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Improving management of resistant hypertension: Rationale and protocol for a cluster randomized trial addressing physician managers in primary care☆

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ABSTRACT

Background: Resistant hypertension (RH) is defined as uncontrolled blood pressure (BP) despite ≥3 antihypertensive agents. It is estimated to account for 12–28% of all hypertensive patients. Despite a higher risk of cardiovascular events, hypertension therapy in these patients is often insufficient. In a previous study we successfully tested an evidence-based, physician manager-centered hypertension management.
Methods: For this cluster randomized trial (CRT), a random sample of 102 German primary care practices will be randomized into two study arms (1:1). Physician managers and practice assistants of the intervention arm will participate in three-session medical education on hypertension management to implement 1) standardized diagnostic and therapeutic procedures for RH patients, 2) structured recall of patients with uncontrolled BP, and 3) teaching and supervision of RH patients on BP self-measurements. Practice tools are provided to facilitate implementation, e.g., how to distinguish true from pseudo RH and guideline-based medication selection. Physicians will specify guideline-algorithms for their practice to manage RH. A secured web-based peer-group exchange with hypertension specialists is offered to both professional groups. Physicians of both study arms will consecutively recruit patients with RH. BP will be measured by ambulatory BP monitoring at baseline and after 12 months. The primary endpoint is defined as treatment success with either normalized BP (24 h < 130/80 mm Hg) and/or a reduction by ≥20 mm Hg systolic and/or ≥10 mm Hg diastolic. Secondary analyses will focus on changes in physicians' knowledge and practice routines.
Discussion: This CRT will determine the effectiveness of a physician manager-centered intervention on treatment success in high-risk patients.

1. Introduction

According to various hypertension guidelines, resistant hypertension (RH) is defined as uncontrolled blood pressure (BP)[1] despite adequate therapy with ≥3 antihypertensive agents, ideally including a diuretic [1,2]. Based on 14,684 hypertensive patients from the ALLHAT-study, those with RH have a 1.47-fold higher risk for cardiovascular (CV) diseases, a 2.11-fold higher risk for nephropathy, and a 1.34-fold higher risk for all-cause mortality [3]. Similar results are shown in population-based studies [4,5]. The prevalence of RH is estimated to account for 12–28% of all hypertensive patients on therapy [6,7,3,4]. RH thus constitutes a common clinical problem. Among those patients receiving three or more antihypertensive agents, 30% are estimated to have additional white coat hypertension that is uncontrolled office BP, but controlled 24-hour ambulatory BP [6].

Given the higher risks for adverse health outcomes, patients with RH need special attention. Yet, when managing these patients, physicians face a number of challenges. The first challenge is to distinguish pseudo from true RH: while pseudo resistance is caused by, e.g., medication non-adherence and/or inadequate medication regimes, true RH is typically attributable to secondary causes of hypertension such as obstructive sleep apnea, primary hyperaldosteronism, or chronic renal disease [8]. For long-term management, additional challenges are the adequate selection and management of complex therapeutic regimes and how to assure long-term medication adherence [8]. Studies in various settings showed that RH patients benefit from structured step-by-step approaches for RH-management, including strategies to support appropriate drug selection [9,10]. Although corresponding guideline recommendations are available [1,11,12], such algorithms are not followed routinely.

Studies identified various physician- and practice-related barriers for insufficient BP control in patients with and without RH [8,13–15], yet optimal intervention strategies are still to be developed. Comparing

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[1] Abbreviations: ABPM: ambulatory blood pressure monitoring; BP: blood pressure; CI: confidence interval; CRT: cluster randomized trial; CV: cardiovascular; DBP: diastolic blood pressure; EMA: European Medicine Agency; ESC: European Society of Cardiology; ESH: European Society of Hypertension; ICC: intra-cluster correlation coefficient; NICE: National Institute for Health and Clinical Excellence; OR: Odds Ratio; PTCA: percutaneous transluminal coronary angioplasty; RH: resistant hypertension; SBP: systolic blood pressure.

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various strategies, a Cochrane-review of 72 cluster randomized trials (CRT) and randomized controlled trials showed that complex interventions were much more effective in reducing BP than single interventions: physician or patient education alone changed BP only marginally (physician education: systolic/diastolic −0.4/+0.6 mm Hg; patient education: −0.6/+0.5 mm Hg), while best effects (−8.0/−4.3 mm Hg) were documented when combining educational and structural approaches [16]. Best results were achieved in the Hypertension Detection and Follow-Up Program: intensified pharmacotherapy combined with systematic recall in a separate hypertension outpatient clinic significantly decreased 5-year mortality [17]. Yet, these intervention studies addressed a case-mix of hypertensive patients rather than focusing on RH.

In a recent CRT on hypertension management with 169 hypertensive patients of 22 German primary care practices [18] we documented improvements in ambulatory BP for all patients. Triggered by physicians' requests for input how to manage difficult patients, our post-hoc sensitivity analysis focused on the subgroup of 52 patients with RH indicating an outcome-relevant interventional effect on systolic BP after five months: adjusted systolic BP changes attributable to the intervention were −6.75 mm Hg (95% confidence interval (CI), −13.36 to −0.13) [19]. In comparison to controls, intervention practices newly applied more tools per RH patient, e.g., prescription for a BP monitor, supervision for BP self-checks and optimization of psychiatric treatment [19].

Based on these results, we are now planning a CRT to evaluate the effectiveness of an evidence-based, physician manager-centered, educational intervention on treatment success in patients with RH. Primary care physicians will be addressed in their dual role as clinicians and physician managers. This is suitable to the German health care system with mainly physician-owned practices which self-organize patient care. Practice assistants assume tasks in practice organization and patient management. Costs for antihypertensive treatment are covered by the statutory and private health insurances. We hypothesize that this intervention, which aims at increasing physician knowledge and implementing hypertension management strategies, will improve BP of patients with RH.

2. Materials and methods

2.1. Study design

The study is designed as a CRT with primary care practices as the unit of randomization. The cluster design is used because the intervention (education) addresses practices, and thereby aims to improve patient outcomes indirectly [20]. Additionally, this design takes into account that patients of a certain practice may be more homogenous regarding medical and socio-demographic characteristics than patients of other practices [20,21].

2.2. Practice and patient recruitment

A random sample of 102 practices will be drawn from a list of all primary care practices located in North Rhine-Westphalia, Germany, which includes about 8,000 practices. All physicians belong to the Association of Statutory Health Insurance Physicians North Rhine and Westphalia-Lippe. For the recruitment process, 500 primary practices from North Rhine-Westphalia will be drawn by random. In packages of 50, these practices will be invited until a total of 102 practices have been recruited. To achieve a high practice response financial incentives (case payment) and CME points will be used. Additionally, a multi-level approach will be applied, which includes up to three letters and up to 10 phone calls on different weekdays and daytimes. If physicians are interested in participating, practice inclusion criteria will be checked. Practices are eligible for participating in the study if they provide health services to hypertensive patients and are equipped with at least one ambulatory blood pressure monitoring (ABPM) device fulfilling internationally accepted calibration standards. Practices specialized in hypertensiology and participants from our previous CRT [18] are excluded. Practice recruitment will be stopped as soon as the anticipated total sample of n = 102 practices is reached.

Each practice will participate with one physician manager and two practice assistants. All participating physicians and practice assistants will be asked to sign an informed consent form. Participating practices will recruit 12 consecutive patients fulfilling the predefined inclusion criteria. To avoid selection bias, each practice will list all eligible patients with the help of the electronic health record system in a first step and then recruit them consecutively as they come for consultation. The list will be used for quality checks. During a practice visit each practice will receive oral and written instructions regarding the patient recruitment scheme by a research team member.

2.3. Randomization and blinding

After the recruitment of all practices, participating practices will be allocated to one of two study arms by central randomization using a stratified 1:1 randomization (Fig. 1). A balanced distribution regarding low and high socio-economic neighborhoods will be applied by postal code.

Practices from both study arms will receive the intervention, but sequentially with control practices receiving the intervention after the follow-up data collection in both study arms is completed (waiting list control group). Patients will be blinded for the intervention status of the practice.

2.4. Inclusion and exclusion criteria for patients

The study will include patients with resistant hypertension. Patients are eligible for recruitment if 1) they are ≥18 years old, 2) capable of understanding the study documents, 3) their 24-hour BP is uncontrolled according to current guidelines (≥130/80 mm Hg in an ABPM) [1], and 4) they receive 3 or more antihypertensive agents. Patients with controlled baseline ABPM, patients with pregnancy-related hypertension, patients with hypertensive crisis, and those undergoing dialysis for renal failure are excluded. Patients fulfilling the inclusion criteria will receive written information about the study and will be asked for participation. Participants will sign an informed consent form.

2.5. Outcome measures

The primary endpoint of the study is treatment success, defined as the rate of patients with normalized BP in a 24-hour ABPM (<130/80 mm Hg) and/or reduction of ≥20 mm Hg systolic and/or ≥10 mm Hg diastolic. This outcome was chosen as recommended for clinical trials by the European Medicine Agency (EMA) [22]. This cut-off allows for comparison with other clinical trials addressing hypertension therapy. The 24-hour ABPM is recommended for the diagnostic work-up in patients with RH, because it helps to detect white-coat hypertension. In addition, it provides accurate nighttime BP readings.

The secondary endpoints of our study are a) the changes in mean systolic blood pressure (SBP) and diastolic blood pressure (DBP) in mm Hg (24 hour, daytime, nighttime), b) changes of non-pharmacological and pharmacological hypertension therapy, c) CV events (myocardial infarction, stroke, bypass surgery, percutaneous transluminal coronary angioplasty (PTCA)/stent or death from any cause, d) change of patients' satisfaction with quality of care, e) physicians' knowledge about diagnostic and therapeutic strategies for RH, f) number and kind of practice tools implemented on a practice level, g) number and kind of practice tools used on the patient level for standardized teaching about self-care, h) degree of implementation of the structured recall for patients lacking BP control. All outcomes will be measured at baseline (before the intervention) and at 12 month