# Assessment of trans-intestinal cholesterol excretion in patients with total biliary obstruction (TICE-PTC)

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To establish the presence of direct trans-intestinal cholesterol excretion (TICE) in humans by faecal recovery of i.v. administered 13C-cholesterol in patients with a total biliary obstruction. This is a so-called proof-of-concept study.

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Gastrointestinal stenosis and obstruction |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON34484

**Source**
ToetsingOnline

**Brief title**
TICE-PTC

### Condition

- Gastrointestinal stenosis and obstruction
- Lipid metabolism disorders

**Synonym**
total biliary obstruction

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Academisch Medisch Centrum
**Source(s) of monetary or material Support:** Ministerie van OC&W

## Intervention

**Keyword:** cholesterol excretion, stable isotopes, total biliary obstruction

## Outcome measures

### Primary outcome

Total faecal 13C-cholesterol recovery during four days after a single

intravenous dose of 13C-cholesterol.

### Secondary outcome

Biliary 13C-cholesterol recovery during four days after a single intravenous

dose of 13C-cholesterol.

# Study description

### Background summary

Reverse cholesterol transport (RCT) is an important anti-atherogenic mechanism, as it mediates the elimination of excess cholesterol out of the body into the faeces. Recently, the concept of RCT has been revisited. In the *classical* concept, the liver is considered to be the only organ capable to eliminate cholesterol via excretion into the bile. However, evidence from animal models suggests that the intestine is also an important secretory organ for cholesterol.
In fact, direct trans-intestinal cholesterol excretion (TICE) accounted for 33% of total faecal sterol excretion in mice. It is unknown whether TICE is present in humans. However, previous human perfusion studies suggest secretion of cholesterol in the small intestine. Based on previous calculations, TICE in humans is estimated to amount to 300mg/day in subjects with an average body weight of 70kg. This is approximately one third of the amount secreted into bile. Finally, several pharmacological compounds have been found to stimulate trans-intestinal cholesterol secretion in mice. This suggests that TICE might be a novel therapeutic target for cholesterol excretion and thereby for cardiovascular disease prevention.

In order to establish the existence of such a direct trans-intestinal cholesterol-excreting pathway, we propose to study faecal recovery of a single dose of intravenously administered 13C-cholesterol (stable isotope) in patients with a total biliary occlusion. If 13C-cholesterol can indeed be recovered from faeces in these patients, the only possible explanation is that it was secreted directly by the intestine to the faeces, since endogenous biliary secretion is completely blocked. Hence, this study will provide the proof-of-concept for the existence of TICE in humans.
If valid, TICE could serve as a novel cholesterol-lowering mechanism, in order to prevent cardiovascular disease. Further research will be necessary to evaluate how to stimulate this cholesterol-lowering mechanism best, in order to accomplish additional reductions in blood cholesterol concentrations and thereby cardiovascular disease.

**Study objective**

To establish the presence of direct trans-intestinal cholesterol excretion (TICE) in humans by faecal recovery of i.v. administered 13C-cholesterol in patients with a total biliary obstruction. This is a so-called proof-of-concept study.

**Study design**

The design of the study is a cross-sectional proof-of-concept study, which comprises a single measurement of cholesterol excretion in a period of 5 days. The study flow chart is depicted on page 16 of the study protocol.

Patients will be recruited via the departments of gastroenterology and intervention radiology of the AMC. Eligible participants will be informed about the study objective and procedures by the gastroenterologist in the outpatient clinic, during the visit in which the PTC-procedure is explained. In case subjects are referred to our hospital from elsewhere, recruitment will take place by the intervention radiologist.
Eligible subjects will be asked for their permission to be contacted by the study physician, who will explain the procedures into more detail and who will obtain informed consent.

Following written informed consent and successful placement of the biliary PTC-drain, a blood sample (12 ml) will be collected for the measurement of lipoprotein levels and the background 13C-cholesterol enrichment. This will be done via the same venous catheter used in the PTC-procedure. Subsequently, at T=0, an intravenous dose of 30 mg of 13C-cholesterol dissolved in 22 ml Liposyn III 10% in ethanol will be administered in 30 minutes, again through the same venous catheter. Four and twelve hours after 13C-cholesterol administration (T=4h and T=12h), the study physician will obtain a blood and biliary sample from the drain at the hospital ward.

In the 4 days following i.v. 13C-cholesterol administration, the study physician will obtain a daily bloodsample in the morning fasting state (T=24h, T=48h, T=72h, T= 96h, 15ml at each timepoint). This will be done either on the hospital ward or at the subjects* homes, depending on their clinical course. Simultaneously, a biliary sample will be obtained from the PTC-drain. Finally, participants are asked to collect daily faecal samples, using a special specimen collection system from day 1 until the end of study (day 4).

In case patients are scheduled for removal of the PTC-drain earlier than day 4, this will be the end of study.

**Study burden and risks**

No serious adverse events are expected to occur in this study. Stable isotopes of cholesterol behave like their natural substrates and therefore carry no known risks. This has also been established by extensive human and animal experience. The dose of isotopes administered to the subjects is small compared to the amount already present in the body. Subjects can experience slight transient burning in the infusion arm during administration of the cholesterol-Liposyn solution. This is not harmful and disappears as soon as administration is cessated.

Although participation to this study does not carry any health risks, it does not carry any benefits or advantages either, neither to the participants themselves, nor to the population of patients with total biliary occlusion as a whole. Participation to this study will only serve a scientific purpose to develop the cardiovascular research field in the search for new cholesterol-lowering strategies.

In addition, subjects are subjected to behavioural changes, such as the collection of faecal stool samples and the subjection to daily blood draws for 5 days. The latter can cause a hematoma at the site of venepuncture.

# Contacts

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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Males and females, aged 18-70 years with a total biliary obstruction and successful placement of a biliary percutaneous transhepatic cholangiographic (PTC) drain.

## Exclusion criteria

Main exclusion criteria are: unsuccessful ERCP procedure as the medical indication for PTC-drainage; use of cholesterol-lowering medication; genetic hyperlipoproteinemia: familial hypercholesterolemia, LPL-deficiency, familial dysbeta-lipoproteinemia, familial hypertriglyceridemia; BMI > 30 kg/m2; diabetes mellitus type I and type II; having received an investigational drug in the last 3 months before the screening visit; unable or unwilling to comply with the protocol requirements or deemed by the investigator to be unfit for the study; likely to leave the study before its completion.

# Study design

## Design

**Study type:** Observational invasive
Masking: Open (masking not used)

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| Control: | Uncontrolled |
| Primary purpose: | Other |

### Recruitment

NL

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| Recruitment status: | Pending |
| Start date (anticipated): | 01-05-2010 |
| Enrollment: | 5 |
| Type: | Anticipated |

## Ethics review

Approved WMO

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| Application type: | First submission |
| Review commission: | METC Amsterdam UMC |

## 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 |
|---|---|
| CCMO | NL32263.018.10 |