Digoxin Evaluation in Chronic heart failure: Investigational Study In Outpatients in the Netherlands

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This study has been transitioned to CTIS with ID 2023-509898-23-00 check the CTIS register for the current data. To study whether low-level digoxin reduces the composite primary endpoint of (repeated) HF hospitalizations, (repeated) urgent HF...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Heart failures
Study type	Interventional

Summary

ID

NL-OMON55484

Source
ToetsingOnline

Brief title
DECISION

Condition

- Heart failures

Synonym
Heart failure

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Disphar International,TEVA Pharma,Tiofarma BV,ZonMW/Hartstichting

Intervention

Keyword: Atrial fibrillation, Digoxin, Heart failure

Outcome measures

Primary outcome

The primary endpoint is the composite of (repeated) HF hospitalizations,

(repeated) urgent HF hospital visits and cardiovascular death.

Secondary outcome

1. All-cause mortality

2. Cardiovascular death

3. (Repeated) HF hospitalization

4. (repeated) urgent HF hospital visits

5. Cost-effectiveness.

6. All-cause hospitalizations

7. Unscheduled cardiovascular hospital visits

8. Days alive out of hospital

9. Quality of Life

10. Heart rate in both AF and sinus rhythm

11. To assess side effects (including SUSARs) associated with study medication

12. Initiation of (recurrence of) AF in patients with sinus rhythm at baseline

13. Conversion to sinus rhythm and maintenance of sinus rhythm in patients with

AF at baseline.

14. Proteomics and validating hits in elisa*s.

Study description

Background summary

Heart failure (HF) is common, disabling, and associated with an impaired survival. Approximately 1-2% of the population in European countries is diagnosed with HF, and in the Netherlands there are currently 150,000 patients with HF, which may even be an underestimation of the true prevalence of HF.The prevalence of HF is still increasing; currently the lifetime risk for developing HF is one in five for both men and women. Although recent advances in pharmacotherapy, patients diagnosed with HF have a poor quality of life and a poor prognosis with a 5-year survival rate less than 50% which is even worse than patients diagnosed with bowel or breast cancer. In addition, HF is also a very costly disease accounting for ~2% of the total health care budget in The Netherlands. Especially hospitalization for HF is extremely expensive yielding 60-70% of the total costs for HF. Therefore, reducing HF hospitalizations will not only improve patient*s quality of life (QoL) and life expectancy but will also lead to a significant reduction in health care related costs.

Atrial fibrillation (AF) is one of the most common comorbidities in patients with HF with a prevalence of 25 to 40%. The combination of AF and HF is associated with even a further increased risk of hospitalizations and mortality. Despite its high prevalence in HF, patients with AF were underrepresented in prior HF trials. So far, none of the rate or rhythm control therapies have shown to improve the prognosis of patients with AF, and all are only used to reduce symptoms.

Digoxin is the oldest drug for HF, and very cheap. A large trial with digoxin revealed a highly significant reduction in HF hospitalizations, but no effect on mortality. Due to these ambiguous findings and since subsequent large trials with ACE-inhibitors, beta-blockers and later mineralocorticoid receptor antagonists demonstrated improved survival, the clinical use of digoxin has largely diminished in the last decade. In everyday clinical practice, digoxin is nowadays used only in a minority (~10%) of the HF patients.

However, later analyses of the DIG study showed that (in hindsight) too high doses were probably used in the DIG trial. Indeed patients with lower serum concentrations of digoxin showed a better survival. While serum digoxin concentrations between 0.5-0.9ng/mL were related to lower mortality, all-cause hospitalization and HF hospitalization, digoxin concentrations >1.0ng/mL were associated with a higher mortality.

In HF patients with AF, digoxin is recommended for rate control to reduce symptoms, but not for prognosis. However, based on post-hoc analysis of several AF databases, digoxin*s use is declining in the last decade due to concerns of

increased mortality risk.15,16 In these datasets the use of digoxin was mostly restricted to sicker patients, leading to confounding by indication and prescription bias, and again (too) high doses were used.

Therefore, a randomized placebo-controlled trial in patients with chronic HF, with a wide range of left ventricular ejection fraction (LVEF) (reduced and mid-range ejection fraction of respectively <40% and between 40 and 50%) is necessary.

Study objective

This study has been transitioned to CTIS with ID 2023-509898-23-00 check the CTIS register for the current data.

To study whether low-level digoxin reduces the composite primary endpoint of (repeated) HF hospitalizations, (repeated) urgent HF hospital visits and cardiovascular mortality, compared to placebo, in chronic HF.

Study design

The proposed trial is a national, multicenter, randomized, double-blind placebo controlled, clinical trial

Intervention

Patients will be randomized to low-level digoxin or placebo in double-blinded fashion. Digoxin will be given orally starting at doses of 0.2mg, or 0.1mg, based on age, renal function and concomitant medication. No loading dose is given. After 4 weeks study medication (digoxin or placebo) concentrations will be measured. Dose adjustments will be made to reach the target serum digoxin concentration range of 0.5-0.9ng/mL.

Study burden and risks

In DECISION, we use low-level digoxin and aim for low serum concentrations (0.5-0.9ng/mL). We will measure serum digoxin concentrations throughout the duration of the trial, to make the chance of overdosing as low as possible. Therefore, we expect side effects or intolerance for digoxin only in a minority of patients. Mostly, digoxin intoxications occur with concentrations >2ng/mL. The most common side effects of digoxin are dizziness, visual disturbances, arrhythmias, nausea, vomiting, diarrhea, and exanthema. For study purpose, patients are seen at outpatient clinic at inclusion, 1-month, and then every 6 months, and between the outpatient visits telephone checks are planned, a minimum of 7 outpatient visits (= routine clinical practice for HF patients), and 6 telephone checks. Blood samples for measurements of serum digoxin concentration will be performed at least 7 times, and 1-month after all study

medication dose adjustments, when interacting medication is started, when renal function decreases (eGFR <45 ml/min/1.73m2), after a hospitalization for HF, and every 6 months during study follow-up. Patients are asked to fill in quality of life and medical consumption questionnaires.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

1. Age >=18 years
2. Outpatients with chronic HF, NYHA II - ambulatory IV
3. LVEF<=50%
4. Serum NT-proBNP concentrations
- Previous HF hospitalization <= 1 year: >=400pg/mL if sinus rhythm; >=800pg/mL if AF
- Previous HF hospitalization > 1 year or in the absence of HF hospitalization:

>=600pg/mL if sinus rhythm; >=1000pg/mL if AF
5. >=14 days stable on guideline-recommended therapy (doses and number of therapies as tolerated by each patient)

Exclusion criteria

1. Heart rate <=60bpm (if sinus rhythm); heart rate <=70bpm (if AF)
2. History of HF hospitalization <=7days
3. History of myocardial infarction, myocarditis, percutaneous intervention, RCT, pacemaker/ICD implantation, cardiac surgery or stroke <=30 days
4. Estimated glomerular filtration rate (eGFR), <=30ml/min/1.73m2
5. The presence of a mechanical assist device
6. Use of inotropic drugs (dopamine, dobutamine, (nor)adrenaline, and milrinon)
7. Scheduled for mechanical assist device or heart transplantation
8. Other non-cardiac conditions with limited life expectancy
9. Amyloid, hypertrophic obstructive or constrictive cardiomyopathy
10. Accessory atrio-ventricular pathway (e.g. Wolf-Parkinson-White syndrome)
11. (Intermittent) complete heart block or second-degree AV block type Mobitz without pacemaker
12. Severe (grade III/III) aortic valve disease
13. Complex congenital heart disease
14. Proven hypersensitivity to digoxin
15. Concomitant medication that interact with digoxin
16. Use of digoxin <=6 months prior to inclusion
17. Participation in another clinical trial (registry studies not included)
18. Women who are pregnant, breastfeeding or may be considering pregnancy during the study period

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	03-07-2020
Enrollment:	982
Type:	Actual

Medical products/devices used

Registration:	No
Product type:	Medicine
Brand name:	Lanoxin
Generic name:	Digoxin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	08-01-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-12-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-06-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	07-10-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-10-2020
Application type:	Amendment

Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-02-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-03-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	17-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-04-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-02-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-02-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	09-09-2024
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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
EU-CTR	CTIS2023-509898-23-00
EudraCT	EUCTR2018-003789-15-NL
ClinicalTrials.gov	NCT03783429
CCMO	NL68235.042.18