Preventing Oxidative stress-induced ischemic injury and systemic inflammation complications during and after invasive cardiac surgery with Alkaline Phosphatase (APPIRED III)

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The purpose of this study (APPIRED III) is to investigate the efficacy of administered prophylactically RESCAP with regard to the prevention of (severe) renal failure, or renal dysfunction, reducing morbidity and mortality. It also looks at systemic...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac valve disorders
Study type	Observational invasive

Summary

ID

NL-OMON49105

Source
ToetsingOnline

Brief title
RESCAP to prevent complications in heart surgery

Condition

- Cardiac valve disorders
- Nephropathies

Synonym
renal failure, systemic inflammatory response

Research involving
Human

Sponsors and support

Primary sponsor: Alloksys Life Sciences BV
Source(s) of monetary or material Support: Alloksys Life Sciences BV

Intervention

Keyword: alkaline phosphatase (AP), cardiothoracic surgery, inflammation, kidney injury/ kidney failure

Outcome measures

Primary outcome

This study has a so-called composite outcome, with a combination of the

parameters described below at OR/OR level:

Reduction of actual morbidity and mortality numbers.

OR

Reduction of the post-surgical complications such as AKI, acute renal failure

by intravenous administration of RESCAP (alkaline phosphatase) in comparison

with the placebo-group. Reduction will be measured to known blood parameters

and renal function parameters, AKIN > 2 (Rise in serum creatinine of by 0.3

mg/dl or 26 µmol/L in 48 hours/ a percentage increase in the serum creatinine

concentration of >=50 percent 10 or a drop in urine output to 0.5 ml/kg/hour for

6 hours)

OR

demonstrate that time to extubation [defined as removal of endotracheal tube]

is reduced

OR

reduce GI Complications : defined as demonstrable nasogastric bleeding > 12

hours , malena or positive fecal occult blood

OR

reduce neurological complications : defined as focal neurological deficit of

central origin lasting more than 72 hours demonstrable on a CT scan.

Secondary outcome

outcomes associated to CPB and AP intervention including

1) the incidence of renal replacement therapy, b) duration of renal replacement

therapy, c) days spent in the

ICU and time spent in hospital, and d) the incidence of arrhythmias in the two

groups

2) Plasma levels of a set of inflammatory markers (IL-6, IL-8, IL-10,

TNF-alpha) and increase endogenous alkaline phosphatase levels and kidney

function markers (IL18, NGAL, TIMP-1, GFR) in the control and AP treated groups.

3. Following the finalisation of APPIRED III study: Estimate the incremental

cost effectiveness ratio (ICER) by comparing the costs and effectiveness

between AP and placebo groups.

Study description

Background summary

Cardiac surgery-associated acute kidney injury (AKI) is a common and serious post-operative complication of cardiac surgery that employs cardiopulmonary bypass (CPB), and it is the second most common cause of AKI in the intensive care unit (ICU). It is estimated that post-operative acute kidney injury (AKI)

increases the risk of mortality three to eight times in cardiac surgery patients This AKI is characterized by an abrupt deterioration in kidney function following cardiac surgery as evidenced by a reduction in the glomerular filtration rate. Approximately 1-3% of all patients on CPB will require permanent renal replacement therapy Permanent dialysis is not only a costly complication, it also significantly impacts the quality of life and reduces the number of years a patient lives after their operation.

During the APPIRED I and II study we demonstrated that intervention with RESCAP benefits can include reduced inflammation, as well as reduced morbidity and mortality . Due to the small size of the number of patients included (ca 100) RESCAP will now be examined in a multicenter study whether these results can be confirmed. Since the main complication of open-heart action surgery renal dysfunction, possibly even acute renal failure, and RESCAP intervention has now been demonstrated in another group of patients with septic shock that the kidney function is greatly improved, it is to be expected that also in this open-heart surgery patients may be observed, these effects of RESCAP. To this end, in order to also clinically significant rulings do a cohort of 1250 patients necessary.

Study objective

The purpose of this study (APPIRED III) is to investigate the efficacy of administered prophylactically RESCAP with regard to the prevention of (severe) renal failure, or renal dysfunction, reducing morbidity and mortality. It also looks at systemic inflammation (inflammation) and the effects of subsequent treatment with RESCAP, an anti-inflammatory drug.

RESCAP intervention is expected to reduce the overall morbidity and will also be able to decrease the mortality rate in the group of RESCAP-treated patients. Reported elsewhere is that a reduction in renal function (Acute Kidney Injury / AKI) during or after the operation is predictive to for a poorer post-surgical quality of life and overall long-term survival. Renal impairment, we hope to prevent with RESCAP intervention, in this group of open-heart surgery patients at increased risk of complications (EUROSCORE II greater or equal 3))

Study design

Multicenter study, prospective, randomized, double-blind, placebo-controlled intervention study.

Study burden and risks

To date, there are no risks identified in administering RESCAP intravenously. The APPIRED I study, 63 patients were included. No serious adverse effects of RESCAP documented. In the APPIRED II study with a total of 52 patients also no

serious adverse events were observed. Data are included in the investigator brochure.

The study burden for patients will include the taking of blood samples up to 5 days after the operation. These can be taken for the most part from the lines already present, or will be taken at times when also routine blood samples are taken. The bolus, as well as the 24-hour infusion can be injected into already affixed intravenous accesses. Patients will be called 30 days after the operation and data on medication use and adverse events will be collected.

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

A potential subject must meet all of the following criteria to participate in the study:

1. greater than 21 years of age (legal adult in Singapore)
2. Undergoing cardiac surgery with planned cardiopulmonary bypass
3. EUROSCORE II greater than or equal 3
4. Ability to provide informed consent (not incapacitated)

Exclusion criteria

Any subjects meeting the following criteria at baseline will be excluded:
1. Already on renal replacement therapy
2. Patients with chronic kidney disease defined as urinary albumin excretion of >=30 mg/day, or equivalent or estimated glomerular filtration rate lower than 60 ml/min/1.73 m2 (CKD stage > 2)
3. Patients who are pregnant
4. Concurrent enrolment in another clinical trial
5. Known allergic reaction to bovine alkaline phosphatase

Study design

Design

Study phase:	3
Study type:	Observational invasive
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	01-11-2017
Enrollment:	150
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	RESCAP
Generic name:	alkaline phosphatase

Ethics review

Approved WMO Date:	14-02-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	22-08-2017
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-07-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	02-04-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-06-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	23-07-2019
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	11-03-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	05-12-2023
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	12-01-2024
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2016-002663-33-NL
CCMO	NL59364.100.16