Directly Observed Therapy in Uncontrolled Hypertensive Patients

Results from a systematized review and preliminary results from a randomized controlled pilot trial

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Directly Observed Therapy in Uncontrolled Hypertensive Patients

Part I:
A systematized review with emphasis on the directly observed therapy procedure

Part II:
A research paper reporting preliminary results from a randomized controlled pilot trial investigating directly observed therapy in a specialist nephrology outpatient clinic

Master Thesis

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Directly Observed Therapy in Uncontrolled Hypertensive Patients

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Abstract

Background and purpose

Directly observed therapy (DOT), or witnessed intake of hypertensive patients’ prescribed medication, has been introduced in hypertension research and reported in the literature since 2011 with emphasis on treatment resistant hypertensive (TRH) patients. Studies have shown a rather clear tendency towards non-adherence to medications in many TRH patients, and attention towards adherence has increased. Our research group has participated actively in the utilization of DOT in hypertension research since 2011. In this compilation summary the aim was to identify how the DOT procedure was applied in ongoing research and published research, and to identify the geographical spread of DOT in hypertension as well as on which level of care the procedure was applied.

Materials and methods

Twelve clinical trials registers were searched for ongoing research, identifying five ongoing trials. A systematic search in four literature databases was conducted resulting in ten selected reports, which were reviewed using the systematized review methodology. Ten key points of information were identified and systematized.

Results

Researchers from four nations were identified being engaged in research of DOT in hypertensive patients. Five ongoing trials of different methodologies were identified, of which three investigated the use of DOT. Ten published reports, hereof five studies, were identified, and ten key points of information, including level of care, were identifiable in eight of ten reports describing the DOT-HTN procedures. Three reports had rather similar procedures with observed full dose of morning medications and a maximum of two hours of post-DOT observation. Three reports had longer post-DOT observation time, two of them with medication administration intervals, and blood pressure measurement intervals. Two were case reports, describing severe post-DOT adverse reactions, contributing with important safety information. All reports either described safety measures or
discussed the safety of DOT. In eight of ten publications, no characteristics of the patients undergoing DOT, were described.

**Conclusion**

A known procedure, DOT, has been introduced to a new population, namely patients with hypertension. Reports are scarce and describe different DOT procedures, as well as lack data on patient characteristics. It is of utmost importance that future research characterizes the patients who are found to be non-adherent after directly observed therapy of antihypertensive medications. Equally important is it that large randomized controlled trials are conducted, to investigate whether the DOT-HTN procedure is safe, and has effect on blood pressure in uncontrolled or treatment resistant hypertensive patients. Ethical challenges regarding the use of DOT-HTN exist and must be debated.
Preface

The present work has been funded by and carried out at the Department of Nephrology and the Section for Cardiovascular and Renal Research (SCRR) at Oslo University Hospital (OUH) – Ullevaal. I have enjoyed quality education, at the Institute of Health and Society at the University of Oslo. Part I of the thesis is a Systematized review of what is known about directly observed therapy in hypertension (DOT-HTN), and ongoing research on DOT-HTN. Part II is a research paper of preliminary results from our randomized controlled trial: Adherence to antihypertensive medication: a randomized controlled pilot trial implementing directly observed therapy prior to ambulatory blood pressure measurement (DRIVE). The paper is formatted to the requirements of the Taylor & Francis journal “Blood Pressure” except that graphics are placed in the text at the readers’ convenience.

Aud Høiegen, MD, PhD, head of the Nephrology outpatient clinic, was my main supervisor and a natural choice in her capacity as project leader of the study providing the main rationale for the DRIVE study conducted as part of this thesis.

Marit Helen Andersen, RN, PhD, was co-supervisor representing the Institute of Health and Society, and Anne Cecilie K. Larstorp, MD, PhD, was co-supervisor and former investigator and colleague from the SCRR. All three have provided quality supervision from their different perspectives, and their collaboration has been valuable and supportive. Thank you all!

Thanks to Vibeke N. Kjær, my colleague at SCRR, for supporting me, and thanks to Fadl Elmula M. Fadl Elmula, MD for crucial inputs to the design of the DRIVE study.

A special thanks goes to Pernille Fabritius Dybvad and Tone Rambjør Heimstad, who with their professional and personal skills have contributed in the planning and execution of every patient visit in the DRIVE study. Thank you for keeping me going!

I thank my family for cheering me along, especially my husband Michael and my son Jens Øivind (10 years) for their patience and loving support. Love always.

Oslo, June 2016

Ulla Pilemand Hjørnholm
### ABBREVIATIONS

<table>
<thead>
<tr>
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<th>Definition</th>
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<tbody>
<tr>
<td>ABP</td>
<td>Ambulatory blood pressure</td>
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<tr>
<td>ABPM</td>
<td>Ambulatory blood pressure measurement</td>
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<td>ADBP</td>
<td>Ambulatory diastolic blood pressure</td>
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<tr>
<td>ASBP</td>
<td>Ambulatory systolic blood pressure</td>
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<tr>
<td>BP</td>
<td>Blood pressure</td>
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<tr>
<td>DOT</td>
<td>Directly observed therapy</td>
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<tr>
<td>DOT-ART</td>
<td>Directly observed therapy-antiretroviral therapy</td>
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<tr>
<td>DOT-HTN</td>
<td>Directly observed therapy-hypertension</td>
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<td>DOTS</td>
<td>Directly observed therapy-short course</td>
</tr>
<tr>
<td>ESH/ESC</td>
<td>European Society of Hypertension/European Society of Cardiology</td>
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<tr>
<td>HIV/AIDS</td>
<td>Human immunodeficiency virus/Acquired immunodeficiency syndrome</td>
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<td>HPLC-MS</td>
<td>High performance liquid chromatography–mass spectrometry</td>
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<td>HTN</td>
<td>Hypertension</td>
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<tr>
<td>NOKC</td>
<td>Norwegian Knowledge Centre for the Health Services</td>
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<td>OBP</td>
<td>Office blood pressure</td>
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<td>OUH</td>
<td>Oslo University Hospital</td>
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<tr>
<td>PRISMA</td>
<td>Preferred reporting items for systematic reviews and meta-analyses</td>
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<tr>
<td>RCT</td>
<td>Randomized controlled trial</td>
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<tr>
<td>RDN</td>
<td>Renal denervation</td>
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<tr>
<td>SCRR</td>
<td>Section for Cardiovascular and Renal Research</td>
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<tr>
<td>SyR</td>
<td>Systematized review</td>
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<tr>
<td>TB</td>
<td>Tuberculosis</td>
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INTRODUCTION

Since 2010 I have been part of the initiation, coordination and implementation of hypertension trials conducted by the research group Section of Cardiovascular and Renal Research (SCRR) (1) located at Oslo University Hospital (OUH). Directly observed therapy (DOT) of hypertensive patients have been part of two SCRR trials and have from the start caught my interest. The procedure brought to immediate attention the rather high proportion of patients deliberately deviating from doctor-patient-agreed antihypertensive treatment, and honestly came as a shock to us, even though non-adherence was a known obstacle in hypertensive treatment.

In Part I of this master thesis I present the background and explanation of rationale, followed by a short historical background of DOT and how DOT over the years has been modified and used within different fields of diseases. With the aim to present and discuss what is known about DOT in hypertension (HTN), I have chosen to make use of the review methodology, described in details in chapter 2. Chapter 3 presents the results of the review, i.e. where research on DOT-HTN is conducted, what research is ongoing throughout March 2016, and how and at which level of care the procedure is applied to the patients. Chapter 4 is a discussion of the systematized review methodology followed by a discussion of the results. Clinical implications and ethical considerations of DOT-HTN are discussed, before I draw my conclusions.

Part I: A systematized review with emphasis on the directly observed therapy procedure

1.1 Background and rationale

DOT-HTN is a health personnel observed, or witnessed intake, of difficult-to-control hypertensive patients’ medication before ambulatory blood pressure measurement (ABPM) and is a method introduced in hypertension research during the past 6 years. SCRR (1) has participated in, and followed the introduction of this method. We have observed and reported
on the method in two SCRR hypertension studies (2, 3), and found only a few reports in the literature addressing the issue (4, 5). DOT, as an adherence assessment method, has been mentioned as part of the design considerations for future clinical trials in HTN (6), and is of particular interest to researchers involved with treatment resistant hypertension (TRH). Patients with TRH have a sustained systolic BP >140 mmHg and/or diastolic BP >90 mmHg despite a minimum of three different antihypertensive drug classes in highest tolerated doses including a diuretic during at least 6 months of treatment (7). Another objective way of measuring adherence in TRH patients has been reintroduced almost simultaneously to DOT. By taking a blood- or urine sample and analysing it with high performance liquid chromatography coupled with mass spectrometry (HPLC-MS/MS), one can detect medication or it’s metabolites, and know for certain if medication has been taken (8).

Prevalence of TRH is highly debated and range from 1-30 % of the hypertension population (7). Studies published during the last 5 years question whether patients are true treatment resistant or rather non-adherent to medication (3, 4). Ceral et al (9) evaluated serum from 84 difficult-to-control hypertensive patients with HPLC-MS/MS and found components of all antihypertensive drugs in only 29 (34,5%) patients, and no detectable drugs in the serum of other 29 (34,5%) patients. Jung et al (10) identified 76 (20%) TRH patients out of 375 uncontrolled hypertensive patients and assessed adherence to antihypertensive medications with urine screening. 40 of 76 (53%) patients were non-adherent to prescribed antihypertensive medications of which 12 patients had no detectable drugs in urine, 28 patients had incomplete adherence and 24 of these had taken less than 50% of the prescribed drugs. Other studies confirm that objective evaluation of serum or urine reduces the number of patients with true TRH (11, 12).

In our study, presented in part II, we chose to include patients with uncontrolled, but not necessarily treatment resistant hypertension. We focused on patients using at least two antihypertensive drugs, knowing that possibly some TRH patients would be amongst the included, which turned out to be true.

In two of four SCRR studies where DOT has been used, our team acquired first-hand experiences of how DOT could lead to extraordinary situations when applied to hypertensive patients. Two of the cases where I was directly involved are described here, based on my memory, because they provide important insight to real life implementation of DOT-HTN and
generates questions that in my view need to be addressed in the process of implementing DOT.

**Case 1:** A young woman was referred from a nephrology specialist at a smaller hospital, with the specific wish to be included in our ongoing renal denervation study. The patient’s husband accompanied her to the visit. They had a seemingly trusting relationship and alternated in telling about the difficulties connected with the wife’s illness. They had three children of younger age and they both expressed deep concern about the severe nature of the wife’s hypertension, explaining how intensive work up had revealed end organ damage in kidneys, and major blood vessels elsewhere in her body. Her systolic BP was habitually around and above 200 mmHg and BP lowering intervention was necessary to prevent early death. She said that she took her medications as prescribed, but with subsequent dizziness and nausea. In the referral letter it was specifically stated that there was no suspicion of non-adherence. She said that she had tried a variety of medications but none had lowered her BP satisfactory. She and her husband seemed in despair, and she expressed a hope of randomization to the study’s treatment arm with renal denervation.

The patient was screened according to procedure, which implicated DOT prior to ABPM. 15 to 20 minutes after DOT she expressed a wish to lay down, looking pale and sweating. Her BP decreased dramatically (13) and she was acutely transferred to the Emergency Department.

In a situation like this, it is important to question the safety of DOT-HTN. Are there any rare conditions or hypertension phenotypes that if recognized could have foreseen the acute development in this case? Can or should DOT-HTN be applied to anyone?

**Case 2:** A much less dramatic, yet interesting case from the present study concerned a middle-aged well-educated man whom in a letter was informed of DOT prior to the visit. His instructions were to bring his antihypertensive medications in original packaging, and not in a pre-dispensed pillbox. He was also informed that the medication should be taken in front of the study nurse.

Arriving to the visit, the first thing he did was to question the reason for using DOT in general terms, “why was this necessary?”. He allegedly accepted the explanation given, that DOT was used in the present study but was not in details informed of initially in the Informed
Consent Form (ICF), otherwise jeopardizing the element of control. I got up to fetch a glass of water facing away from the patient. When turning around again the patient declares: “now I have taken the medication”, without me witnessing the intake.

This patient clearly did not want to take any medication under observation. He did not withdraw from the study, but deliberately deviated from instructions given. Would prior detailed information about DOT, have made him decline participation? Did he feel mislead?

These and other extraordinary cases in addition to reports from the literature (14) inspired me to conduct a review in order to elaborate more on DOT-HTN. The procedure also satisfies the ubiquitous demand for innovative initiatives in health research, which served as an additional argument to elucidate the practice of DOT within the field.

1.2 Historical background of directly observed therapy (DOT)

I begin with a short version of the inescapable historical background and the work of Dr. Karel Styblo (15) resulting in a global implementation of DOT. Directly observed therapy – short course (DOTS) was in 1994 endorsed by the World Health Organization (WHO) (16) to fight the deadly contagious disease tuberculosis (TB). DOTS was a strategy to improve TB treatment adherence and outcome, and had five components: government commitment, quality laboratory facilities to assure diagnosis, continuous supply of high-quality drugs, management and documentation of progress and treatment effect on an individual level (monitoring, recording and reporting), and direct observation by health personnel of patients swallowing pills (15, 17). By 2008 the implementation of DOTS in more than 190 countries had cured 36 of 43 million patients (18). DOTS furnished countries of poor health infrastructure with a long awaited framework enabling the health authorities to manage and treat a deadly contagious disease. DOTS has since been criticized both in regards to its effect on adherence and outcome (19, 20), and the ethical aspect of the legislation forced on people. In Norway, all asylum-seeking refugees are screened according to the DOTS framework incorporated in the law (21), and treated if disease is detected. TB medications are highly toxic, with possible severe adverse effects on liver and eyes that can lead to death or blindness. The close monitoring of medication intake and adverse reactions in patients are therefore crucial functions of the DOTS framework (19).
A few years after DOTS was globally implemented an initiative was launched to do the same in the treatment of human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) (22). The similarities of the two diseases in terms of uncontrolled global spread and need for uninterrupted high-quality drug supplies as well as monitoring and reporting are obvious, and the term directly observed therapy with antiretroviral therapy (DOT-ART) has since labeled the procedure and enabled researchers and stakeholders to separate it from DOTS. The most visible difference between DOTS and DOT-ART is the lifelong treatment profile of HIV/AIDS, in comparison to the “short course” profile of TB (15).

1.3 DOT in hypertension

The use of DOT-HTN is rather new. Studies have reported the use of DOT prior to 24 hour ABPM since 2011 (2-4, 13, 23). In 2016 Hameed et al (5) reported having established a “DOT clinic” in 2007 at the Birmingham Heartlands Hospital, UK, headed by a clinical pharmacist and run by a specialist hypertension nurse. Other such initiatives might exist (4) but are not to our knowledge reported in the literature.

A one-time adherence control with DOT prior to ABPM will after only 24 hours, give you the results of the patients true BP lowering effect of the prescribed regimen – in writing. DOT provides an objective measurement tool that exempts physicians from relying on their own (poor) judgement of the patient’s adherence (24) or the patient’s own (unreliable) declaration of adherence (25, 26).

SCRR was among the first to introduce DOT in hypertensives (Fig. 1), as a screening tool in studies regarding renal denervation (RDN) in treatment resistant hypertensive patients (2, 3). Contemporary randomized controlled RDN trials conducted between 2010-2015 (13) did not use DOT as direct assessment method of treatment adherence, instead they used plasma drug concentration (27, 28), one of these in combination with a questionnaire (28), or indirect assessment methods like diaries (29-31) and interviews (32).
Figure 1. In Oslo RDN Study 13 patients were confirmed non-adherent to their antihypertensive medication after DOT prior to ABPM, from reference (3) used with permission.

1.3.1 Safety

The safety profile of DOT-HTN has been reported to vary from drug-induced adverse effects of light hypotension (5) to severe hypotension (3, 5) leading to renal failure (14). One element of extreme importance to safety is that health personnel do not administer medications from pre-dispensed pill-boxes brought by the patient, but dispense from original packaging brought by the patient, alternatively prescribed from the hospital pharmacy (5).

No! Yes!

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2 METHODS

Inspired by the SCRR studies and their extraordinary cases as well as the literature I wanted to further investigate the use of DOT-HTN. On the Norwegian Knowledge Centre for the Health Services (NOKC) (33) website I found information on how to summarize research. NOKC’s mandate to promote utilization of research results and measure the quality of health services to improve patient safety (33) was all in-line with my wish to gain further knowledge in a scientifically satisfactory way of DOT-HTN. I was inspired by the PRISMA 2009 checklist (34), as a tool to build my review, though not the entire 27 items, since I did not conduct a meta-analysis, and did not have any focus on effect, i.e. DOT’s effect on BP.

Besides NOCK and PRISMA I used the definitions in Grant and Booth’s 2009 (35) review article: A typology of reviews: an analysis of 14 review types and associated methodologies. Grant and Booth describe in understandable terms the differences and similarities between the various kinds of reviews, and how to best fit the right review methodology to the question it is meant to address (35). Choosing the right review is not completely simple. The nature of the research question decides the methodology, however you have to consider how rigorous you need or wish to be, combined with your time window and skills (35). I wanted to perform a scientifically satisfactory review within the time scope of my master, and based on my current skills as a master student. In the discussion I provide ethical considerations regarding DOT-HTN, based on a comparison of one of the case reports identified in the literature, and case # 1 described in section 1.1 p. 3, followed by suggestions of ethical considerations prior to future research on DOT-HTN.

2.1 Research question

2.1.1 Summarizing the evidence base

The questions I wanted to find answers to were:

1) What has been published on DOT-HTN so far, that can inform us of the geographical spread of DOT-HTN, and on which level of care the procedure is applied, and what kind of research on DOT-HTN is ongoing?

2) Do DOT-HTN procedures exist, that could form a future safe standard research procedure?
2.2 Review methodologies

In Grant and Booth’s (35) review there are seven of fourteen review methodologies which in their own ways could be used to answer my questions (2.1.1), confirming that there are no “one size fits all” approach to a review process (35). The review methodologies that in their different ways are fit for purpose in the current review are the literature review, the mapping review, the overview, the rapid review/rapid evidence assessment, the scoping review, the systematic search and review and the systematized review (35).

Based on the research questions (2.1.1) and my status as a master student I decided to do a systematized review (SyR) (35). In a SyR one attempts to do a systematic review without the comprehensiveness fundamental to a systematic review. SyRs are typically conducted by postgraduate students, with limited resources and experience. The SyR methodology requires a systematic literature search and a subsequent cataloging of citations. A SyR may proceed a more extensive work or a research project (35).

2.2.1 Literature search

A specialist medical librarian from the University of Oslo Library assisted the literature search, as recommended in the methodology literature (33, 35). We chose to search PubMed, Ovid MEDLINE, The Cochrane Library, and EMBASE for citations through March 31st 2016, using the search terms “directly observed therapy” and “witnessed intake of medication” in title and abstract, to further focus the search on reports with emphasis on DOT. To allow others to repeat the search, the entire search strategy is present in appendix 1.

2.2.2 Selection criteria

All identified citations in English, regardless of date of publication, type of report and scientific quality, were eligible in the review, with the exception of abstracts and short commentaries. Non-eligible were citations from the field of TB and HIV/AIDS. Grey literature (e.g. internal web-based standard operational procedures) was not part of the search. Due to DOT-HTN being a novel procedure, the selection criteria were deliberately broad to capture all types of reported attempts to use DOT-HTN. I would add citations found by hand searching bibliographies in relevant papers, and corresponded with colleagues to identify
missed citations. All selected citations were exported to my EndNote Library and checked for duplicates.

2.2.3 Search in international trials registers

To identify the present use of DOT in HTN research (36) an advanced search in International Committee of Medical Journal Editors (ICMJE) (37) endorsed primary registries of WHO International Clinical Trials Registry Platform (ICTRP) (38) was conducted using the terms: directly observed therapy, witnessed intake of medication and hypertension.

In summary four literature databases (39-42) and twelve trial registers (43-55), were searched in the effort to map what have come out of already conducted research on DOT-HTN and what research is ongoing on DOT-HTN.

2.2.4 Data extraction

Published research

Extracted data from the published material included year of publication, research location, type of report, method/design, participant characteristics, number of antihypertensive drugs, pre- and post-DOT-HTN blood pressure measurements.

DOT-HTN procedure

To describe the procedure the following ten key points of information were extracted: Level of care, group of patients, anamnestic- and investigational procedures prior to DOT, information given to patients prior to DOT, time of DOT, administration of medications, medical observations immediately after DOT, safety measurements, information given to patients after DOT, and follow-up visits.

Ongoing research

Extracted data from the ongoing research were trial register, unique study ID-number, location of study, commercial status, study title, main objective, primary endpoint, planned number of subjects to be included, and the role of DOT-HTN.
3 RESULTS

3.1 PRISMA flowsheet of literature search

Records identified through search in PubMed, Ovid MEDLINE, The Cochrane Library, EMBASE
n = 132

Records after duplicates removed
n = 116

Records screened
n = 116

Records on non-HTN research excluded
n = 103

Records excluded:
Abstracts n= 2
Short commentary n= 1

Full-text records assessed for eligibility
n = 13

Studies included in systematized review
n = 10

Figure 2. PRISMA (34) flowsheet, showing the record selection process
### 3.2 Identified ongoing trials

Search in trial registers identified three (2, 3, 56) of the five published trials and five ongoing trials. I cite (in italic) and point to the reference only once per study.

Two of the ongoing trials were found in the EU Clinical Trials Register (45):

1. **EudraCT Number 2005-001004-39, University of Edinburgh, UK (non-Commercial) (57):**

   **Title:** “Investigation of combined phosphodiesterase 5 inhibitor and isosorbide mononitrate for the treatment of resistant hypertension”.

   **Study design:** Randomized controlled trial

   **Main objective:** “to characterize the effect on blood pressure of a combination of single doses of sildenafil and isosorbide mononitrate in patients with resistant hypertension”.

   **Primary endpoint:** “Effect on blood pressure of the drug combination”.

   **Planned number of subjects to be included:** “40”.

   DOT was used as a screening tool and were “performed prior to qualifying ABPM”. No description of the DOT-procedure was available.

2. **EudraCT Number 2013-001227-40, Serodus ASA, Norway (Commercial) (58):**

   **Title:** “A study assessing the safety, tolerability and efficacy of a new medication (SER100) in patients with Isolated Systolic Hypertension (ISH) insufficiently treated with 1-3 other anti-hypertensives”.

   **Study design:** Randomized controlled trial

   **Main objective:** “Evaluate safety and tolerability of SER100 vs. placebo in patients with ISH”.

   **Primary endpoint:** “Adverse events”.


Planned number of subjects to be included: “30”.

DOT was used as a screening tool to “prove resistance to treatment” and the DOT-procedure was described as “intake of the underlying 1-3 anti-hypertensives must be witnessed by clinic staff prior to the qualifying ABPM”.

The third ongoing trial was found in the British ISRCTN trial register (44):

3. ISRCTN57475376, Royal Devon & Exeter Hospital (Wonford), (funded by Gawthorn Cardiac Trust (UK)) (59):

Title: “Diagnosing and treating severe hypertension (Acronym: DASHER)”.

Study design: Retrospective interventional

Main objective: “exploring whether a new nurse-led treatment protocol can successfully treat patients with a new diagnosis of severe hypertension within 18 weeks, whilst examining the reasons for failure to achieve blood pressure goals in this cohort”.

Primary endpoint: “The proportion of patients with a new diagnosis of severe hypertension who achieve a BP target of < 140/90 mmHg at 18 weeks”.

Planned number of subjects to be included: “100”.

DOT was in this study, together with TDM, a secondary outcome measure of “the proportion of patients not reaching target BP who are found to be non-adherent to treatment using directly observed therapy (DOT) and urinary panel testing”. No description of the DOT-procedure was available.

In the American ClinicalTrials.gov (43) the fourth and fifth ongoing trails were identified:

4. NCT02362893, Oslo University Hospital, Norway (non-Commercial) (60):

Title: “Treatment of Hypertension: an Interventional Approach to Improve Blood Pressure Control (Acronym: DRIVE)”.

Study design: Randomized controlled trial (pilot)
Main objective: “access the change in mean daytime systolic blood pressure in participants with essential hypertension not adequately controlled...randomly assigned to either an intervention group with one-time only DOT immediately followed by ABPM or a control group with standard ABPM”.

Primary endpoint: “Difference in change in mean 24 hour ambulatory systolic daytime blood pressure between the two groups from baseline to follow-up”

Planned number of subjects to be included: “20”.

DOT was used as an adherence assessment in the intervention group and the DOT-procedure was described as “patients allocated to the intervention group take their medication (from original blister packaging) in front of the investigator who observe the patient swallowing the medication. To secure the principals of Direct Observed Therapy, the patient do not leave the clinic for two hours.”

5. NCT02513524, Ottawa Hospital Research Institute, Canada (non-Commercial) (61):

Title: “The Prevalence of Pseudo-resistant Hypertension using the Direct Observed Therapy Test: A Prospective Observational Study”.

Study design: Prospective observational

Main objective: “Measure the proportion of patients with resistant hypertension who are non-adherent based on direct observed therapy, and follow them up to examine the impact of this diagnosis”.

Primary endpoint: “The proportion of patients who continue to have resistant hypertension after administration of direct observed therapy, on the basis of the 24 hour ambulatory testing”.

Planned number of subjects to be included: “60”.

DOT is used as an adherence assessment in all patients. The DOT-procedure, being part of standard care procedure in the department executing the trial, is described as “1. Administer and observe ingestion of usual morning antihypertensive medications. 2. Monitor BP every 30 minutes, using 5 readings of an automated oscillometric BP
device (BP-TRU), until plateau affect achieved, defined as 3 consecutive cycles of BP readings declining by less than 10 mmHg per cycle. 3. Registered Nurse (RN) repeats standing BP prior to initiation of 24 hour Ambulatory Blood Pressure Monitoring (ABPM). 4. RN initiates 24 hour ABPM

In summary two trials (57, 58) were pharmaceutical RCTs, where DOT was part of the screening of eligibility before enrolment, planning to enrol 40 and 30 participants, respectively. One study (58) described the DOT-procedure used. The remaining three trials were designed as retrospective interventional (59), RCT (pilot) (60) and prospective observational (61), planning to enrol 100, 20 and 60 participants, respectively. Two studies (60, 61) described the DOT-procedure used.

3.3 Identified published research

The literature search identified 10 publications (Fig. 2). Among the ten citations reviewed, three came from Norway, the others from the United Kingdom (UK), Germany and Canada. Half of the citations were studies (2-4, 56), the remainder consisted of two reviews (62, 63), two case reports (14, 64) and one editorial (65) (Table 1). All citations referred to DOT-HTN of treatment resistant hypertensive patients. One study (4) used DOT to identity non-adherence in uncontrolled hypertensive patients. Three studies (2, 3, 56) and one case report (14) used DOT as a screening tool to verify resistance to hypertensive medications prior to RDN. One patient in the other case reported (64) had already had the renal denervation procedure done before adherence assessment with DOT-HTN. One study (5) reported on patients who were worked-up following a standard protocol mainly prior to RDN. In total sixty-eight patients were reported non-adherent after DOT in seven citations.

In eight (2-5, 14, 56, 62, 64) of ten citations the DOT-procedure was described (Table 2). Ten key points of information were identified in the eight reports that described DOT-procedures. Three reports, all Norwegian, had rather similar procedures with a maximum of two hours of post-DOT observation. The two case reports, described severe post-DOT adverse reactions. Three reports had longer post-DOT observation time, two of them with medication administration intervals, instead of complete morning dose administration. All reports either described safety measures or discussed the safety of DOT. In eight of ten publications, no characteristics of the patients undergoing DOT were described. The two case reports (14, 64)
provided detailed information about their cases including age, gender, and number of antihypertensive medications including diuretics. The five studies provided no demographic information about the patients who were non-adherent after DOT.

Three studies (3-5) reported pre- and post DOT blood pressure measurements, one of them (3) ABP, two of them (4, 5) OBP and ABP. One study (56) provided no data on the 2 patients with non-adherence after DOT.
Table 1. Differences in the reporting of patient characteristics after directly observed therapy in hypertension

<table>
<thead>
<tr>
<th>NCT no.</th>
<th>NCT01673516</th>
<th>NA</th>
<th>NCT01673516</th>
<th>NA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year of report (reference)</td>
<td>2011 (4)</td>
<td>2013 (2)</td>
<td>2013 (62)</td>
<td>2014 (3)</td>
</tr>
<tr>
<td>Location</td>
<td>London, UK</td>
<td>Oslo, Norway</td>
<td>Ottawa, Canada</td>
<td>Oslo, Norway</td>
</tr>
<tr>
<td>Type of report</td>
<td>Research Letter</td>
<td>Original Article</td>
<td>Case Report</td>
<td>Original Article</td>
</tr>
<tr>
<td>Method/design</td>
<td>Prospective observational</td>
<td>Prospective observational</td>
<td>Case report</td>
<td>Randomized Controlled Trial</td>
</tr>
<tr>
<td>Patients with applied DOT (% women)</td>
<td>n=37 (64.8%)</td>
<td>n=18 (11%)</td>
<td>n=1 (100%)</td>
<td>n=65 (-)</td>
</tr>
<tr>
<td>Age, all patients, years, mean (range)</td>
<td>57 (20-87)</td>
<td>(39-68)</td>
<td>53</td>
<td>–</td>
</tr>
<tr>
<td>Patients confirmed true treatment resistant after DOT</td>
<td>n=14</td>
<td>n=6</td>
<td>n=0</td>
<td>n=19</td>
</tr>
<tr>
<td>Patient considered non-adherent after DOT (%)</td>
<td>n=23 (62.2%)</td>
<td>n=3 (16.6%)</td>
<td>n=1 (100%)</td>
<td>n=13 (20%)</td>
</tr>
<tr>
<td>Age, years</td>
<td>–</td>
<td>–</td>
<td>53</td>
<td>–</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>–</td>
<td>–</td>
<td>Female</td>
<td>–</td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>–</td>
<td>–</td>
<td>6</td>
<td>–</td>
</tr>
<tr>
<td>On diuretics (%)</td>
<td>–</td>
<td>–</td>
<td>1 (100%)</td>
<td>–</td>
</tr>
<tr>
<td>OSBP in mmHg at referral or baseline, mean</td>
<td>179</td>
<td>–</td>
<td>177</td>
<td>–</td>
</tr>
<tr>
<td>ODBP in mmHg at referral or baseline, mean</td>
<td>98</td>
<td>–</td>
<td>106</td>
<td>–</td>
</tr>
<tr>
<td>OSBP in mmHg after applied DOT, mean</td>
<td>144</td>
<td>–</td>
<td>97 (after 1 h)</td>
<td>94 (after 2 h)</td>
</tr>
<tr>
<td>ODBP in mmHg after applied DOT, mean</td>
<td>83</td>
<td>–</td>
<td>68 (after 1 h)</td>
<td>68 (after 2 h)</td>
</tr>
<tr>
<td>Decrease in OSBP in mmHg pre- to post-DOT</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Decrease in ODBP in mmHg pre-DOT to post-DOT</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>ASBP in mmHg at referral or baseline, mean (±SD)</td>
<td>–</td>
<td>–</td>
<td>176 (after 5 h)</td>
<td>24h 160 (20)</td>
</tr>
<tr>
<td>ADBP in mmHg at referral or baseline, mean (±SD)</td>
<td>–</td>
<td>–</td>
<td>100 (after 5 h)</td>
<td>24h 99 (16)</td>
</tr>
<tr>
<td>ASBP in mmHg after applied DOT, median (range) or mean (±SD)</td>
<td>–</td>
<td>–</td>
<td>139 (111, 207)</td>
<td>dt 135</td>
</tr>
<tr>
<td>ADBP in mmHg after applied DOT, median (range) or mean (±SD)</td>
<td>–</td>
<td>–</td>
<td>80 (63, 97)</td>
<td>dt 69</td>
</tr>
<tr>
<td>Decrease in ASBP in mmHg pre-DOT to post-DOT</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Decrease in ADBP in mmHg pre-DOT to post-DOT</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>DOT procedure described</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Health personnel applying DOT</td>
<td>specialist nurse</td>
<td>physician</td>
<td>–</td>
<td>physician/nurse</td>
</tr>
<tr>
<td>Defined cut-off value to indicate non-adherence</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Safety reported/discussed</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
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</tbody>
</table>

NCT no.= ClinTrial.gov identification, - = Not reported, NA= Not applicable, RCT= Randomized controlled trial, DOT = Directly observed therapy, OSBP= Office systolic blood pressure, ODBP= O Diastolic BP, ASBP= Ambulatory SBP, h= hour(s), dt= daytime, nt= nighttime, †= reported in figures not numbers
Table 1. (continued) Differences in the reporting of patient characteristics after directly observed therapy in hypertension

<table>
<thead>
<tr>
<th>NCT no.</th>
<th>Year of report (reference)</th>
<th>Location</th>
<th>Type of report</th>
<th>Method/design</th>
<th>Patients with applied DOT (% women)</th>
<th>Age, all patients, years, mean (range) or (±SD)</th>
<th>Patients confirmed true treatment resistant after DOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>NA</td>
<td>2014 (14)</td>
<td>Homburg/Saar, Germany</td>
<td>Letter to the Editor</td>
<td>Case report</td>
<td>n=1 (0%)</td>
<td>59 (n= 48)</td>
<td>n=0</td>
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<tr>
<td>NCT 01630928</td>
<td>2015 (5)</td>
<td>Birmingham, UK</td>
<td>Original Article</td>
<td>Retrospective Observational</td>
<td>n=50/48* (52.1%)</td>
<td>62.0 (11.0) (n= 23)</td>
<td>n= 25/23* (21%)</td>
</tr>
<tr>
<td>NA</td>
<td>2015 (54)</td>
<td>Tromso, Norway</td>
<td>Original Article</td>
<td>Prospective Observational</td>
<td>(n= 23)</td>
<td>53 (8.4)</td>
<td>-</td>
</tr>
<tr>
<td>NCT 0630928</td>
<td>2015 (60)</td>
<td>Ottawa, Canada</td>
<td>Review</td>
<td>Review</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>NA</td>
<td>2015 (61)</td>
<td>Oslo, Norway</td>
<td>Review</td>
<td>Review</td>
<td>-</td>
<td>-</td>
<td></td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Patient considered non-adherent after DOT (%)</th>
<th>n=1 (100%)</th>
<th>n= 25 (50%)</th>
<th>n= 2 (8%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>59</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>Male</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>No. of antihypertensive drugs</td>
<td>10</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>On diuretics (%)</td>
<td>1 (100%)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>OSBP in mmHg at referral or baseline, mean(±SD)</td>
<td>-</td>
<td>184.1 (23.9)</td>
<td>-</td>
</tr>
<tr>
<td>ODBP in mmHg at referral or baseline, mean(±SD)</td>
<td>-</td>
<td>102.5 (21.4)</td>
<td>-</td>
</tr>
<tr>
<td>OSBP in mmHg after applied DOT</td>
<td>70</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ODBP in mmHg after applied DOT</td>
<td>50</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Decrease in OSBP in mmHg pre-DOT to post-DOT</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Decrease in ODBP in mmHg pre-DOT to post-DOT</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>ASBP in mmHg at referral or baseline, daytime/nighttime mean</td>
<td>168/169</td>
<td>†</td>
<td>-</td>
</tr>
<tr>
<td>ADBP in mmHg at referral or baseline, daytime/nighttime mean</td>
<td>108/114</td>
<td>†</td>
<td>-</td>
</tr>
<tr>
<td>ASBP in mmHg after applied DOT, daytime/nighttime mean</td>
<td>97/90</td>
<td>†</td>
<td>-</td>
</tr>
<tr>
<td>ADBP in mmHg after applied DOT, daytime/nighttime mean</td>
<td>60/54</td>
<td>†</td>
<td>-</td>
</tr>
<tr>
<td>Decrease in ASBP in mmHg pre-DOT to post-DOT, mean(±SD)</td>
<td>24h 19.5 (10.7)</td>
<td>dt 18.4 (11.3)</td>
<td>nt 20.6 (18.1)</td>
</tr>
<tr>
<td>Decrease in ADBP in mmHg pre-DOT to post-DOT, mean(±SD)</td>
<td>24h 9.4 (8.2)</td>
<td>dt 8.4 (8.3)</td>
<td>nt 11.4 (10.9)</td>
</tr>
<tr>
<td>DOT procedure described</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Health personnel applying DOT</td>
<td>physcian</td>
<td>hypertension nurse</td>
<td>physcian</td>
</tr>
<tr>
<td>Defined cut-off value to indicate non-adherence</td>
<td>≥5 mmHg</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Safety reported</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
</tbody>
</table>

NCT no.= ClinTrial.gov identification, - = Not reported, NA= Not applicable, RCT= Randomized controlled trial, DOT= Directly observed therapy, *) total n/n with reported gender, OSBP= Office Systolic Blood Pressure, ODBP= O Diastolic BP, ASBP= Ambulatory SBP, 24h= 24 hour, dt= daytime, 
nt= nighttime, †= reported in figures not numbers
3.4 DOT procedures reported in the reviewed literature

To emphasize what was published on the DOT-HTN procedure, I chose in this section to provide a narrative summary of all critical information clearly stating the procedures used, beginning with the earliest identified report from 2011, followed by tabulated key points in Table 2.

**Bunker et al 2011** (4): “How common is true hypertension?” (Journal of Hypertension)

Bunker et al reported from a specialist nurse-led clinic where drugs were administered under observation ideally combined with a subsequent ABPM. Patients should meet medication fasting between 9-10 am. BP was recorded with a validated automated monitor using a standardized technique, immediately followed by oral drug administration. BP was then measured in intervals of 10-15 minutes for 2-4 hours. “In patients on three or more drugs the initial administration consisted of giving two of their prescribed drugs (usually a calcium channel blocker and an angiotensin converting enzyme inhibitor or angiotensin receptor blocker) with the additional drugs (diuretics, β-blockers, α-blockers etc.) administered at appropriate intervals over the ensuring 2-4 hours, depending on blood pressure responses.” (4) Due to an adverse response with severe hypotension after administration of the α-blocker doxazosin they “…proposed that for patients prescribed higher doses of doxazosin, a maximum dose of 4 mg...should be administered in the context of the tablet feed.” (4)

**Fadl Elmula et al 2013** (2): “Renal Sympathetic Denervation in Patients With Treatment-Resistant Hypertension After Witnessed Intake of Medication Before Qualifying Ambulatory Blood Pressure” (Hypertension)

“Patients were asked to bring their prescribed medication to the clinical visit...Medication was documented and administered by the investigator and swallowed by the patient under continuous observation, to secure the intake of prescribed medication, in prescribed doses. Patients were then continuously under the observation by the investigator to prohibit throwing up again of the pills until 24-hour ambulatory BP device had been mounted and tested out in a somewhat more lengthy procedure than usually to prolong the period of observation. Patients stayed in the hospital for 2 hours to capture those with potential symptomatic hypotension caused by full intake of medication. Visits with subsequent
ambulatory BP measurement were done in the morning, and further observation of patients in the hospital was done during working hours.” (2).


“To exclude pseudo-resistance from non-adherence, filling records for the patients antihypertensive medications were verified with her pharmacy…” The patient was asked “…not to take her morning medication and present to the clinic at 8 AM, at which time she was seated in the office, and casual and resting sitting, as well as upright, BP were recorded...She was then given her usual morning antihypertensive medications. Subsequently, hourly BP monitoring...showed a dramatic reduction in BP.” (64)

Fadl Elmula et al 2014 (3): “Adjusted Drug Treatment Is Superior to Renal Sympathetic Denervation in Patients With True Treatment-Resistant Hypertension” (Hypertension)

“Patients were asked to bring their prescribed medication in original packaging to the clinical visit...Medication was documented and administered by the investigator and swallowed by the patient under continuous observation, in order to secure the intake of prescribed medication, in prescribed doses. Patients were then under the observation by the investigator in order to prohibit throwing up the pills until 24-hour ambulatory BP device had been mounted and tested and clinical examinations had been carried out. Patients stayed in the hospital for 2 hours in order to capture those with potential symptomatic hypotension caused by full intake of medication. Visits with subsequent ambulatory BP measurement were done in the morning, and further observation of patients in the hospital was done during daytime working hours.” (3)

Brown M. 2014 (65): “Resistant hypertension: resistance to treatment or resistance to taking treatment?” (Heart.bmj.com)

Being an editorial, no procedures were described. Nevertheless Brown writes that: “An increasingly common clinical practice is to undertake “directly observed therapy” (DOT), and most hypertension specialists have anecdotes of patients who swear to compulsive tablet taking, but collapse on the ward floor when administered a fraction of their supposed...
regimen. DOT is not a trivial exercise, requiring staff, time and a bed for the collapsing patient.” (65)

**Linicus et al 2014** (14): “Witnessed drug intake before planned denervation – Always harmless?” (International Journal of Cardiology)

Blood analyses detected only Carvedilol. “*During the morning ward round the patient was asked to take his medication under supervision of the treating physician. Two hours later he felt dizzy, light headed and suffered from nausea. Blood pressure reached levels of 70/50 mmHg...*” and he subsequently had indications of kidney failure. New blood analysis detected the presence of all drugs. After 2 days with a new five-component medication regimen he was normotensive without adverse drug effects (14).

**Hameed et al 2015** (5): “Non-adherence to antihypertensive medication is very common among resistant hypertensives: results of a directly observed therapy clinic” (Journal of Human Hypertension)

Hameed et al followed a strict procedure in a special DOT clinic headed by a pharmacist and run by a specialist hypertension nurse. Patients were asked to meet medication fasting bringing their own medication. The pharmacist prescribed the patient’s usual medication on a chart, which was then dispensed from the hospital pharmacy. The patient brought the medication to the DOT clinic where the hypertension nurse compared the patient’s own medication to the pharmacy-dispensed medication. “*If patients were taking any branded medications, they were given their dose of the branded medication from their own supply instead of the generic medication supplied by the hospital pharmacy*”. (5) ABPM device was mounted prior to any administration of drugs. “*Each prescribed drug was administered at its current dose by the nurse, under the guidance of the clinical pharmacist; the first drug 1 h after arrival and thereafter at 60-min intervals. Patients were directly observed by the nurse for 7 h and all symptoms were recorded.*” (5)

An arbitrary cut-off value of ≥5 mmHg was used to indicate non-adherence to treatment (5).

**Miroslawska et al. 2015** (56): “Renal sympathetic denervation: effect on ambulatory blood pressure and blood pressure variability in patients with treatment-resistant hypertension. The ReShape CV-risk study” (Journal of Human Hypertension)
“Patients were asked to bring their prescribed medication in original package to the clinical visit with one of the study nurses. Medication was documented, administered by the nurse and swallowed by the patient under continuous observation, to secure intake of the medication in prescribed doses. Patients were then continuously under observation by the nurse until 24-h ABPM device had been mounted and tested.” (56)


“In our tertiary care referral clinic, we observe the patient for 4-6 h after directly observed administration of prescribed morning dose of BP-lowering drugs until the BP response plateaus. At this point, the patient is discharged home with a 24-h ambulatory BP-monitoring device”. (62)

Eskås et al 2015 (63): Adherence to medication and drug monitoring in apparent treatment-resistant hypertension” (Blood Pressure)

Eskås et al states that: “DOT is used to ensure intake of medication before assessing the treatment effect. In the assessment of hypertensive patients, the method is based on the patient taking the prescribed medications from original packaging in the correct doses, while being observed by a physician or trained nurse, before ambulatory BP measurement. The patient is often observed for some time to prevent them from spitting out the medications or vomiting, and for safety reasons, as a non-adherent patient may experience severe hypotension when all the medications are taken at once.” (63)
Table 2. Key points of information in published reports on the DOT-HTN procedure

<table>
<thead>
<tr>
<th>Year of report (reference)</th>
<th>Location</th>
<th>Type of report</th>
<th>Level of care</th>
<th>Group of Patients</th>
<th>Anamnestic and investigational procedures prior to DOT</th>
<th>Information given to patient prior to DOT</th>
<th>Time of DOT</th>
<th>Administration of medication</th>
<th>Medical observations immediately after DOT</th>
<th>Safety measures</th>
<th>Information given to patients after DOT</th>
<th>Follow-up visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011 (4)</td>
<td>London, UK</td>
<td>Research Letter</td>
<td>Specialist HTN Centre</td>
<td>Uncontrolled hypertensives on ≥3 aHTN drugs</td>
<td>aHTN drug &amp; dose adjustments, exclusion of secondary HTN, patient-confirmed drug adherence</td>
<td>Omission of morning aHTN drugs</td>
<td>9-10:00 AM</td>
<td>BP recorded followed by oral adm of aHTN drugs. Patients with ≥3 drugs: 2 drugs adm first, the rest during 2-4 h.</td>
<td>BP recorded at 10-15 min intervals for 2-4 h</td>
<td>α-blocker doxazosin max 4 mg</td>
<td>If normalized BP patient informed of non-eligibility to HTN-study</td>
<td>1 to 18 month</td>
</tr>
<tr>
<td>2013 (2)</td>
<td>Oslo, Norway</td>
<td>Original Article</td>
<td>Nephrology HTN Centre</td>
<td>Treatment resistant hypertensives</td>
<td>CT, MRI and BT verified normal renal function, type 1 diabetes &amp; secondary HTN excluded, aHTN drugs &amp; doses stabil for 2 w, no preplanned changes for 6 m</td>
<td>Patients asked to bring prescribed aHTN drugs in original packaging</td>
<td>Morning</td>
<td>Physician documented &amp; adm aHTN drugs &amp; observed patient swallow pills</td>
<td>Prolonged mounting and testing of ABPM device</td>
<td>2 h on the hospital premises</td>
<td>Follow-up 6 h, future recommendation: 4 h follow-up</td>
<td></td>
</tr>
<tr>
<td>2013 (62)</td>
<td>Ottawa, Canada</td>
<td>Case Report</td>
<td>Renal HTN Clinic</td>
<td>Individual case</td>
<td>Co-morbidity status, exclusion of end organ damage, filling records verified with patients pharmacy, ABPM, RDN. Casual and resting sitting BP</td>
<td>Patient asked to omit morning aHTN drugs</td>
<td>8:00 AM</td>
<td>Morning aHTN drugs adm</td>
<td>Hourly BP monitoring</td>
<td>2 h on the hospital premises</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014 (3)</td>
<td>Oslo, Norway</td>
<td>Original Article</td>
<td>Nephrology HTN Centre</td>
<td>Treatment resistant hypertensives</td>
<td>CT, MRI, BT verified normal renal function, type 1 diabetes &amp; secondary HTN excluded, aHTN drugs &amp; doses stabil for 2 w, no preplanned changes for 6 m</td>
<td>Patients asked to bring prescribed aHTN drugs in original packaging</td>
<td>Morning</td>
<td>Physician documented &amp; adm aHTN drugs &amp; observed patient swallow pills</td>
<td>Mounting and testing of ABPM device, clinical examination</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2014 (63)</td>
<td>Cambridge, UK</td>
<td>Editorial</td>
<td>Nephrology HTN Centre</td>
<td></td>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

NCT no.= ClinTrial.gov identification, - = Not Reported, NA = Not applicable, DOT = Directly Observed Therapy, HTN = Hypertension, aHTN = antihypertensive, CT = Computed Tomography, MRI = Magnetic Resonance Imaging, BT = Blood Test, adm = administer, h = hour, w = week, m = month, BP = Blood Pressure.
Table 2. (continued) Key points of information in published reports on the DOT-HTN procedure

<table>
<thead>
<tr>
<th>Year of report (reference)</th>
<th>Year of report (reference)</th>
<th>Year of report (reference)</th>
<th>Year of report (reference)</th>
<th>Year of report (reference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Location</td>
<td>Location</td>
<td>Location</td>
<td>Location</td>
</tr>
<tr>
<td>Homburg/Saar, Germany</td>
<td>Birmingham, UK</td>
<td>Tromsoe, Norway</td>
<td>Ottawa, Canada</td>
<td>Oslo, Norway</td>
</tr>
<tr>
<td>Type of report</td>
<td>Type of report</td>
<td>Type of report</td>
<td>Type of report</td>
<td>Type of report</td>
</tr>
<tr>
<td>Letter to the Editor</td>
<td>Original Article</td>
<td>Original Article</td>
<td>Review</td>
<td>Review</td>
</tr>
<tr>
<td>Level of care</td>
<td>Level of care</td>
<td>Level of care</td>
<td>Level of care</td>
<td>Level of care</td>
</tr>
<tr>
<td>Internal Medical Department</td>
<td>Specialist HTN Clinic/DOT Clinic</td>
<td>Cardiology and Nephrology specialist centre</td>
<td>Cardiology and Nephrology specialist centre</td>
<td>Nephrology HTN Centre</td>
</tr>
<tr>
<td>Group of Patients</td>
<td>Group of Patients</td>
<td>Group of Patients</td>
<td>Group of Patients</td>
<td>Group of Patients</td>
</tr>
<tr>
<td>Individual case</td>
<td>Uncontrolled hypertensives</td>
<td>Treatment resistant hypertensives</td>
<td>Treatment resistant hypertensives</td>
<td>Treatment resistant hypertensives</td>
</tr>
<tr>
<td>Anamnestic and investigational procedures prior to DOT</td>
<td>Anamnestic and investigational procedures prior to DOT</td>
<td>Anamnestic and investigational procedures prior to DOT</td>
<td>Anamnestic and investigational procedures prior to DOT</td>
<td>Anamnestic and investigational procedures prior to DOT</td>
</tr>
<tr>
<td>Co-morbidity status, exclusion of secondary HTN, ABPM, RDN, TDM in serum/urine</td>
<td>Standard protocol: medical history, clinical examination, OBP, BT, ABPM, ECG, ECHO. Serum/urine hormone screening if suspected secondary HTN, CTA renal. Lifestyle modification advice, adjustment of aHTN drugs, drug use review, prescription refill frequency (verified with pharmacy)</td>
<td>Standard clinical evaluation, BT, exclusion of secondary HTN, ABPM</td>
<td>Indirect adherence assessment methods (i.e. pill count, refill records, phone or internet based reminders.</td>
<td></td>
</tr>
<tr>
<td>Information given to patient prior to DOT</td>
<td>Information given to patient prior to DOT</td>
<td>Information given to patient prior to DOT</td>
<td>Information given to patient prior to DOT</td>
<td>Information given to patient prior to DOT</td>
</tr>
<tr>
<td>Patients advised to omit aHTN drugs on the day of the DOT clinic</td>
<td>Patients asked to bring prescribed aHTN drugs in original packaging</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time of DOT</td>
<td>Time of DOT</td>
<td>Time of DOT</td>
<td>Time of DOT</td>
<td>Time of DOT</td>
</tr>
<tr>
<td>Morning</td>
<td>Morning</td>
<td>Morning</td>
<td>Morning</td>
<td>Morning</td>
</tr>
<tr>
<td>Administration of medication</td>
<td>Administration of medication</td>
<td>Administration of medication</td>
<td>Administration of medication</td>
<td>Administration of medication</td>
</tr>
<tr>
<td>During morning ward round the patient was asked to take his medication under supervision of the treating physician</td>
<td>Clinical pharmacist prescribed patient aHTN drugs on a chart. Nurse compared patients aHTN drugs with drug chart. If patients took branded aHTN drugs they were adm own drugs. Nurse adm 1 drug every 60 min</td>
<td>aHTN drugs were documented &amp; adm by nurse, and observed swallowed</td>
<td>Morning dose aHTN drugs observed taken by the patient</td>
<td></td>
</tr>
<tr>
<td>Medical observations immediately after DOT</td>
<td>Medical observations immediately after DOT</td>
<td>Medical observations immediately after DOT</td>
<td>Medical observations immediately after DOT</td>
<td>Medical observations immediately after DOT</td>
</tr>
<tr>
<td>2 h post-DOT patient reacted to aHTN drugs, subsequent kidney failure</td>
<td>All symptoms recorded</td>
<td>Patients under continuous observation until 24h ABPM device was mounted and tested</td>
<td>BP measurements until BP plateaus</td>
<td></td>
</tr>
<tr>
<td>Safety measures</td>
<td>Safety measures</td>
<td>Safety measures</td>
<td>Safety measures</td>
<td>Safety measures</td>
</tr>
<tr>
<td>aHTN drugs adm with 60 min intervals, patients observed for 7 h</td>
<td></td>
<td>4-6 hour post-DOT observation of the patient until BP plateaus</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Information given to patients after DOT</td>
<td>Information given to patients after DOT</td>
<td>Information given to patients after DOT</td>
<td>Information given to patients after DOT</td>
<td>Information given to patients after DOT</td>
</tr>
<tr>
<td>Follow-up visits</td>
<td>Follow-up visits</td>
<td>Follow-up visits</td>
<td>Follow-up visits</td>
<td>Follow-up visits</td>
</tr>
</tbody>
</table>

NCT no.= ClinicalTrial.gov identification, NR = Not Reported, - = Not applicable, DOT = Directly Observed Therapy, HTN = Hypertension, aHTN = antihypertensive, TDM = Therapeutic drug monitoring, BT = Blood Test, BP = Blood Pressure, OBP = Office BP, ABPM = Ambulatory BP Measurement, ECG = Electrocardiogram, ECHO = Echocardiography, adm = administer, h = hour, w = week, m = month
4 DISCUSSION

4.1 Methods

This is, to my knowledge, the first review conducted on DOT with emphasis on the DOT procedure. Using the systematized review methodology assisted by a specialist medical librarian enabled access to a presumed majority of publications regarding DOT-HTN. Conducting a systematized review of published literature on DOT-HTN has provided important knowledge of the use of DOT-HTN and how the procedure is applied differently. Interestingly the review revealed a clear knowledge gap concerning the characteristics of post-DOT-HTN non-adherent patients, further discussed in section 4.2. Even though the systematized review is not at all as comprehensive as the systematic review, still the literature search is systematic and reproducible (35). The search in clinical trial registers of ongoing trials provided important supplementary information about the DOT-HTN procedure in terms of use and location (35). The conducted systematized review can, as suggested by Grant and Booth (35) be modified and repeated at a later point of time, by a team of researchers as in a Systematic Review, and would be an ideal next step in following and investigating DOT-HTN in the years to come.

Since DOT is a new tool in hypertension research, with only a few quite different types of publications with diversities in methods and design, this early-stage systematized review was a useful methodology (66). With the narrative and categorizing nature of the review, shortcomings in the reporting of patient characteristics as well as highly important safety information were interesting extractions.

As mentioned earlier seven out of fourteen review methodologies were, in their different ways fit for purpose in this thesis. Grant and Booth communicate a need for internationally agreed mutually exclusive review types (35), to make it clearer what is required in terms or resources to negotiate commissioned reviews. In this thesis the Systematized review methodology provided an informative narrative and tabular synthesis of what is known about DOT-HTN, and contributed to future focus on the knowledge gap. High-profile organizations, like The Cochrane Collaboration (67) and the Campbell Collaboration (68) now includes a wide range of study designs in their reviews (35), signaling that other designs than RCTs (exclusively reviewed years back (69)), can inform health personnel and other stakeholders in future health
decisions, taking into consideration that the majority of the literature in the HTN field is from non-randomized and epidemiological studies (70). It is in my opinion useful to have a review methodology fit for purpose in a master thesis, since practicing review methodology is an important step toward one day being good at it.

There are several methodological limitations to the conducted review. An obvious limitation of course was that only one master student, reviewed and described the literature (35). Compared to a systematic review with at least two, and often a team of skilled researchers behind the review, the systematized review is less solid. No critical appraisal of the methods and results of the reviewed literature was part of the systematized review. Relevant citations might had been identified by expanding the use of keywords, i.e. with terms used in one of the reviewed articles (4): “supervised drug administration”, “tablet feed” “observed drug administration”. Citations might as well have been missed as a consequence of limiting the search to title and abstract. Maybe in studies where DOT was used as a screening tool, the word-limitations to most abstracts left out the mentioning of DOT in the abstract. An obvious limitation to this narrative and categorizing systematized review was the inclusion of only five ongoing trials and seven published patient-involving reports, and therefor caution must be taken to conclude from such limited evidence. The systematized review is a first step toward more solid research.

4.2 Results

This review identified five ongoing studies, five published studies and five other citations regarding DOT-HTN. All published patient-involving reports and three out of five ongoing trials provided information about the DOT-HTN procedures used. None of the published studies provided information on patient characteristics, in terms of age, gender, number of antihypertensive medications or duration of treatment, only the two case reports provided such information. One of the published (4) studies and three of the ongoing studies (59-61) used DOT as a post-enrolment adherence assessment method. Publications from these three ongoing studies are of great importance in terms of filling the information gap on the patients who are found to be non-adherent after DOT. The remaining studies, published and ongoing, used DOT as a screening tool in their inclusion criteria, except the one case report (64) where DOT was used post renal denervation. Publications from the two last mentioned ongoing studies (57, 58) are probably not expected to contribute with data on patients with screening
failure, due to normalization of blood pressure after DOT. However, using DOT as an adherence assessment method in a pharmaceutical trial, thereby ensuring that enrolled patients actually have high blood pressure despite taking their medications, strengthens the result of the trials, and protects them from confounding white coat adherence (5). White coat adherence is, when patients take their medication only prior to visits to their doctor, but not in between visits.

**DOT-HTN procedures**

There were differences in the DOT-HTN procedures used. In the three Norwegian studies (2, 3, 56) where DOT-HTN was a screening tool prior to enrolment in RDN studies, the DOT procedures were almost identical. Patients were instructed to bring their medication in original packaging and were observed taking their morning dose of prescribed drugs followed by mounting of ABPM device. The Oslo-studies (2, 3) reported 2-hour post-DOT observation time, the Tromsø-study did not report any post-DOT observation time. The Norwegian procedures were relatively time efficient and easy implementable. One severe adverse reaction of hypotension was reported (3). The Canada procedure (62) entailed observing the patients’ intake of morning dose of antihypertensive medications, and monitored the blood pressure until it plateaued. They recommended 4-6 hours of post-DOT observation. In the Birmingham study (5) they informed patients to omit morning dose of antihypertensive medications on the day of the visit and used a pharmacist-supported comprehensive standard DOT protocol. Drugs were administered in intervals of one drug every 60 minutes, allowing a reduction in number of medications administered, given symptoms of hypotension. Interval blood pressure monitoring were conducted. They had a 7-hour post-DOT observation time. This procedure was time and labor consuming compared to the Norwegian procedure. The London study (4) had a less comprehensive DOT protocol compared to that of Birmingham, however they initialized the drug administration with a maximum of 2 drugs, while measuring the post-DOT blood pressure in intervals of 10-15 minutes. The rest of the drugs were administered during 2-4 hours with continuous BP measuring in 10-15 minutes intervals. The two case reports gave examples of extreme cases where DOT-HTN was used. Ruzicka et al described a 53-year old female, treated with antihypertensive medications for 20 years, and at the time of report, was on post-RDN medical treatment with six different antihypertensive drugs. DOT-HTN in this case was a long awaited resolve of the patient’s treatment resistant hypertension. She had undergone invasive procedures before DOT-HTN revealed her real
problem of non-adherence. Linicus et al described a 59-year old male, diagnosed with severe hypertension for 4 years, awaiting the invasive RDN procedure, and at the time of report was on ten different antihypertensive drugs. In this case the patient suffered a severe adverse reaction following a DOT of ten antihypertensive drugs including doxazosin, a rather potent α-blocker often administered in the evening. The number and type of drugs considered, this was an example of what not to do in the future, and contributes with important safety information regarding DOT-HTN. In summary the reviewed reports revealed huge differences in how DOT-HTN procedures were implemented, ranging from ten drugs at one time to one drug every 60 minutes, with implications to the patients involved. Ethical considerations are important here as well, and will be discussed later in this chapter.

**Hypertensive patients with post-DOT non-adherence**

The results of this review revealed the very limited, almost non-existing knowledge of the patients who have been proven non-adherent with DOT-HTN, in terms of age, gender, number of antihypertensive medications, treatment duration and other background information. Looking exclusively at the 10 identified published and ongoing studies, 60 % used DOT to determine patients’ eligibility to further participation, which for the published studies part might have led to less attention being paid to the reporting of i.e. demographics on the post-DOT non-adherent patients. Only from the case reports, we got demographic information. The matter of fact might be that the reporting, rather than the actual knowledge is failing, though a shame since - as Douglas G. Altman writes - “reading a paper we cannot assume things that are not stated” (71). In the absence of knowledge about these patients, it can be relevant to look at other patients with similarities to those of the DOT-patients.

What we know in general from the literature on adherence in hypertensive patients is that estimated 50 % of patients stop taking their medications after one year of treatment (24, 72, 73). We also know that the higher the number of antihypertensive drugs the more it affects adherence in a negative way (25). One review (74) stated that reducing the number of pills taken, was the single most effective adherence promoter. In one review (75) of qualitative studies, medicinal side-effects were an important reason for patients to adjust or stop their antihypertensive medication intake. It was also found that complicated drug regimens, costs of drugs, older age, poor social support, cognitive problems and depression were associated with non-adherence (75). One qualitative study (n = 118) (76) found gender-specific differences in adherence, i.e. that older age in men promoted adherence to antihypertensive
drugs, as well as less education and fewer side effects. Women´s adherence was associated with i.e. more causal attribution to risk factors and mental balance and less personal control (e.g. greater respect for authority). For both gender, adherence was associated with a better understanding of their illness (76).

It is known that large intra-individual variability in factors influencing the patients non-adherence behaviour exist (77) and Lisa Rosenbaum´s paper “Beyond Belief – How People Feel about Taking Medications for Heart Disease” (78) published in the New England Journal of Medicine in 2015 is a must-read, with an interesting view into the patients perceptions of taking medications. Her last sentence states that: “I want to believe that if patients knew what I know, they would take their medicine. What I´ve learned is that if I felt what they feel, I´d understand why they don’t” (78).

4.2.1 Where is DOT in hypertension used and why?

All the fifteen reviewed reports and ongoing trials originated from only four different nations. The United Kingdom (London, Cambridge, Birmingham, Exeter and Edinburgh), Norway (Oslo and Tromsø), Canada (Ottawa) and Germany (Homburg/Saar). This could imply that DOT-HTN to date has gained limited transnational interest, or that in particular the researchers who initiated the use of DOT-HTN in research, have found it of interest to investigate the use of the procedure. The latter might be explained by the highly visible impact the procedure has, in terms of quick, measurable and visible responses in patients who do not adhere to their medications. One could speculate that seeing patients with long histories of severe apparent resistant hypertension reach treatment target of < 140/90 mmHg, or even collapse from hypotension after actually ingesting the drugs they have secretly omitted, awakens both astonishment and curiosity and drives the observer to find out more about who and why! An example could be the researchers from Ottawa, Canada, with Primary Investigator Marcel Ruzicka, who published a case report (64) in 2013, a review (62) in 2015 and are now recruiting to a prospective observational study (61) of sixty participants investigating a four-step DOT protocol, which have been implemented as part of the standard care in their Nephrology Department (61). Our Norwegian research team also published a prospective observational study (2) in 2013, an RCT (3) in 2014, a review (63) in 2016 and are now recruiting to a pilot RCT (60) of 20 participants, investigating DOT based on a 2013 procedure (2). Researchers engaged in hypertension are not the only researchers interested in
how a modification of the original DOTS might help their patients. Within the fields of hemodialysis (79), diabetes (15, 80), chronic hepatitis C (81), anticoagulation (82) and major mental illness (83) DOT has been investigated.

### 4.3 Clinical implications

**Who qualifies to undergo DOT-HTN?**

Since the literature tells us almost nothing about the patients found non-adherent after DOT, it is impossible to say exactly which patients qualify for DOT-HTN. Patients with uncontrolled hypertension leaning towards severe apparent treatment resistant hypertension, and who declare adherence to antihypertensive medications, would obviously be good candidates. The apparent treatment resistant hypertensive patients represent inadequately treated patients, patients with white coat hypertension, patients with secondary causes of hypertension, and the patients who secretly omit their drugs and are non-adherent to treatment. The question is who and when health personnel should test adherence with DOT-HTN. If the patient claims to be adherent to the treatment regimen agreed on, and treatment has been adjusted in case of adverse reactions, the next step is often a costly investigation of secondary causes to HTN, in a hospital setting. Secondary investigations can be expensive and time and labor demanding, and include blood test screening for kidney function and hormones. It can include a sleep apnea test, or infusion of a chemical substance, a contrast, prior to Computed Tomography with Angiography (CTA) or Magnetic Resonance Imaging (MRI) of kidneys to look for stenosis in kidney arteries or adenomas in adrenal glands (or other kidney disease that could explain the high blood pressure) (7). In the editorial by Morris J. Brown (65) he states that patients who do not willingly allow a test of adherence, e.g. by the use of DOT-HTN or blood screening to identify antihypertensive drugs, maybe should not gain the opportunity to be investigated for secondary causes with costly methods. Ethically this is problematic of course. Health personnel cannot force people to live healthy lives, or take prescribed medication, or follow advice, and when they fall ill or illness is suspected, we must investigate to find a cause. In a newly published paper (84) from our research group (SCRR) it was found that 30% of apparent treatment resistant hypertensive patients referred for renal denervation had secondary causes to hypertension, corresponding with findings in other RDN studies (85). The proportion of patients with poor post-DOT drug adherence was in the SCRR study 32% (84), which was lower than in the Birmingham (5) and London (4) studies with 50% and
60 %, respectively. An explanation could be, that more patients (n = 83) were screened in the SCRR study compared to the Birmingham study (n = 50) (5) and the London study (n = 37) (4), in combination with differences in the selection of patients. It seemed that both in Birmingham and London, they had an eye out for the non-adherent patients, in contrast to the SCRR study, where the proportion of non-adherent patients came as a surprising secondary finding.

What we can try to do in this case, is to explain to the patients why tools like DOT-HTN can be a first step before commencing costly investigations. If we present DOT-HTN to patients in positive wording and not as a control, which if they decline would lead to limitations in which investigations we can offer them, then maybe the important trust between health personnel and patient prevails. Given a positive and supporting attitude from health personnel towards the patient, a DOT-HTN resulting in a fall in blood pressure indicating poor adherence, might even strengthen that relationship, in terms of an understanding of what is really the problem, and a new fresh start. It is of utmost importance that health personnel do not condemn the non-adherent patients, since that might prevent future collaboration.

**Where should DOT-HTN take place?**

Both in the Birmingham (5) and London (4) studies, results was reported from specialist pharmacist- or nurse-led clinics, using comprehensive DOT protocols with safety measures like interval drug administration and continuous blood pressure monitoring. Both the Norwegian, Canadian, German and British researchers in the review, reported cases of severe hypotension, in some cases in connection with the α-blocker doxazosin in higher doses than 4 mg. This could suggest that even though the patient declares adherence, health personnel should not fully rely on such declaration (25, 26), and limit the use of DOT-HTN to hospital settings where adequate care can be attributed.

**DOT-HTN strengths**

The absolute strength of DOT-HTN is that the therapeutic response of the antihypertensive medications is clarified within 24 hours at the most. With precautions to number and types of drugs, and in a hospital setting DOT-HTN has the potential to be a useful tool.
DOT-HTN weaknesses

The procedure has in some patients resulted in severe hypotension, even with one reported case of kidney failure, and is probably not safe to use outside a hospital setting. It has been reported to be a time and labor demanding procedure, but there is no present consensus on the DOT procedure in the literature. DOT-HTN do not measure adherence in a long term perspective. Treatment of hypertension is often lifelong, and using DOT-HTN is like a snap shot of the patient’s adherence.

In summary, the DOT-HTN procedure can be useful, but much more high-quality research is needed before we can say that DOT-HTN is ready for clinical practice.

4.4 Ethical considerations

Ethical considerations are a crucial part of all health service and especially when we ask patients to participate in research. The young woman described in the case at the beginning of the thesis, were examined thoroughly in a collaboration between her general practitioner and the local hospital-based specialist nephrologist prior to tertiary referral to OUH hypertension specialists. Due to her young age (< 35 years) and diagnosis of end organ damage, she was at high risk of further disease development. She wanted the renal denervation procedure and was referred specifically for eligibility assessment prior to participation in a renal denervation study conducted by our research group (3). After she had ingested her morning dose of antihypertensive medications under the observation of a physician, she and her husband talked to me for a while about her despair and fear of early death. The subsequent severe hypotensive reaction honestly came as a shock to me, and in the after-math of a situation like that, one need to think about what caused the situation and how to avoid it in the future. It was a possibility that she had lied to me, but I found myself in a situation where I questioned if she knew the consequences of an intake of antihypertensive drugs “unknown” to her body, given that she habitually omitted them.

This particular case of DOT-HTN have some similarities to the case report of the middle-aged women in Canada (64), who had a long history of hypertension, which led to renal denervation. Post-RDN her doctors suspected that she omitted her antihypertensive drugs and performed a DOT-HTN, resulting in a dramatic fall in her blood pressure from 177/106 mmHg to 97/68 one hour post-DOT increasing to 140/75 mmHg after six hours.
My theory is that this case kick started the Canadian interest in DOT-HTN, the way that the case with the young woman started mine. Assuming that the two women lied all along, it is very important to understand why. We already know that self-declaration of adherence is a highly questionable adherence assessment method, and it would be ethically wrong not to investigate the reasons why patients with very high blood pressure choose to omit drugs and lie about it. A worse-case scenario could be life threatening adverse reactions to antihypertensive medications, at locations, i.e. the general practitioner’s office, where necessary life-saving resources are not present. When introducing a known method to a new population, valuable information can be gained from published case reports, for other researchers to learn from, because they highlight crucial information related to safety and patient perspective. Both cases made me wonder if qualitative research, like that of Lisa Rosenbaum (78), would be able to elucidate the patients’ reasoning, in a way that could help health personnel understand how to communicate to severe hypertensive patients the importance of treatment.

An important ethical challenge regarding DOT-HTN in a research setting is that informing the patients about an upcoming control of their adherence obviously induces the risk that they start taking their medications. Patients with poor adherence might even decline participation, and selection bias is a fact. Even if you randomize patients to DOT-HTN and control, the control group might improve their adherence as well, simply due to the attention brought to their treatment, known as the Hawthorn effect (86).

## 4.5 Future research

In our planning of a larger RCT including DOT-HTN, the focus should be on safety, in terms of the DOT-HTN procedure itself, and where it is applied. It is of utmost importance that we acquire comprehensive background information on the patients who are found non-adherent after DOT-HTN including their perspective on antihypertensive treatment. Knowledge about the patient perspective can be of invaluable help to health personnel in the important follow-up of non-adherent patients. A simple way to measure a patient’s experience of DOT-HTN is i.e. to use a visual analogue scale where the patients quantify his or her experience of their observed intake of medications. To learn about the patient’s reasoning the researcher can use a qualitative- or mixed method approach (87). In-depth interviews of DOT-revealed non-adherent patients could be a very interesting future project.
5 CONCLUSION

A known procedure of directly observed therapy, has been introduced to a new population, and it is important that large randomized controlled trials are conducted, to investigate whether the DOT-HTN procedure is safe, and have any effect on adherence to antihypertensive medications and blood pressure in uncontrolled or treatment resistant hypertensive patients. This review found that no consensus exist on how DOT-HTN is applied, and that no information about the patients found non-adherent after DOT exists. It is only when we gain knowledge of who they are, and why they don’t take their medications, that we can improve patient adherence. Gaining information about how other research groups have implemented the procedure enables our research group to continue to approve the way we use DOT-HTN in research. Knowledge about ongoing trials and the identification of research groups interested in DOT-HTN is of importance in terms of transnational collaboration and future research funding, enabling high-quality research.


59. ISRCTN. ISRCTN57475376 Diagnosing and treating severe hypertension [Internet]. 2016 [23 March 2016]. Available from: http://www.isrctn.com/search?q=directly+observed+therapy&filters=condition%3Acirculatory+y-system&searchType=advanced-search.
APPENDIX

PubMed:

PubMed search strategy:

\(((\text{"witnessed intake"}[\text{tiab}] \text{ OR } \text{"directly observed therapy"}[\text{tiab}]) \text{ OR } (\text{"directly observed therapy"}[\text{MeSH Terms}] \text{ OR } (\text{"directly"}[\text{tiab}] \text{ AND } \text{"observed"}[\text{tiab}] \text{ AND } \text{"therapy"}[\text{tiab}]) \text{ OR } \text{"directly observed therapy"}[\text{tiab}])) \text{ AND } (\text{"hypertension"}[\text{MeSH Terms}] \text{ OR } \text{"hypertension"}[\text{tiab}])\)

99 hits through 31.03.16

Ovid MEDLINE:

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

Search Strategy:

1 witnessed intake.mp. (3)

2 exp directly observed therapy/ (1369)

3 (directly adj3 observed adj3 therapy).ti. (271)

4 (witnessed adj3 intake).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (6)

5 1 or 2 or 3 or 4 (1507)

6 *Hypertension/ (151351)

7 hypertension.mp. (401531)

8 6 or 7 (401531)

9 5 and 8 (8)

8 hits through 31.03.16
EMBASE

Database: Embase <1974 to 2016 March 30>

Search Strategy:

1 witnessed intake.mp. (6)

2 exp directly observed therapy/ (1329)

3 (directly adj3 observed adj3 therapy).ti. (299)

4 (witnessed adj3 intake).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (12)

5 1 or 2 or 3 or 4 (1507)

6 *Hypertension/ (194436)

7 hypertension.mp. (692210)

8 6 or 7 (692210)

9 5 and 8 (25)

25 hits through 31.03.16
Part II: A research paper reporting preliminary results from a randomized controlled pilot trial investigating directly observed therapy in a specialist nephrology outpatient clinic

Adherence to antihypertensive medication: a randomized controlled pilot trial implementing directly observed therapy prior to ambulatory blood pressure measurement.

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Word count: 4718
Adherence to antihypertensive medication: a randomized controlled pilot trial implementing directly observed therapy prior to ambulatory blood pressure measurement

Purpose

Methods to control hypertension on the individual level is warranted, since > 50% of antihypertensive patients may not adhere to treatment, and fail to reach blood pressure target of ≤ 140/90 mmHg. We aimed to investigate if directly observed therapy (DOT) of uncontrolled antihypertensive patients, would decrease blood pressure.

Material and methods

A randomized controlled pilot trial was conducted at a Nephrology outpatient clinic. 184 patients referred for ambulatory blood pressure measurement (ABPM) were screened, and 13 patients with a baseline ambulatory systolic blood pressure (ASBP) of ≥ 135/80 mmHg were randomized to standard ABPM or DOT prior to ABPM and a visual analogue scale (VAS) assessment of how they experienced DOT. Data from 9 patients were analysed.

Results

There were no significant differences in change in daytime ASBP between groups (p = 0.624), or in the office systolic blood pressure between groups (p = 0.140). All DOT patients (n = 6) reported DOT as not problematic.

Conclusions

Due to few participants (n = 9), the study outcome was inconclusive. Interestingly, DOT was less problematic to the patients than first assumed. Future RCTs with more participants are needed with emphasis on the DOT procedure itself, how patients perceive DOT and the characteristics of patients with DOT-revealed non-adherence.

Keywords: Hypertension, Adherence, Antihypertensive, Directly Observed Therapy
INTRODUCTION

Hypertension (HTN) is the direct cause of estimated 9.4 million deaths a year globally [1], and treatment failure due to patient non-adherence to treatment is a well-known key factor [2, 3, 4, 5]. Estimated > 50% of hypertensive patients fail to reach blood pressure (BP) target of < 140/90 mmHg [6], mainly due to non-adherence to treatment [6]. Failed attempts to introduce invasive treatment procedures of HTN [7, 8, 9, 10], have increased focus on how to best detect and deal with the core problem of non-adherence to treatment.

Single-factor indirect adherence assessment methods, such as pill count, electronic pillboxes [11] and patient questionnaires [12] have in general shown inferiority to multi-factor approaches characterized by multidisciplinary teams (i.e. physicians, nurses and pharmacists) targeting multiple factors such as optimization of drug regimen, educational interventions, self-monitoring, questionnaires, motivational interviewing, refill-reminders etc. [3, 13, 14, 15]. In a global non-adherence perspective, multidisciplinary approaches might be time consuming and costly [14].

Researchers have investigated two direct objective adherence assessment methods in the hypertension population; therapeutic drug monitoring (TDM), where blood or urine samples are analyzed for drug components, and directly observed therapy (DOT), where health personnel observe patients taking their medication prior to ambulatory blood pressure measurement (ABPM).

The highly objective TDM with high performance liquid chromatography coupled with mass spectrometry (HPLC-MS/MS), has regained raison d'être, after in the 1970s to be discarded as a suboptimal assessment method in relation to adherence in hypertensives [16]. Recent studies have by use of HPLC-MS/MS method, revealed
presumed treatment resistant patients as complete non-adherent in 12-53 % of cases [4, 17, 18, 19, 20, 21, 22].

DOT, originally used as a tuberculosis treatment strategy [23] with the purpose of ensuring the intake of medication, has been modified and used in HTN research with promising results regarding presumed treatment resistant patients [9, 24, 25, 26]. DOT of hypertensive patients involves a health personnel observed intake of medications prior to ABPM [9]. No or little (< 5 mmHg) change in daytime ambulatory systolic blood pressure (dASBP) before and after DOT has in one study been interpreted as an indication of adherence, whereas change >5 mmHg was an indication of non-adherence [26]. Still no consensus exists on what decrease in dASBP is considered as indication of non-adherence. TDM with HPLC-MS/MS method is clearly more time consuming as well as machinery- and personnel dependent, and hence more expensive than DOT. More importantly, the method is not yet available for routine measurement of antihypertensive drugs in Norway. Yet another limitation to the TDM method, compared to DOT, is that it does not measure the therapeutic response [26]. We therefore aimed to investigate DOT as a one-time control of adherence in uncontrolled hypertensive patients referred to a specialist nephrology department for ABPM with or without a subsequent specialist appointment. Additionally we investigated the patient´s experience of being observed taking their medication.

The study was approved by The National Committee for Research Ethics in Norway (2015/159) and the institutional research committee at Oslo University Hospital and the University of Oslo. All patients provided written informed consent.
MATERIAL AND METHODS

Trial design
A parallel assignment, open label, randomized controlled pilot trial was conducted at an outpatient clinic at the Department of Nephrology in collaboration with Section of Cardiovascular and Renal Research (SCRR) at the Oslo University Hospital - Ullevaal, Norway.

Participants
All referrals from general practitioners or external specialists regarding ABPM received at the outpatient clinic were assessed for eligibility. Additionally outpatients under follow-up in the Department of Nephrology referred for ABPM were assessed. Inclusion criteria were defined as subjects of both sex, ≥ 18 years of age, residing in Oslo/Akershus in Norway, having uncontrolled HTN defined as dASBP ≥ 135 mmHg despite ≥ 2 antihypertensive drugs and capability of speaking and reading Norwegian. Exclusion criteria were critical illness under active treatment, known atrial fibrillation or heart valve stenosis, myocardial infarction, angina pectoris or stroke during the past 6 months, known severe renal impairment (eGFR < 30 ml/min/1.73 m²), history of DOT prior to ABPM or ongoing participation in other clinical trials.

All presumably eligible patients after screening assessment would receive study information in their appointment letter, granting them time to consider their participation. The information did not give detailed specifications related to DOT, otherwise jeopardizing the element of control. Patients were informed that the intervention involved close monitoring of treatment. Arriving to the appointment the outpatient nurse would ask for the patient’s willingness to participate. Consenting patients provided written informed consent to the investigator.
Characteristics of screened patients and reasons for exclusion

During the 12 months course of the trial from February 2015-2016, 184 patients age 59 (± 15.3) were screened: 71 (38.6 %) women, aged 60.4 (± 17.6), 16 (22.5 %) being of ethnic minority aged 52.1 (± 10.1). 113 (61.4 %) men aged 58 (± 13.6), 30 (26.5 %) being of ethnic minority aged 53 (± 12.5). 102 patients under internal follow-up were identified of which 72 (70.5 %) were excluded due to: decline n = 2, reached BP target n = 28, < 2 antihypertensive medications n = 7, critical illness n = 2, multiple co-morbidity n = 2, severe renal impairment n = 4, severe pain n = 1, previous DOT prior to ABPM n = 7, inadequate language skills n = 4, non-residents n = 3, not possible to schedule n = 3, restricted access to medical records n = 9. 76 patients were referred
from external physicians (51 (67 %) from external specialists) of which 69 (90.7 %) were excluded (49 (96 %) from external specialists). Reasons for exclusion were: decline n = 6, post baseline withdrawal n = 1, post baseline dASBP < 135/80 mmHg n = 1, dASBP < 135/80 mmHg n = 7, < 2 antihypertensive medications n = 4, critical illness n = 2, multiple co-morbidity n = 1, severe renal impairment n = 1, atrial fibrillation n = 4, MI or stroke within 6 month n = 13, coronary illness under investigation n = 3, carotid artery stenosis n = 1, cognitive impairment n = 1, planned hospitalization during study period n = 1, inadequate language skills n = 2, non-residents n = 1, not possible to schedule n = 9, visit cancelled n = 1, restricted access to medical records n = 10. The 12 patients not possible to schedule reflected personnel vacation time (n = 7), and busy outpatient schedule (n = 5). The 19 patients with non-accessible medical records reflected a strict information security regulation in Norway. 36 (19.6 %) of the 184 screened patients qualified to receive a study information letter. 17 of the 36 participants (82.4 % men) went through baseline visit whereof 13 were randomized.

**Randomization**

Personnel not related to the study or the research group handled the randomization process. A random allocation sequence was generated using an electronic generator on www.randomization.com [27] with subsequent preparation of sequentially numbered envelopes kept at third location. Participants were randomized in 5 blocks of 4 with allocation ratio 1:1.

**Baseline**

Baseline measurements were carried out in the outpatient clinic by a nurse. Initially patients were asked if they had taken their medication on that day. Office blood pressure
(OBP) measurements in both arms and ambulatory blood pressure (ABP) were carried out. OBP was measured using a semiautomatic oscillometric OMRON M-3 device (Matsusaka Co. Ltd., Matsusaka, Japan) preceded by fitting of appropriate cuff according to measurement of upper arm circumference. ABPM was measured using a Spacelabs Healthcare model 90217-1Q device (Spacelabs Medical, Inc. 5150 220th Ave SE Issaquah, WA 98029, USA) and dASBP was defined as readings from 8 am to 8 pm. Both OBP and ABP were measured according to European Society of Hypertension/European Society of Cardiology 2013 guidelines [6]. Baseline data on demographics, comorbidity and medication status were collected. The day after baseline on delivery of the ABPM device, ABP results were printed and eligibility checked. Patients with normalized dASBP were excluded at this point. Subjects were subsequently randomized either to a control group with follow-up measurements of standard care OBP and ABP, or to an intervention group with a follow-up measurement of OBP and DOT immediately followed by 24 hour ABPM. Follow-up was scheduled 3 weeks ± 7 days relative to baseline.

DOT, if applicable, was informed of in a letter immediately prior to follow-up visit. Patients were asked to meet medication-fasting bringing their medication in original packaging, for the purpose of taking them in front of the investigator.

Follow-up
For both groups follow-up OBP measurements were carried out in the outpatient clinic by an outpatient nurse blinded for patient allocation to minimize information bias. The atmosphere during follow-up visit was planned to be equally relaxed in both groups to minimize the impact of control on intervention patients.
Follow-up in control group
Control patients were asked if they had taken their antihypertensive medication that day. They were equipped with an ABPM device and asked to complete a questionnaire on civil status, years of education, working hours and lifestyle factors such as smoking, alcohol consumption and physical activity. ABPM device was tested twice before the patient was discharged. If ABP results indicated a need for further post study follow-up, a doctor appointment was scheduled.

Follow-up in intervention group
Immediately prior to DOT, patients in the intervention group were asked to dispense their brought medications from original packaging. DOT was performed by investigator observing the patients intake of prescribed medication (morning dose) with one or two glasses of water followed by mounting of ABP device. To further ensure the absorption of medication, patients were asked to remain seated and complete the above mentioned questionnaire. Investigator stayed with the intervention patients throughout the completion, approximately 30 minutes. The ABPM device was controlled twice and the patients were asked to stay on the premises for up to a minimum of two hours post DOT enabling documentation of possible adverse reactions, mainly for safety reasons [9]. At device delivery the intervention patients were asked by an outpatient nurse to complete a self-reported visual analogue scale assessment (VAS) [28, 29] of their experience of having DOT, by marking a 10 cm line: 0 signifying “not problematic at all” and 10 signifying “very problematic”. If intervention patients would express problematic experience concerning DOT, a meeting with their responsible physician would be possible. If result of the dASBP showed either continued uncontrolled BP or a decrease in BP indicating non-adherence to treatment, the patient was scheduled for further post-study medical follow-up.
Clinical outcomes

Primary endpoint was defined as difference in change in mean daytime ambulatory systolic blood pressure, between baseline and follow-up between the two groups.

Secondary endpoint was defined as difference in change in mean office systolic blood pressure, between baseline and follow-up between the two groups.

Statistical methods

All analyses were performed using IBM SPSS version 22 (SPSS, Chicago, IL). Data on patients were analyzed by descriptive statistics. As few participants were eligible for randomization (n = 13), non-parametric tests were applied to determine any significant differences between groups at baseline. The data were presented by median. Mann-Whitney U test, was used to investigate differences in primary and secondary outcome continuous variables between groups from baseline to follow-up with two-sided tests at the 5 % level of significance.

RESULTS

12 subjects completed the study with a follow-up time in the intervention group and the control group of median (min-max) 15 (14-28) days and 23 (14-29) days respectively.

There were no significant differences in baseline characteristics between groups (Table 1).
Table 1. Baseline characteristics

<table>
<thead>
<tr>
<th></th>
<th>Intervention (n= 6)</th>
<th>Control (n= 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, men (%)</td>
<td>6 (100)</td>
<td>5 (83)</td>
</tr>
<tr>
<td>Age, years (median (min-max))</td>
<td>52.5 (42.0-69.0)</td>
<td>54.0 (45.0-69.0)</td>
</tr>
<tr>
<td>Ethnicity, Caucasian (%)</td>
<td>5 (83.3)</td>
<td>6 (100)</td>
</tr>
<tr>
<td>Body mass index, kg/m² (median (min-max))</td>
<td>29.2 (22.6-37.5)</td>
<td>27.6 (24.7-32.8)</td>
</tr>
<tr>
<td>Waist circumference, cm (median (min-max))</td>
<td>105.5 (88.0-132.0)</td>
<td>99.0 (93.0-03.0)</td>
</tr>
<tr>
<td>Number of prescribed drugs (median (min-max))</td>
<td>3 (2-6)</td>
<td>3 (3-6)</td>
</tr>
<tr>
<td>Diuretics (%)</td>
<td>6 (100)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Years of BP treatment, (median (min-max))</td>
<td>8 (0-21)</td>
<td>13 (0-32)</td>
</tr>
<tr>
<td>Patients with co-morbidity* (%)</td>
<td>3 (50.0)</td>
<td>5 (83.3)</td>
</tr>
<tr>
<td>Smoker, yes (%)</td>
<td>0 (0)</td>
<td>2 (33)</td>
</tr>
<tr>
<td>Alcohol, units/month (median (min-max))</td>
<td>2.5 (0.0-50.0)</td>
<td>9.0 (0.0-48.0)</td>
</tr>
<tr>
<td>Education, years (median (min-max))</td>
<td>16.5 (15.0-21.0)</td>
<td>14.5 (11.0-18.5)</td>
</tr>
<tr>
<td>Full time work, yes (%)</td>
<td>4 (67)</td>
<td>3 (50)</td>
</tr>
<tr>
<td>Living alone, yes (%)</td>
<td>2 (33)</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>

BP = Blood Pressure, *) Patient reported diabetes, cardiovascular- and cerebrovascular disease, other.

Protocol violations
There were two cases – one in each group - of change in medication regimen between baseline and follow-up (Fig. 2-3). There was one case of deviation from DOT procedure in the intervention group where a patient did not bring antihypertensive medication in
original packaging and hasty swallowed the medication when investigator turned to fetch a glass of water in spite of patient being otherwise instructed (in writing and orally) (Fig. 2). BP results (n = 3) were removed from the statistical analysis of endpoints.

**Figure 2.** Intervention group changes in daytime ambulatory systolic blood pressure from baseline to follow-up. The upper small dotted line represents the excluded patient with change in medications between baseline and follow-up. The lower small dotted line represents the excluded patient with an unsuccessful DOT. The fat line represents the patient declaring “same-day” non-adherence at baseline.

**Figure 3.** Control group changes in daytime ambulatory systolic blood pressure from baseline to follow-up. The upper small dotted line represents the excluded patient who both admitted to incorrect baseline self-declaration of “same-day” adherence, and had changes in medications between baseline and follow-up.
**Primary analysis**

Randomly applying DOT to patients with no changes in medications between baseline and follow-up (n = 4) resulted in a baseline median (min-max) daytime ASBP and ADBP of 147 mmHg (142-149) and 89 mmHg (83-109) respectively, and a follow-up median (min-max) daytime ASBP and ADBP of 142 mmHg (130-150) and 87 mmHg (79-97) respectively. In the control group with no changes in medication between baseline and follow-up (n= 5) the baseline median (min-max) daytime ASBP and ADBP were 144 mmHg (144-149) and 95 mmHg (87-98) respectively, and follow-up median (min-max) daytime ASBP and ADBP were 142 mmHg (139-153) and 92 mmHg (87-100) respectively. The Mann-Whitney U analysis (Table 2) showed no significant difference in daytime systolic ABP decrease between the groups (p = 0.624).
Table 2. Between group difference in change in ambulatory- and office blood pressure from baseline to follow-up, Mann-Whitney U test

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group</th>
<th>n</th>
<th>median</th>
<th>U</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difference in Daytime Systolic Ambulatory BP*, mmHg</td>
<td>DOT</td>
<td>4</td>
<td>-3.5</td>
<td>8.0</td>
<td>0.624</td>
</tr>
<tr>
<td>Difference in Daytime Systolic Ambulatory BP, mmHg</td>
<td>Control</td>
<td>5</td>
<td>-3.0</td>
<td></td>
<td>0.618</td>
</tr>
<tr>
<td>Difference in Daytime Diastolic Ambulatory BP, mmHg</td>
<td>DOT</td>
<td>4</td>
<td>-2.0</td>
<td>8.0</td>
<td>0.618</td>
</tr>
<tr>
<td>Difference in Daytime Diastolic Ambulatory BP, mmHg</td>
<td>Control</td>
<td>5</td>
<td>0.0</td>
<td>8.0</td>
<td>0.618</td>
</tr>
<tr>
<td>Difference in Office Systolic BP, mmHg</td>
<td>DOT</td>
<td>4</td>
<td>1.5</td>
<td></td>
<td>0.140</td>
</tr>
<tr>
<td>Difference in Office Systolic BP, mmHg</td>
<td>Control</td>
<td>5</td>
<td>-11.5</td>
<td>4.0</td>
<td>0.140</td>
</tr>
<tr>
<td>Difference in Office Diastolic BP, mmHg</td>
<td>DOT</td>
<td>4</td>
<td>5.0</td>
<td></td>
<td>0.086</td>
</tr>
<tr>
<td>Difference in Office Diastolic BP, mmHg</td>
<td>Control</td>
<td>5</td>
<td>-3.0</td>
<td>3.0</td>
<td>0.086</td>
</tr>
</tbody>
</table>

*) BP= Blood Pressure, DOT = Directly observed therapy

Secondary analysis

The office systolic blood pressure showed no significant difference from baseline to follow-up (p = 0.140).

Descriptive analysis showed that one intervention patient answered no to the question of “same day” adherence at baseline with a subsequent fall in mean daytime ASBP and ADBP of 18 and 18 mmHg respectively from baseline to follow-up (Fig. 2). One control patient initially declared adherence to antihypertensive medication, and then due to high mean daytime ABP (186/98 mmHg) and subsequent consultation with
a physician admitted to non-adherence to diuretic with a subsequent fall in mean
daytime ASBP and ADBP of 27 and 16 mmHg respectively from baseline to follow-up
(Fig. 3).

Safety and patient experience of DOT
There were no cases of adverse reactions ≤ 2 hours post-DOT in the intervention group.
Experience of DOT (n = 6) showed a median (min-max) of 0.05 cm (0.0-0.3), 0 cm
signifying “not problematic at all”, 10 cm signifying “very problematic”.

DISCUSSION
We found no statistically significant between group differences in change in daytime
systolic ambulatory blood pressure (p = 0.624) from baseline to follow-up. Neither did
we find any significant between group difference in change in mean office systolic
blood pressure (p = 0.140) from baseline to follow-up. The study population in our RCT
was small (n = 12) though, and predominantly male (83.3 %) (Table 1). Comparing our
study with other hypertension studies investigating DOT was challenging in the sense
that our study, to the best of our knowledge, was the first RCT to investigate DOT in
uncontrolled hypertensive patients. Other studies used other methodologies, or had
DOT as a screening tool, not an intervention, in addition to the patients being treatment
resistant [25, 26, 30]. However all of our patients, but two, were treated with 3 or more
medications including a diuretic and therefore could be regarded as treatment resistant
[6], noting that the resistance to treatment in some cases are rather non-adherence to
treatment [4, 18, 22]. Hameed et al [26] reported retrospectively, and without prior
consent, on all patients (n = 50) with presumed treatment resistant HTN referred to a
DOT clinic over a period of 66 months (< 1 patient per month), in comparison to our
consenting sample (n = 12) prospectively randomized over 12 months (1 patient per
month). Compared to our study, Hameed et al reported more female participants (52.1% vs. 8.3%), higher age (mean (± SD) 62.0 (11.0) vs. median (min-max) 54.0 (44.0-69.0)), higher proportion of non-caucasians (22 (45.8%) vs. 1 (8.3%)), more antihypertensive drugs (median (IQR) 5 (4-5) vs. median (min-max) 3 (2-6)), longer treatment period (n = 41, median (IQR) 12.0 (7.5-22.0) vs. median (min-max) 10.5 (0.0-32.0)), higher BMI (mean (± SD) 32.0 (5.5) vs. median (min-max) 28.3 (22.6-37.5)), less never-smokers (20 (41.7%) vs. 9 (75%)), and higher pre-DOT daytime ambulatory systolic blood pressure (mean (± SD) 164.7 (21.2) vs. median (min-max) 145.5 (137.0-186.0)) as well.

The major methodological differences between the two studies might indicate that given more time to enroll participants in the current study, the two study samples would become more comparable. Unless the methodological differences per se would extort any comparison, due to the fact that we in our RCT asked participants for willingness to participate in a study involving close monitoring of treatment, hence may have lost some deliberately non-adherent patients, or, as a consequence of our exclusion criterias, may have have lost patients with co-morbidities or unhealthier lifestyle, resulting in selection bias. However in our screened population (n = 184) 71 (38 %) were women, and 36 were non-caucasian (women 44.4%), suggesting that with less solid methodology we could have reported higher gender equality and ethnical variance.

Our aim was to investigate DOT as a one-time control of adherence in uncontrolled antihypertensive patients using a pilot RCT design with 20 participants. The study gave an important description of the selected population of referred difficult to control antihypertensive patients during the one year course of the trial with insights to the referents, the inclusion rate and the corresponding time and number needed to screen. The low inclusion rate in our study of 7% could be viewed as a limitation,
however our strict adherence to the CONSORT guideline [31] might indeed have provided a more precise description of the workload following an RCT in HTN. The low inclusion rate corresponded with other resent HTN studies reporting 7.3 % [32], 7.5 % [33] and 7.1 % [34] inclusion rates. The mentioned studies differed from our study i. e. by investigating treatment resistant patients, though with more or less similar BP entry criterias as ours, ambulatory systolic blood pressure ≥ 130 mmHg [32], daytime ambulatory blood pressure ≥ 135/≥ 85 mmHg [33] and daytime ambulatory blood pressure ≥ 135-149/90-94 mmHg [34].

Number of participants in the DOT group was small (n = 6), however, a thorough description of baseline characteristics of all participants in the DOT group, makes it different from other comparable studies we know of. Using the goldstandard ABPM as inclusion criteria excluded patients with masked HTN, whom could have otherwise biased the results and made it impossible to discriminate between non-adherence and masked HTN [30].

**Limitations**

Our study has several limitations. After a study duration of 12 months, 13 patients were randomized, 1 was lost to follow-up and 9 were included in the primary analysis, providing no statistical power to make valid conclusions about the endpoint of difference between the two groups regarding the change in BP after applying DOT. The H0 of no difference was kept, with the risk of a type 2 error. In a previous SCRR study, the Oslo RDN Study [30], 25 (30 %) of the screened treatment resistant patients achieved BP control after DOT prior to ABPM, 17 (68 %) of these due to non-adherence to prescribed medication [30]. In the current study 1 (16.6 %) patient on three medications including a diuretic, had a substantial decrease in dASBP after DOT of 18/18 mmHg, changing from 148/109 mmHg to 130/91 mmHg. The patient answered
no to the question of “same day” adherence. Nevertheless a referral to a specialist nephrology department due to difficult-to-control hypertension provides some information in itself. It could have strengthened the study to investigate patient-reported adherence in general, unless it is in fact easier for the patient to answer an honest “no” to “same-day” adherence than adherence in general.

Any post baseline changes in medication of course would bias the follow-up BP results, but due to safety reasons two patients had changes in medication during our study and were therefore withdrawn from analysis. To avoid such post randomization violations of protocol, one could have screened all patients with ABPM in order to adjust and optimize medication regimen, prior to baseline and follow-up ABPM, hence of course prolonging the study duration.

The current DOT procedure did not result in any cases of hypotension as seen in other studies [9] and case reports [35] but due to the small n, no conclusions regarding the safety of the applied DOT procedure could be made. The patient with a non-successful DOT was not confronted with the failed procedure, since the purpose of the study was to observe, describe and compare blood pressure with or without DOT. In the Oslo RDN study [36] there was one quite similar situation with a patient pretending to swallow the medication meanwhile keeping the pills hidden in one hand. To gain more knowledge of why patients deliberately deviate from instructed DOT procedures, would demand a qualitative research approach and could provide important knowledge about the patient perspective of DOT. An interpretive phenomenological study of tuberculosis nurses’ relational work [37] stated the importance of the nurses’ ability to balance the dual surveillance-care role, i. e. both providing comfort and being watchful. All of our patients, including the patient with the non-successful DOT, and the patient with a post-DOT decrease in dASBP and dADBP of 18/18 mmHg, interestingly reported non-
problematic experiences with DOT to an outpatient nurse not involved in the DOT procedure, however it would have strengthened the reliability of the result if VAS had been collected anonymously.

The limited n in the final analysis, compared to the number of patients screened was partly explained by the screening of internal patients initially refered to ABPM and still under follow-up in the Department of Nephrology, i.e. the 28 (15 %) patients who had normalized their BP. Our inclusion rate (7.0 %) might have been increased by challenging on a regulatory level the restricted access to some patient records (n = 19). Less restrictive exclusion criterias might also have increased the inclusion rate, under the argument that no participant would be exposed to any additional risk, since no changes in medications were done, and since we merely wanted to observe their intake of already “doctor-patient-agreed” prescribed medications. However research has revealed both patient declared adherence [3] and physician´s ability to judge patient´s adherence [16] as questionable, making it unsafe and unethical to actually “expose” patients with additional vulnerability in terms of the co-morbidities listed in our exclusion criteria, to their medications. As a consequence of that, a group of patients (n =51) were almost entirely (96 %), excluded from the current study, namely those referred for tertiary care (specialist to specialist), which made it impossible to gather information on this important group of hypertensive patients.

**Future research**

To assist future power calculations more studies with more participants are needed to evaluate what degree of blood pressure decline after DOT should be considered significant to suspect non-adherence. Hameed et al [26] used, in the absence of a defined cut-off value in the literature an arbitrary cutoff of ≥ 5 mmHg to determine non-adherence. From a patient perspective one could question the reasonability of a cutoff
value as low as \( \geq 5 \text{ mmHg} \), since a predicate of non-adherence might be difficult for the patient to accept, and might jeopardize the important trust between doctor and patient \[6\]. Future high-quality RCTs with more participants are needed to define a cut-off value and state the sensitivity and specificity of DOT as an adherence assessment method. A one-time control with DOT, as we investigated in this study, does not provide information on the patient’s long-term adherence. Qualitative studies to grasp the patient’s perspective are inevitable in future research regarding adherence to antihypertensive medications, and the use of DOT.

**CONCLUSION**

Though no significant primary finding, the RCT pilot gave important information about the patient experience of DOT, as well as the importance of how the DOT procedure is applied to ensure a valid result. A standardization of the DOT procedure in hypertension is warranted.

**Funding**

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**Declaration of interest**

The authors declare no conflict of interest.

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3. Graphical abstract. This is an image to give readers a clear idea of the content of your article. It should be a maximum width of 525 pixels. If your image is narrower than 525 pixels, please place it on a white background 525 pixels wide to ensure the dimensions are maintained. Save the graphical abstract as a .jpg, .png, or .gif. Please do not embed it in the manuscript file but save it as a separate file, labelled GraphicalAbstract1.

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5. 5-8 keywords. Read making your article more discoverable, including information on choosing a title and search engine optimization keywords. Read making your article more discoverable, including information on choosing a title and search engine optimization.

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7. Disclosure statement. This is to acknowledge any financial interest or benefit that has arisen from the direct applications of your research. Further guidance on what is a conflict of interest and how to disclose it.

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12. Tables. Tables should present new information rather than duplicating what is in the text. Readers should be able to interpret the table without reference to the text. Please supply editable files.

13. Equations. If you are submitting your manuscript as a Word document, please ensure that equations are editable. More information about mathematical symbols and equations.

14. Units. Please use SI units (non-italicized).

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In order to be published in a Taylor & Francis journal, all clinical trials must have been registered in a public repository at the beginning of the research process (prior to patient enrolment). Trial registration numbers should be included in the abstract, with full details in the methods section. The registry should be publicly accessible (at no charge), open to all prospective registrants, and managed by a not-for-profit organization. For a list of registries that meet these requirements, please visit the WHO International Clinical Trials Registry Platform (ICTRP). The registration of all clinical trials facilitates the sharing of information among clinicians, researchers, and patients, enhances public confidence in research, and is in accordance with the ICMJE guidelines.

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Please ensure that all research reported in submitted papers has been conducted in an ethical and responsible manner, and is in full compliance with all relevant codes of experimentation and legislation. All papers which report in vivo experiments or clinical trials on humans or animals must include a written statement in the Methods section. This should explain that all work was conducted with the formal approval of the local human subject or animal care committees (institutional and national), and that clinical trials have been registered as legislation requires. Authors who do not have formal ethics review committees should include a statement that their study follows the principles of the Declaration of Helsinki.

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Updated April 2016
Forespørsel om deltakelse i forskningsprosjektet

"Behandling av høyt blodtrykk: en intervensjonsstudie for å forbedre pasientoppfølgning" (DRIVE)

Bakgrunn og hensikt

Hva innebærer studien?
I studien følges blodtrykksutviklingen hos den enkelte deltaker over en periode på 2-4 uker med 3 besøk på nyremedisinsk poliklinikk. Studiedeltakerne fordeles ved loddtrekkning i to grupper, som adskiller seg ved at den ene gruppen følges tettere opp. Alle som deltar får målt blodtrykket sitt ved studiepersonalet, samt får montert et 24 timers blodtrykksapparat som skal måle blodtrykket det følgende døgn. Dette gjentas ved hvert besøk. Dessuten skal alle svare på et spørreskjema ved studiens start. Studiens resultater inngår i et mastergradsprosjekt på Universitetet i Oslo, Avdeling for helsefag.

Mulige fordeler og ulemper
Vi kan ikke garantere at du får et lavere blodtrykk, men de som deltar kan være med å bygge viten om hvordan man kan forbedre oppfølgingen av pasienter med høyt blodtrykk. Det kan oppleves som en ulempe å måtte bruke ekstra tid på ekstra undersøkelser.

Hva skjer med prøver og informasjonen om deg?
Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysninger vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet som har adgang til navnelisten og som kan finne tilbake til deg. Hvis du sier ja til å delta i studien vil opplysninger om deg fra studien (spørreskjemasvar, blodtrykk, 24-timers blodtrykk, bivirkninger, journaldata om hvilke medikamenter du bruker sykehistorie som er relevant for blodtrykhet ditt, samt opplysninger fra henvisningen din lege har sendt til nyremedisinsk poliklinikk) bli registrert. Det er bare helsepersonell relatert til studien som får tilgang til din pasientjournal og dine opplysninger. Alle opplysninger behandles uten navn og fødselsnummer, slik som beskrevet ovenfor. De kodele opplysninger lagres på en sikker forskningsserver på Oslo universitetssykehus, som bare studierelatert helsepersonell har tilgang til. 5 år etter studiens avslutning og senest ved utgangen av 2023 anonymiseres samtlige opplysninger slik at det ikke lengere er mulig å finne tilbake til den enkelte deltakers identitet. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse

Utdypende forklaring av hva studien innebærer:

- For å kunne delta må du bruke minimum 2 blodtrykksmedikamenter eller minimum 1 kombinasjonsmedikament og likevel ha et 24 timers blodtrykk med et dagsgjennomsnitt over eller lik 135 mmHg i overtrykket (sistolisk). Du skal være henvist til, eller ha en planlagt 24 timers blodtrykksmåling på nyremedisinsk poliklinikk på Oslo universitetssykehus – Ullevål.
- Resultatet av den første 24 timers blodtrykksmåling vil være avgjørende for om du kvalifiserer til å bli med videre i studien. Er resultatet over eller lik 135 mmHg systolisk kan du bli med videre og får en ny time hos en sykepleier på nyremedisinsk poliklinikk, som planlegges til kl. 8.30 eller 9.00 og tar ca. 3 timer. De følgende studiebesøk blir i tidsrommet fra kl. 9.00-14.00, og tar ca. en time. Det er planlagt 3 besøk i alt.

Personvern
Dine opplysninger merkes som tidligere beskrevet med en kode og lagres på Oslo universitetssykehus sin forskningsserver.

Studien er godkjent av Regionale Komitéer for medisinsk og helsefaglig forskningsetikk, Internt personvernombud ved Oslo universitetssykehus og Kvalitetsutvalget ved Institutt for Helse og Samfunn, Universitet i Oslo.

Oslo universitetssykehus ved administrerende direktør er databehandlingsansvarlig.

Rett til innsyn og sletting av prøver og opplysninger om deg
Hvis du sier ja til å delta i studien, har du rett til å få innsyn i hvilke opplysninger som er registrert om deg. Du har videre rett til å få korrigert eventuelle feil i de opplysningene vi har registrert. Dersom du trekker deg fra studien, kan du kreve å få slettet innsamlede opplysninger, med mindre opplysningene allerede er inngått i analyser eller brukt i vitenskapelige publikasjoner.

Økonomi
Studien og biobanken er finansiert av Oslo universitetssykehus, Enhet for indremedisinsk forskning og nyremedisinsk poliklinikk.

Forsikring
Deltakere i studien er pasienter og er forsinket på samme måte som andre pasienter som behandles ved Oslo universitetssykehus.

Informasjon om utfallet av studien
Deltakerne har rett til å få informasjon om utfallet/resultatet av studien.
Samtykke til deltagelse i studien

Jeg er villig til å delta i studien

(Signert av prosjektdeltaker, dato)

Jeg bekrefter å ha gitt informasjon om studien

(Signert, rolle i studien, dato)
**Inklusjonskriterier**

≥ 18 år  
Bosatt i Oslo  
ABT (daggjennomsnitt) ≥ 135 mmHg systolisk  
Står på ≥ 2 hypertensjonsmedikamenter/≥ 1 kombinasjonspreparat (2-3 virkestoffer)  
Skal kunne forstå og lese norsk

**Eksklusjonskriterier**

Alvorlig sykdom/tilstand i behandlingsfase (eksempelvis men ikke begrenset til: kreft, psykisk sykdom, smerte, rus)  
Kjent atrielimmer  
Kjent stenose i hjerteklaffer  
Hjerteinfarkt, angina pectoris eller hjerneslag de siste 6 mnd.  
Kjent alvorlig nedsatt nyrefunksjon (eGFR < 30 ml/min/1.73 m²)  
Tidligere DOT ifm ABTM  
Deltakelse i annen helsefaglig intervensjonsstudie

**Inklusjonskriterier oppfyllt baseline (dag1):** ja □ nei □  
**Eksklusjonskriterier oppfyllt baseline (dag 1):** ja □ nei □

**Inklusjonskriterier oppfyllt baseline (dag 2):** ja □ nei □  
**Eksklusjonskriterier oppfyllt baseline (dag 2):** ja □ nei □
# Kontorblodtrykk (OMRON M-3)

**Baseline dato:**
___ / ___ 2015 kl._________

**Sykepleier:**
_______ (init.)

**Spørre** om pasienten har tatt sine hypertensjonsmedikamenter:  

- **ja / nei** (sett O rundt)  
  - hvis nei, begrunn:___________________________________________________

**Omkrets:**  
- høyre arm: _________ cm  
- venstre arm: _________ cm

**Mansjett størrelse:**  
- M  
- L  
  (sett O rundt)

**Måling i begge armer mulig:**  

- **ja / nei** (sett O rundt)  
  - hvis nei, begrunn:___________________________________________________

(Sitte i ro 5 min.)

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<th>Blodtrykk venstre arm</th>
<th>1 min mellom hver måling</th>
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<th>Blodtrykk høyre arm</th>
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<th>(evt. 4. og 5. måling hvis syst. BT varriere med &gt; 6 mmHg)</th>
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**Kommentar:**

____________________

____________________
ABTM/24 timers blodtrykk (Spacelabs)

Baseline dato:
____ / ____ 2015 kl._______

Sykepleier:
_______ (init.)

Mansjett størrelse:  Small □  Medium □  Large □  X-Large □  (sett X)

Dominant arm:  Høyre □  Venstre □  (sett X)

Målearm:  Høyre □  Venstre □  (sett X)
(arm mansjett er montert på)

Sjekk at apparatet virker før pasienten drar hjem:  □  (sett X)

Pasientinformasjon til 24-timers måling utlevert:  □  (sett X)

Pasientdagbok utlevert, informasjon om bivirkningsregistrering:  □  (sett X)

Pasienten leverer apparat d. ____ / ____ 2015 kl. ______

Evt. kommentar:_____________________________________________________________
__________________________________________________________________________
# 24-timers blodtrykksmåling – pasientdagbok

| Dato: _______________ |

---

**Screening nummer _____ Randomisering nummer _____ Pt initialer _____**

**Første måling __ Andre måling ___** (Sett X. Utfylles av sykepleier)

Vennligst fyll ut nedenstående i kveld og i morgen tidlig

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<th>Våknet kl: _____</th>
<th>Morgenmedisin inntatt kl: _____</th>
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Søvnkvalitet: □ Dårlig □ Middel □ God

Vennligst beskriv hendelser som kan ha påvirket blodtrykket ditt dette døgn (aktivitet/tilstand):

**Eksempel: løpe etter bussen, ekstraordinær stress på jobb eller hjemme (mental belastning)**

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Vennligst beskriv dette døgns bivirkninger du forbinder med medisinen du tar for blodtrykket:

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Kommentar (obs dato/init.):

Deltaker etikett
**Forklaringsvariabler**

Sykepleier: 
________ (init.)

**Baseline dato:**
____ / ____ 2015  kl._______

**Oppfølging, dato:**
____ / ____ 2015  kl._______

Kjønn: Kvinne □  Mann □
Etnisitet: _____________

Høyde: _____ cm  Vekt: _____ kg  Livvidde: _____ cm  Hoftevidde: _____ cm

**Oppfølging:**
Vekt: _____ kg  Livvidde: _____ cm  Hoftevidde: _____ cm

Hypertensjon oppdaget når: _______________ mnd/årstall

Samsykelighet:

Diabetes type I / II (sett O): Start:_______________ mnd/årstall

Cardiovaskulær sykdom: ja / nei (sett O): Spesifiser, inkl start (mnd/årstall):_______________

Cerebrovaskulær sykdom: ja / nei (sett O): Spesifiser, inkl start (mnd/årstall):_______________

Annet: ja / nei (sett O): Spesifiser, inkl start (mnd/årstall): ________________________________
Kontorblodtrykk (OMRON M-3)

Oppfølging, dato:
____ / ____ 2015 kl._______

Sykepleier:
________ (init.)

Mansjett størrelse: _______ Målearm: _______

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Evt. kommentar: ________________________________________________

________________________________________________________________________
Oppfølging d. _____ / _____ 2015            Utfylles KUN hvis ENDRING i medikamenter, endringer: ja___ nei ___

DRIVE-studien 2015-16 versjon 1.0 01.04.15
[ ved kombinasjonspreparater ]

| Forhandler navn | Generisk navn | ATC kode | Dose medikament 1 | Dose medikament 2 | Dose medikament 3 | Tatt kl. | Admin. | Start dato | Stop dato | √ | Fortsatt |
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|                 |               |          |                   |                   |                   |         |        |            |           |   |         |

Kommentar (obs dato/init.): ____________________________________________
__________________________________________
__________________________________________
__________________________________________

Deltaker etikett
**ABTM/24 timers blodtrykk (Spacelabs)**

**Oppfølging, dato:**  
____ / ____ 2015 kl._________

Sykepleier:  
________ (init.)

Mansjett størrelse: ______ Målearm:______

Gr. I □  Gr. II □

Hvis Gr II:  
Spør om pasienten har tatt sine hypertensjonsmedikamenter:  : ja / nei (sett 0)  
hvis nei, begrunn:_________________________________________________________

Sjekk at apparatet virker før pasienten drar hjem: □ (sett X)

Pasientinformasjon til 24-timers måling utlevert: □ (sett X)

Pasientdagbok utlevert: □ (sett X)

**Pasienten leverer apparat d. ____ / ____ 2015 kl. ______**

Bivirkningsregistreringsskjema innhentet: □ (sett X)

Evt. kommentar:_____________________________________________________________
24-timers blodtrykksmåling – pasientdagbok

<table>
<thead>
<tr>
<th>Screening nummer</th>
<th>Randomiserings nummer</th>
<th>Pt initialer</th>
<th>Første måling</th>
<th>Andre måling</th>
</tr>
</thead>
</table>

Vennligst fyll ut nedenstående i kveld og i morgen tidlig

Sovnet kl: ___.___   Våknet kl: ___.___   Morgenmedisin inntatt kl: ___.___

Søvnkvalitet: □ Dårlig □ Middel □ God

Vennligst beskriv hendelser som kan ha påvirket blodtrykket ditt dette døgn (aktivitet/tilstand):

_Eksempel: løpe etter bussen, ekstraordinær stress på jobb eller hjemme (mental belastning)_

<table>
<thead>
<tr>
<th>Klokkeslett</th>
<th>Hendelse</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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</tr>
</tbody>
</table>

Vennligst beskriv dette døgns bivirkninger du forbinder med medisinen du tar for blodtrykket:

<table>
<thead>
<tr>
<th>Klokkeslett</th>
<th>Bivirkning</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
</tbody>
</table>

Dato:_______________
Spørreskjema

Hensikten med dette spørreskjema er å skaffe informasjon om de faktorer som forskning viser kan være med å påvirke blodtrykk generelt. Det er viktig at du leser spørsmålene grundig, og svarer på alle spørsmålene. Takk.

Sivilstand: (sett ét kryss)
- Gift eller samboer
- Enke/enkemann
- Separert /skilt
- Enslig

Hvis du ikke bor alene, hvem bor du sammen med?:
- Ektefelle/samboer
- Foreldre/svigerforeldre
- Andre voksne
- Barn 0-15 år
- Barn 16-20 år

Antall barn: ______

Utdanningsnivå (antall skoleår ETTER obligatoriske 9 år): _____ år

Arbeidsstatus? (sett ét kryss)
- Full tid
- Deltid: _______%
- Arbeidsledig

Hvordan har din fysiske aktivitet vært i det siste året?
(Tenk deg et ukentlig gjennomsnitt for året)

Timer per uke

<table>
<thead>
<tr>
<th>Timer per uke</th>
<th>Ingen</th>
<th>&lt;1 time</th>
<th>1-2 t</th>
<th>3-6 t</th>
<th>7-10 t</th>
<th>11-20 t</th>
<th>&gt;20 t</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aktivitet (svett/anpusten)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Kommentar:______________________________
Nytelsesmidler

Har du noen gang røykt?  
Ja  Nei

Røyker du nå?    
Ja  Nei  Av og til

Hvis ja, hvor mange sigaretter røyker du vanligvis daglig: __________ stk

Hvis av og til, hvor mange per måned:________ stk

Hvor mange år til sammen har du røykt daglig?:________ år

Bruker du snus  
Ja  nei

Drikker du alkohol?  
Ja  nei

Hvor mange alkoholenheter drikker du vanligvis i måneden? (se boks under)  
(Regn ikke med lettøl. Sett 0 hvis mindre enn 1 i måneden)

Antall: __________

Hvor ofte har du drukket alkohol det siste året?  
(Regn ikke med lettøl og alkoholfritt øl)

4-7 ganger i uken
2-3 ganger i uken
ca. 1 gang i uken
2-3 ganger i måneden
ca. 1 gang i måneden
Noen få ganger siste år
Ikke siste året

<table>
<thead>
<tr>
<th>Enheter alkohol</th>
</tr>
</thead>
<tbody>
<tr>
<td>For å sammenligne ulike typer alkohol spør vi etter det vi kaller alkoholenheter (= 1,5 cl ren alkohol). En alkoholenhet tilsvarer:</td>
</tr>
<tr>
<td>1 flaske rusbrus / cider</td>
</tr>
<tr>
<td>1 glass (0.33 liter) øl</td>
</tr>
<tr>
<td>1 vinglass (12 cl) rød eller hvitvin</td>
</tr>
<tr>
<td>1 hetvinsglass (7,5 cl), sherry eller annen hetvin</td>
</tr>
<tr>
<td>1 drammeglass (4 cl) brennevin eller likør</td>
</tr>
</tbody>
</table>
Visuell analog skala

Spørsmål:
Hvordan opplevde du å skulle ta dine medikamenter under oppsyn av helsepersonale?

Svaralternativer:
0 = Ikke ubehagelig i det hele tatt
10 = Meget ubehagelig

Markér med et kryss på linjen mellom 0 og 10 hvordan du opplevde det.

0 10

Ikke ubehagelig Meget ubehagelig i det hele tatt
Aud Høieggen

2015/159  Behandling av høyt blodtrykk: en intervensjonsstudie for å forbedre pasientoppgjøring

Forskningsansvarlig: Oslo universitetssykehus
Prosjektleder: Aud Høieggen

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nord) i møtet 12.02.2015. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10, jf. forskningsetikkloven § 4.

Prosjektleders prosjektomtale
Behandlingssetterlevelse (adherens) hos pasienter med høyt blodtrykk er etter 1 års behandling < 50 % iflg litteraturen. Studien skal gi ny kunnskap om endring i blodtrykk ved bruk av måling av behandlingssetterlevelse (adherens) hos pasienter med høyt blodtrykk (HT). I et randomisert klinisk design undersøkes endring i ambulatorisk blodtrykk i en intervensjonsgruppe versus en kontrollgruppe med og uten ångangskontroll av adherens med direkte observert terapi (DOT). DOT innebærer at pasienter i intervensjonsgruppen møter medikamentfastende, tar sine medikamenter foran studiepersonell, får påmontert ambulatorisk blodtrykksmåler og leverer apparatet dagen etter. Resultatet må forventes å være pasientens sanne blodtrykk med gitt behandling. Endring i ambulatorisk blodtrykk fra baseline (første måling) til første kontrollmåling (andre måling) er studiens primære utfallsmål. Studien undersøker endring i kontorblodtrykk som sekundært utfallsmål.

Vurdering

I protokollen er formålet med studien beskrevet slik «Formålet med studien er overordnet å utvikle ny kunnskap om bruk av DOT som ångangskontroll av adherens før blodtrykksmåling hos hypertonikere før metoden kan anbefales brukt i klinisk praksis.»

Komiteen har ingen innvendinger mot prosjektet.

Vedtak
Med hjemmel i helseforskningsloven §§ 2,9 og 10, samt forskningsetikkloven § 4 godkjennes prosjektet.

Sluttmelding og søknad om prosjektendring
Prosjektleder skal sende sluttmelding til REK nord på eget skjema senest 30.06.2019, jf. hfl. § 12. Prosjektleder skal sende søknad om prosjektendring til REK nord dersom det skal gjøres vesentlige endringer i forhold til de opplysninger som er gitt i søknaden, jf. hfl. § 11.

Klageadgang
Du kan klage på komiteens vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes til REK nord. Klagefristen

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er tre uker fra du mottar dette brevet. Dersom vedtaket oppretholdes av REK nord, sendes klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag for endelig vurdering.

Med vennlig hilsen

May Britt Rossvoll
sekretariatsleder

Kopi til: oushfdlgodkjenning@ous-hf.no
Angående søknad om godkjenning av mastergradsprosjekt

Prosjekt: Behandling av høyt blodtrykk: en intervensjonsstudie for å forbedre pasientoppfølging.

Vi viser til revidert søknad datert 23. februar 2015 om godkjenning av ovennevnte forskningsprosjekt som masteroppgave ved Avdeling for helsefag, Universitetet i Oslo. Søknaden er vurdert av kvalitetssikringsutvalget ved Avdeling for helsefag.

Forskningsetisk vurdering


Vedtak

Tillatelse til gjennomføring av prosjektet gis under forutsetning av at det gjennomføres slik det er anført i søknaden og prosjektbeskrivelsen og de bestemmelser som følger av helseforskningsloven med forskrifter. Veiledningsavtalen godkjennes.

Lykke til med prosjektet.

Med hilsen

Hilde Bondevik
programleder, førsteamanuensis

Lisbeth Thoresen
leder, kvalitetssikringsutvalget
Hei,

Takk for melding. Vi har ingen personvernmessige innvendinger og ønsker dere lykke til med prosjektet.

Bestilling av lagringplass er videresendt til Sykehuspartner med vår godkjenning. Saksnr. hos Sykehuspartner er SD2015845 Purring skjer direkte til Sykehuspartner med henvisning til dette saksnr. Det går vanligvis ikke mer enn 2-3 dager før bestillingen er gjennomført av SP.

Brukerne kan selv sjekke om mappen er tilgjengelig. Det forutsetter imidlertid at man har logget av først, dersom man har for vane å la PCen være pålogget hele døgnet.

mvh

Johan Martin Hindrum
Personvernrådgiver
Seksjon for informasjonssikkerhet og personvern | Stab pasientsikkerhet og kvalitet
Oslo universitetssykehus HF
Telefonnummer: 22 11 75 88
Besøk: Kirkeveien 166 (Ullevål sykehus)
www.oslo-universitetssykehus.no/personvern

________________________________________________________________________

Fra: Elsa Roland
Sendt: 20. januar 2015 14:21
Til: Ulla Hjørnholm; Aud Høieggen
Kopi: OUSHF PB Personvern
Emne: SV: Skjema for behandling av helseforskningdata

Hei

Takk for mottatt prosjektdokumentasjon. Studien er registrert i ForPro og arkivert i e-phorte med nr. 2015/1145

Vennlig hilsen Forskningsstøtte
Avdeling for forskningsadministrasjon og biobank

IKKE SENSITIVT INNHOLD

________________________________________________________________________

Fra: Ulla Hjørnholm
Sendt: 19. januar 2015 17:18
Hei,

Med vennlig hilsen

Ulla Pilemand Hjørnholm
Studiekoordinator|Enhet for indremedisinsk forskning|Medisinsk klinikk
Tlf: 22 11 93 38 | E-post: ulla.hjornholm@ous-hf.no

Denne meldingen inneholder ikke sensitiv informasjon som bryter med Oslo Universitetssykehus HF's krav til informasjonsstikkerhet.

<< Fil: A Skjema for behandling av helseforskningsdata_190115.doc >>      << Fil: ProtokollV3_190115.pdf >>     << Fil: Info_Samtykke_V2_190115.pdf >>