfusion, donation after cardiac death, non-anastomotic strictures, t-PA

## Outcome measures

### Primary outcome

The primary eindpoint of the current study will consist of the reduction of the incidence of non-anastomotic biliary strictures.

NAS usually is diagnosed when patients present themselves with symptoms such as abdominal pain, jaundice, fever, itching or abnormal liver enzymes such as an elevated alkaline phosphatase (AF) or gamma glutamyl transferase (GGT).

However, patients may not have symptoms at all. It is therefore important to evaluate all patients in order to also detect silent NAS. Therefore a MRCP will be performed at one year after transplantation for all patients. MRCP is a non-invasive diagnostic tool with high sensitivity and specificity in detecting NAS. All NAS with symptoms and hospitalization and number of admissiondays will be registered in the participating centers. ERCPs, MRCPs, PTCs and surgical interventions needed to treat NAS will also be registered.

### Secondary outcome

• Graft survival

• Patient survival

• Number of graft failures due to NAS

• Number of ERCPs, PTCs and surgical interventions performed to treat NAS in

the first year

• Number of hospitalizations and time of hospitalization

• Number of admission days to the Intensive Care Unit (ICU)

• Number of episodes of cholangitis

• Adverse events (AE) and serious adverse events (SAE)

• Ischemia times and relation to NAS

• Transaminase peaks (ALAT/ASAT, bilirubin)

• Peri-operative blood loss

• Clotting, fibinolysis and remnants of t-PA in the recipients plasma

• Primary non-function

• Hepatic artery thrombosis (HAT)

• Retransplantations due to NAS

• Liverbiopsy: during surgery (60 minutes post-reperfusion). Optionally, after 6 months a liver biopsy will be performed for evaluation of ischemia-reperfusion damage. Particiating centers will decide independently whether to perform the liver biopsy at 6 months. (Ischemia/reperfusion evaluation according to Franchello et al. Am J Tr. 2009)

# Study description

**Background summary**

The incidence of biliary complications such as non-anastomtotic biliary strictures (NAS), also called ischemic type biliary lesions (ITBL), may be as high as 25% in DCD donors. NAS are associated with an increased risk of infection of the biliary tree, frequent admissions to the hospital, endoscopic treatment and retransplantation. NAS are most likely the result of a complex mechanism involving ischemic, immunologic and toxic processes which all affect

the the vascular system of the biliary tree. The microvascular supply of the biliary tree, the peribiliary plexus, stems from the hepatic artery branches and flows into the hepatic sinusoids. Recent literature has shown that a decreased blood flow in the peri-biliary plexus after orthotopic liver transplantation is involved in the development of NAS. The reduction of blood flow in the peri-biliary plexus is most likely the result of microthrombi which develop during the cold ischemic time (CIT) and WIT.
The mechanisms which might be involved in the development of NAS are of great importance since they may provide new insights to develop strategies in order to prevent this complication. First of all, research has shown that flushing donor livers with the abovementioned preservation fluids at an increased pressure reduces the incidence of NAS. Secondly, not properly controlled studies suggest that adding a thrombolytic agent such as t-PA to the preservation fluid also seems to reduce the incidence of NAS, probably by dissolving the microthrombi in the micro-vascular system of the biliary tree. The most important thrombolytic agents are streptokinase, urokinase and recombinant tissue-type plasminogen activator. These agents have been widely used in the clinic and are considered safe. Several studies have been performed by using thrombolytic agents in order to prevent NAS, which in some cases showed drastic reductions in NAS. These studies have also shown that the risk of intra-operative bleeding is not increased.

**Study objective**

Prevention of NAS will result in less retransplantations due to NAS. This in turn will result in a shorter waiting list with less morbidity and more important less mortality while waiting for a donor liver. Patients will also be less often hospitalized after OLT for the treatment of NAS which also will reduce the morbidity and mortality rate after OLT. This will also have an impact on cost-effectivity of OLT since fewer investigations and interventions (abdominal ultrasounds, magnetic resonance cholangiography (MRCP), endoscopic treatments such as endoscopic retrograde cholangio- en pancreaticography (ERCP) and percutaneous transhepatic cholangiography (PTC)) will have to be performed to diagnose and treat NAS.

**Study design**

The primary objective of the current study is to perform a prospective double-blinded randomized controlled trial, investigating the effect of adding t-PA to the UW preservation fluid, injected under high pressure during the procedure of donation after cardiac death (DCD), on the incidence of NAS. Secondary objectives are impact on ASAT and ALAT peak in the first week after OLT, side effects, remnants of t-PA or its activity after OLT, patient and graft survival, and cost-effectiveness (including admissions and interventions)
All three liver transplantation units (LUMC, UMCG, EMCR) in the Netherlands will participate in this prospective study, as well as all Dutch centers where

procurement of donors takes place.
Tissue-type plasminogen activator (t-PA or PLAT) is a protein involved in the breakdown of blood clots, also known as thrombolysis. Tissue plasminogen activator is a naturally-occurring enzyme, manufactured with DNA recombinant technology. The enzyme binds to fibrin-bound plasminogen at the site of a clot, thus converting plasminogen to plasmin. Plasmin digests the fibrin strands of the clot and restores perfusion to the occluded artery. t-PA is widely used in clinical setting for the treatment of various indications such as pulmonary embolism, myocardial infarction, and stroke. Clot lysis often occurs within 60-90 minutes and the effective duration is * hour (80% cleared in 10 minutes). In the current study we hypothesize that t-PA will help dissolve microthrombi in the microcirculation of the peri-biliary plexus. This helps to preserve bile duct integrity. t-PA may also reduce ischemia-reperfusion injury to the liver in general by preserving sinusoidal flow.

**Intervention**

Intervention group:

Procurement procedures will be performed according to protocol. The abdominal cavity will be opened by a midline laparotomy followed by an open cannulation of the aorta. A human liver weighs approximately 1.5 kg and approximately 1.5 mg of t-PA will be flushed per 100 mg of human liver. This means that a total of 23 mg is needed for sufficiently flushing the liver. However, it is estimated that approximately 50% of the fluids will be lost in the abdominal cavity through the aorta. This would mean that 46 mg of t-PA would be needed for the procedure.
A pressure bag containing 46mg of t-PA solved in 2 liters of UW preservation fluid will be flushed through the aorta under a pressure of 200 mmHG (=2.7 m H20). After procurement the donor liver will be stored on ice and sent to the recipient transplantation hospital according to the normal procedure.

**Study burden and risks**

Risks:

t-PA is known for its fibrinolytic properties. One of the endpoints is monitoring the amount of blood loss per-operatively.Previous research has shown that there is no significant difference in clotting times and bleeding in use of t-PA in liver transplants.
In clinical practice, t-PA used in Cerebro Vascular Disorders (CVA) and cardiac ischemia. The quantities which are used in these clinical settings are much higher than the amount used in this study. In addition, t-PA directly administered systemically for the above mentioned disorders, the risk of hemorrhage appears to be very low. However, theoretically, the use of t-PA might induce a prolonged bleeding time. For this the total blood loss will be

registered during transplantation.To monitor the amount of blood loss due to an increased activity of fibrinolysis, thrombo-elastography (TEG) will be used. TEG is used to evaluate the viscoelastic properties of clot formation. In the case of a(n) (excess), bleeding due to increased fibrinolytic activity per-operatively, measurements such as administration of transexamic acid (Cyklokapron) 1000mg/50ml NaCl 0.9% in 15 minutes can be taken.

Burdens:

In the current setting of post-transplantation care, patients are often seen in the outpatient clinic of the Gastroenterology and Hepatology department for frequent evaluation of the liver function. According to standard protocol blood is drawn from patients at each visit to the outpatient clinic in order to evaluate liver function. In the current study additional tubes of blood will be drawn from patients during these moments at which blood is drawn for protocol. One of the major advantages is that no additional venepuncture procedure will be necessary. Another advantage is that patients will not be requested for extra visits to the outpatient clinic.
Since not all NAS cause symptoms such as fever or abdominal pain, a MRCP will be performed at one year follow-up. Patients will be requested to visit the hospital one time for this diagnostic procedure. MRCP is a non-invasive diagnostic procedure. The procedure will take approximatley 45 minutes.

## Contacts

**Public**
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2300 ZC
NL
**Scientific**
Leids Universitair Medisch Centrum

Albinusdreef 2
Leiden 2300 ZC
NL

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

Recipient inclusion criteria;- All patients who are eligible for liver transplantation;Donor inclusion criteria;- Donors from donation after cardiac death (DCD)

### Exclusion criteria

Patients eligible for liver transplantation younger than 18 years
Pregnant women

## Study design

### Design

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| Study phase: | 3 |
| Study type: | Interventional |
| Intervention model: | Parallel |
| Allocation: | Randomized controlled trial |
| Masking: | Double blinded (masking used) |

**Primary purpose:** Prevention

### Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 02-06-2014 |
| Enrollment: | 194 |

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| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 04-06-2013 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 05-06-2013 |
| Application type: | First submission |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 27-09-2013 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |
| Approved WMO Date: | 15-10-2013 |
| Application type: | Amendment |
| Review commission: | METC Leids Universitair Medisch Centrum (Leiden) |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| EudraCT | EUCTR2012-002478-30-NL |

| Register | ID |
| --- | --- |
| CCMO | NL40800.058.12 |