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1-Year outcomes of hypertension management in 13,000 outpatients under practice conditions: Prospective 3A registry☆,☆☆

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ABSTRACT

Background: Current data on characteristics and outcomes of patients with high blood pressure (BP) managed under clinical practice conditions are limited.
Methods and results: The 3A registry is an open, prospective observational cohort study in German primary care offices, with a 4:1:1 inclusion ratio to either aliskiren (ALIS), an ACE inhibitor/angiotensin receptor blocker (ACEI/ARB), or to an antihypertensive agent not affecting the renin angiotensin system (non-RAS). A nonlinear mixed regression model was used to assess BP changes during follow-up regarding different BP values at inclusion in the various groups. ClinicalTrial.gov identifier is NCT01454583.
In the total cohort of 13,433 patients with 1-year follow-up results, the mean age of patients was 64.7 years, 54% were men. Mean number of antihypertensive drugs was higher in the ALIS group compared to the other groups (3.0 drugs versus 2.5 in ACEI/ARB versus 1.6 in non-RAS; $p < 0.0001$). Statistical regression analysis revealed baseline BP as the dominant covariate. After adjustment for baseline BP and 12 other confounders, no significant differences in BP reduction between the three groups were observed. The rate of major cardiac events (death, myocardial infarction, and stroke) was 1.3% in the total cohort, and did not differ across groups.
Conclusions: ALIS at beginning of the observation was mostly used by the physicians in patients with higher BP at entry and in higher risk populations. By study end, in all groups, stringent BP lowering measures, usually with combination therapy, led to significant improvements; more than half of these at-risk patients reached the BP targets.

1. Introduction

Essential hypertension is the leading diagnosis made by physicians in the primary care setting [1,2]. For example, recent studies have shown that 35–50% of patients treated by family physicians or cardiologists have hypertension, and that compared to other European countries, the control rates in Germany are among the lowest [2–5]. As essential hypertension is the key risk factor for cardiovascular events such as stroke and coronary heart disease (CHD) including myocardial infarction [6,7], effective management of hypertension is an important therapy goal not only for the benefit of the patient but also from a public health perspective [8].

A plethora of randomized controlled trials (RCT) in hypertensive patients have been conducted that provide robust information on the efficacy and safety of drugs compared to placebo or active controls [9,10]. According to a large meta-analysis of 147 studies by Law et al., all the main classes of blood pressure (BP) lowering drugs have a similar effect in reducing CHD events and stroke for a given reduction in BP, and risk reductions were similar regardless of starting BP, and presence or absence of existing cardiovascular disease [9]. However, RCT apply manifold inclusion and exclusion criteria on the basis of their experimental setting: the highly selected patient population only reflects about up to 50% of the actual population treated, and usually excludes the high-risk patients (at higher age, with multiple co-morbidities and co-medications).

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In order to obtain a representative and meaningful picture of the actual treatment situation of hypertensive patients, real-life data from non-interventional studies, surveys or registries are needed [11,12]. Registries generate such data (in contrast to clinical trials) on diagnostic procedures and therapies, allow replication of the results of RCT under everyday clinical conditions also in patients usually excluded from such studies, provide insight on treatment patterns over time, and allow analyses on guideline adherence [13,14]. In the light of these benefits, the number of such studies performed by professional organizations such as the European Society for Cardiology, the pharmaceutical industry and universities is steadily rising: currently 17% of all studies registered in ClinicalTrials.gov are observational [15].

Against this background, the 3A registry was set up as one of the largest projects of its kind in hypertension. As a prospective Germany-based registry, it documents characteristics, management and outcomes of consecutive outpatients with newly diagnosed or known hypertension, and allows the review of adherence to current ESC/ESH guidelines in diagnostic procedures and treatment in patients with hypertension [10]. The aims, design and a description of the cohort at baseline has been published elsewhere [16]. In the present report, we present the 1-year outcomes of the registry.

2 . Patients and methods

2.1 . Registry design and description

The 3A registry is a prospective, non-interventional, multi-center cohort study. It was initiated in August 2008 by the Institut für Herzinfarktforschung (http://www.herzinfarkt-forschung.de/) in Ludwigshafen, Germany, and its follow-up period was finished in July 2012. Participating primary care physicians (n = 899) are distributed throughout Germany. General/family physicians account for 45%, internists including cardiologists for 47%, nephrologists, diabetologists, or other specialties for the remainder. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in a priori approval by the institution's human research committee (Medical Ethical Committee, Mainz, Germany). The registry has been published in Clinicaltrials.gov under NCT01454583 and the German Association of Research-based Pharmaceutical Companies (VfA) database [17].

2.2 . Patients and schedule

Patients were eligible to participate if they met the following criteria: (1) aged 18 years or above, (2) with known or newly diagnosed arterial hypertension, (3) newly initiated or modified drug treatment of hypertension, (4) ability and willingness to attend follow-up visits, and (5) written informed consent. Physicians were requested to include eligible patients in a consecutive manner into the study to avoid selection bias. The only exclusion criteria were (1) participation in a randomized controlled clinical trial or (2) foreseeable problems to perform follow-up visits. Physicians decided independently and per best clinical judgment about the therapy of their individual patients. Prescribing of the drugs was in accordance with governing German regulations and reimbursement criteria.

Since one of the aims of the registry was to collect information on the use of the new compound aliskiren (ALIS), patients were categorized into three exposure groups in a targeted 4:1:1 ratio: (1) treatment with the direct renin inhibitor ALIS, or (2) treatment with either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin receptor blocker (ARB), or (3) agents not blocking the renin angiotensin system ("non-RAS"). These drugs were to be administered alone (monotherapy) or in addition to an existing drug regimen (combination therapy). Each site was requested to enroll 12 patients in a consecutive manner, i.e. from the initiation of study, the next 8 eligible patients treated with ALIS, the next 2 patients on an ACEI or an ARB, and the next 2 patients on non-RAS therapy. This sequential, stratified recruitment aimed at reducing sampling bias.

BP measurement was performed with the standard devices available at the physicians' office (manual sphygmomanometers or semi-automated devices), which according to German legislation must carry a calibration stamp. Further, the guidance for BP measuring (sitting patient under resting conditions, repeat measurements) had to be followed [18].

2.3 . Data collection and entry

Data were collected during the baseline visit and the follow-up visit after 1 year via a secure internet connection on electronic case report forms (eCRF). Measures of quality control included automated plausibility checks during data entry, queries provided by the data manager after review of the data, and in 10% of the patients on-site monitoring with source data verification.

2.4 . Parameters

Detailed sociodemographic and clinical parameters (risk factors, comorbidities) were collected at baseline, as were data on hypertension history and blood pressure (office and if available, 24 hour ambulatory ABPM), cardiac medication, and available laboratory values [16]. At the follow-up visit after 1 year, current antihypertensive medication, blood pressure (office and ABPM), and laboratory values were documented. Further, physicians were asked to report all deaths and cardiac events. To avoid underreporting, they received a list with tick boxes on deaths (sudden cardiac death, other cardiovascular, malignancy, other), cardiac events (myocardial infarction, percutaneous coronary intervention PCI, coronary bypass artery graft (CABG), application of an implantable cardioverter defibrillator (ICD), or stroke events).

2.5 . Data entry and analysis

Continuous variables were summarized with descriptive statistics (absolute numbers n, means, standard deviation [SD], or medians, with 25th and 75th percentiles as appropriate). All summaries were presented on available data. Categorical data were described by the number (n) and percentage (%) of subjects in each category. Comparisons between treatment groups were performed by Pearson's chi-squared test for categorical variables, or Kruskal–Wallis test for continuous measures. No adjustments were made for testing multiple hypotheses in this post-hoc specified analysis.

To assess differences in BP between the 3 groups that differ at baseline, a specific statistical approach was chosen. With respect to BP changes follow-up and baseline variances, individual patient means, and the linear function linking baseline means and other confounders to follow-up means were estimated for the three medication groups via SAS procedure "nlmixed", maximizing the likelihood by a quasi-Newton algorithm and integrating over the random effects via adaptive Gauss–Hermite quadrature.

Beyond that, the model included the following potential confounders: age, male gender, smoking, dyslipidemia, diabetes mellitus, chronic kidney disease (defined as MDRD GFR <60 mg/ml/1.73 m^2), cardiovascular disease, severity of hypertension, number of additional antihypertensive drugs, body mass index, family history of cardiovascular disease and duration of hypertension.

The term "standardized mean reduction" (results in Table 3) refers to mean covariates, i.e. mean baseline BP and the theoretical average patient with respect to each confounder.

Events were documented without the date, and analyzed separately or if appropriate, in combination (major cardiovascular events, MACCE). Percentages were calculated on the basis of patients with data for each respective parameter (i.e., no percentages for missing values are provided). p-Values ≤ 0.05 were considered significant. All p-values are results