NOSTONE Trial: Randomized double-blind placebo-controlled trial assessing the efficacy of standard and low dose hydrochlorothiazide treatment in the recurrence prevention of calcareous nephrolithiasis

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Trial Rationale

Nephrolithiasis is a global healthcare problem with a current lifetime risk of up to 18.8 % in men and 9.4 % in women. Without specific treatment, 5- and 20-year recurrence rates are 40 % and 75 %, respectively. Given the high cost of medical treatments and surgical interventions as well as the morbidity related to symptomatic stone disease, medical prophylaxis for stone recurrence is an attractive approach.

Hypercalciuria is the most common metabolic abnormality encountered in patients with recurrent nephrolithiasis and most stones contain calcium. The effect of thiazides to reduce the risk of stone recurrence has been attributed to their ability to decrease urinary calcium excretion. Efficacy of thiazides for stone prevention was tested in 11 trials in the past. However, all these trials had major methodological deficiencies. Furthermore, high doses of thiazides were employed in all trials, in the case of hydrochlorothiazide (HCTZ) up to 100 mg daily. At such high doses, side effects occur frequently. Nowadays, thiazides are widely used in the treatment of recurrent nephrolithiasis and arterial hypertension, but at significantly lower doses. In the case of recurrent nephrolithiasis, however, this practice is not supported by randomized evidence. Thus, evidence for benefits and harms of thiazides in the prevention of calcium-containing kidney stones in general remains unclear. In addition, the efficacy of the currently employed low dose thiazide regimens to prevent stone recurrence is not known.

Aims and Outcomes

We plan to assess the efficacy of standard and low dose HCTZ treatment in the recurrence prevention of calcium-containing kidney stones. More specifically, we aim to assess the dose-response relationship for three different dosages of HCTZ.

Primary outcome: Incidence of stone recurrence (a composite of symptomatic or radiologic recurrence) during study treatment and dose group.

Key secondary outcomes: Individual components of the composite primary outcome, changes in urinary biochemistry elicited by HCTZ treatment and impact of baseline disease severity, biochemical abnormalities and stone composition on treatment response.

Treatment Groups and Randomization

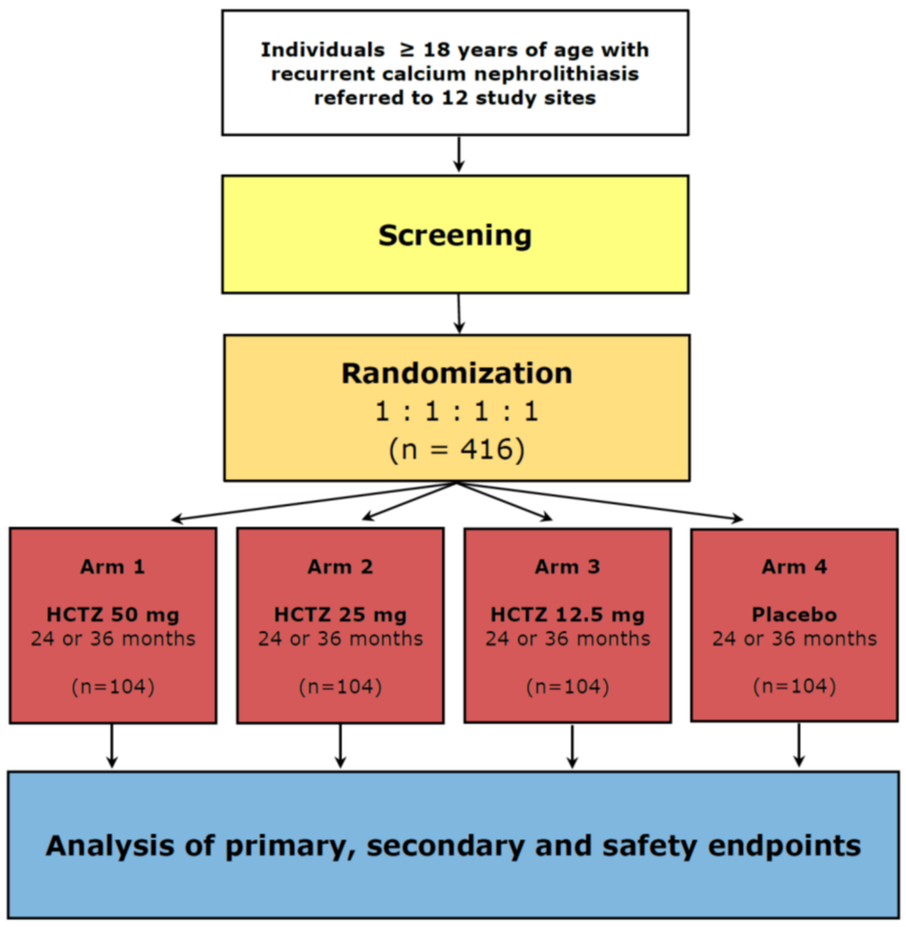


Fig 1 | Trial design schematic
416 patients in total, 104 patients per study arm.
Follow-up of 24 or 36 months, respectively.
Intention-to-treat analysis.

Main inclusion criteria:

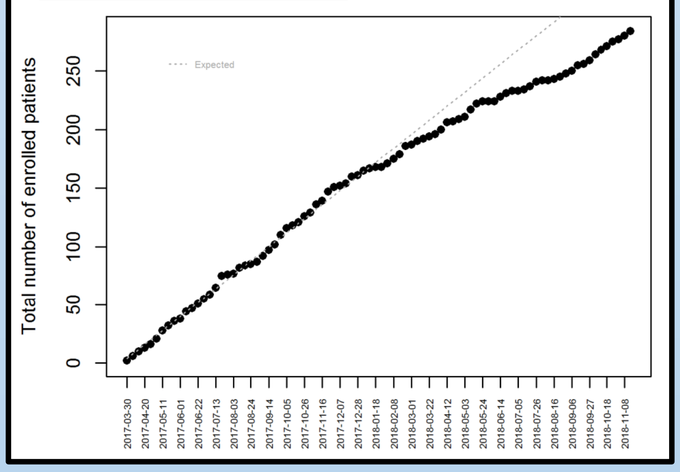
- ≥ 2 stone events within the last 10 years
- Prior stone analysis with ≥ 50% calcium oxalate, calcium phosphate or mixture of both

Main exclusion criteria:

- Patients with secondary causes of recurrent calcareous nephrolithiasis
- Drugs influencing stone progression
- CKD (eGFR < 30 ml/min)

Current Status of the Trial

The first patient was randomized March 30 2017 at the Inselspital. As of November 28 2018, **293 patients are enrolled in the trial**.



Investigational Medicinal Product (IMP)

HCTZ 12.5 mg, 25 mg or 50 mg once daily po or placebo for 24 or 36 months. Patients in all treatment arms receive state-of-the-art dietary recommendations for stone prevention according to current guidelines.

HCTZ and placebo are prepared by Laboratorium Dr. G. Bichsel AG, Interlaken, Switzerland.

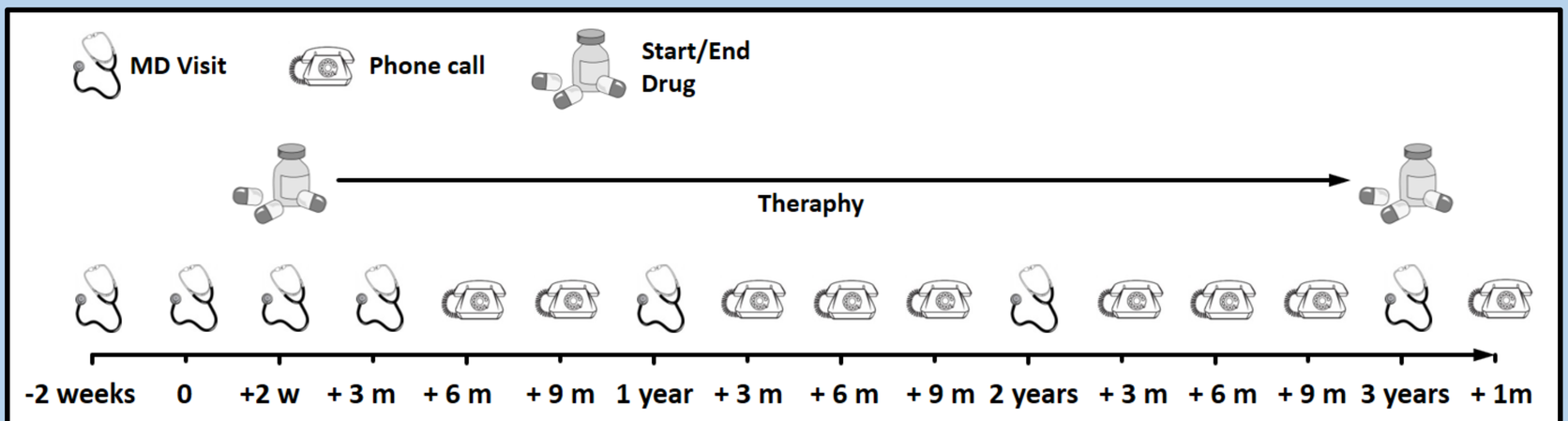


Fig 2 | Schedule of assessments
At baseline (randomization) and at the end of the study, a low-dose CT is performed.

Further information

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