

PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (<http://bmjopen.bmj.com/site/about/resources/checklist.pdf>) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Nocturnal antihypertensive treatment in type 1 diabetes patients with autonomic neuropathy and nondipping of blood pressure during night: Protocol for a randomised, placebo-controlled, double-blind, two-way cross-over study.
AUTHORS	Hjortkær, Henrik; Jensen, Tonny; Kofoed, Klaus; Mogensen, Ulrik Madvig; Køber, Lars; Hilsted, Karen; Corinth, Helle; Theilade, Karen; Hilsted, Jannik

VERSION 1 - REVIEW

REVIEWER	Frank Pistrosch, MD Medizinische Klinik III Universitätsklinik Carl Gustav Carus
REVIEW RETURNED	15-Aug-2014

GENERAL COMMENTS	This paper is a description of the design and rationale of a small single centre study. This issues dont need a peer review and should be published in a clinical trials database.
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REVIEWER	Gordon Smith University of Utah United States
REVIEW RETURNED	27-Aug-2014

GENERAL COMMENTS	<p>It is not clear whether the sample size is based on mean BP, systolic or diastolic BP.</p> <p>There are several primary outcome measures identified. Based on the background, one might expect the percent dipping to be the primary outcome.</p> <p>The references need to be confirmed. There are instances of inaccurate citation (e.g. reference 25, bottom of page 8) and statements requiring references (last sentences page 8, first page 9).</p> <p>There are a number of minor grammatical and spelling errors.</p> <p>Is there really equipoise in regards to the effect of nocturnal versus morning therapy on nocturnal dipping? Presumably the question of interest is whether correcting the reduced dipping results in reduced LV mass (and improved outcomes). It is interesting that LV mass is a secondary outcome, not the primary.</p>
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	<p>Will inclusion of patients already taking ACE inhibitors less the likelihood of a treatment effect?</p> <p>Will patients previously found to be poorly responsive to ACE inhibitors be enrolled?</p>
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VERSION 1 – AUTHOR RESPONSE

Reviewer 2:

Question 1 "Is there really equipoise in regards to the effect of nocturnal versus morning therapy on nocturnal dipping? Presumably the question of interest is whether correcting the reduced dipping results in reduced LV mass (and improved outcomes) It is interesting that LV mass is a secondary outcome, not the primary"

Answer: We thank the Reviewer for this question. We certainly agree with the reviewer that left ventricular mass is an important end-point. However, in our opinion, it has not yet been shown in a double-blind randomised study that it is possible to correct the reduced nocturnal dipping in diabetic patients with autonomic neuropathy. It is correct that previous studies have shown lower night blood pressure in patients treated with antihypertensive drugs in the evening. But, to our best knowledge, all the studies have been observational and not blinded or randomised. The risk of bias influencing compliance and nocturnal blood pressure is not negligible in such studies. Also, we want to study LV mass as a primary end point, but before doing that we want to know the effect and possible mechanism of action of nocturnal antihypertensive treatment.

Question 2 "Will inclusion of patients already taking ACE inhibitors less the likelihood of a treatment effect?"

Answer: We don't think so. We believe that most type 1 diabetic patients with long diabetes duration receive ACE inhibitors. Despite this a significant number have nondipping of blood pressure during night. Our idea is that correcting of nondipping depends on time of dosage of the antihypertensive medication. therefore, we want to compare morning and bedtime dosing of Enalapril.

Question 3 "Will patients previously found to be poorly responsive to ACE inhibitors be enrolled"

Answer: No. If we have information that a patient has experienced clinical significant side effects to ACE inhibitors or previously has been poorly responding to ACE inhibitors he will not be enrolled in the study.

Correction

Hjortkær H, Jensen T, Kofoed K, *et al.* Nocturnal antihypertensive treatment in patients with type 1 diabetes with autonomic neuropathy and non-dipping of blood pressure during night time: protocol for a randomised, placebo-controlled, double-blind, two-way crossover study. *BMJ Open* 2014;4:e006142. The name of the first author of this paper was spelled incorrectly. This author's correct name is Henrik Øder Hjortkær.

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