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Classes of antihypertensive agents and mortality in hypertensive patients with type 2 diabetes—network meta-analysis of randomized trials

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ABSTRACT

Aims: The aim of this study was to evaluate the effects of antihypertensive drug classes in mortality in patients with type 2 diabetes.
Methods: MEDLINE, EMBASE, Clinical Trials and Cochrane Library were searched for randomized trials comparing thiazides, beta-blockers, calcium channel blockers (CCBs), angiotensin-converting inhibitors (ACEi) and angiotensin-receptor blockers (ARBs), alone or in combination for hypertension treatment in patients with type 2 diabetes. Outcomes were overall and cardiovascular mortality. Network meta-analysis was used to obtain pooled effect estimate.
Results: A total of 27 studies, comprising 49,418 participants, 5647 total and 1306 cardiovascular deaths were included. No differences in total or cardiovascular mortality were observed with isolated antihypertensive drug classes compared to each other or placebo. The ACEi and CCB combination showed evidence of reduction in cardiovascular mortality comparing to placebo [median HR, 95% credibility intervals: 0.16, 0.01–0.82], betablockers (0.20, 0.02–0.98), CCBs (0.21, 0.02–0.97) and ARBs (0.18, 0.02–0.91). In included trials, this combination was the treatment that most consistently achieved both lower systolic and diastolic end of study blood pressure.
Conclusions: There is no benefit of a single antihypertensive class in reduction of mortality in hypertensive patients with type 2 diabetes. Reduction of cardiovascular mortality observed in patients treated with ACEi and CCB combination may be related to lower blood pressure levels.

1. Introduction

Association between hypertension and diabetes mellitus (DM) is common. There is a 2.5 times higher risk of DM among hypertensive patients and hypertension affects up to 70% of patients with type 2 DM (Ferrannini & Cushman, 2012; Vijan & Hayward, 2003). Hypertension increases 7.2 times the risk of death in patients with DM, especially due to cardiovascular disease (Bakris & Sowers, 2008).

Treatment of hypertension in patients with type 2 DM diminishes the risk of micro- and macrovascular outcomes. In United Kingdom

Author contributions: LRR, CBL, and JLG, conceived and designed the meta-analysis LRR, CBL, CKK, and LPK identified and acquired reports of trials, and extracted data. LRR, SD, and JLG performed statistical analysis and, interpreted the data. SD, NJW, and AEA provided statistical advice and input. CBL, and CKK, contributed to the interpretation of the data. LRR and JLG drafted the manuscript. CBL, CKK, SD, NW, AEA, critically reviewed the manuscript.

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Prospective Diabetes Study (UKPDS), intensive control of hypertension reduced diabetes related deaths, stroke, and microvascular complications, especially diabetic retinopathy (UK Prospective Diabetes Study Group, 1998a).

There is still debate about which would be the most favorable antihypertensive class in patients with type 2 DM. Current guidelines usually recommend that drugs blocking the renin–angiotensin–aldosterone system are preferred agents in the treatment of diabetic patients due to their potential beneficial effects besides reduction of blood pressure (Anonymous, 2014). However, their actual effect on mortality is controversial. Some systematic reviews and traditional meta-analyses have been performed to evaluate the efficacy of antihypertensive drug classes in mortality and cardiovascular events in patients with and without diabetes. However, network meta-analysis (NMA), also known as mixed treatment comparisons (MTC), method is not commonly used, therefore limiting interpretation of the results (Turnbull et al., 2005; Wright & Musini, 2009). NMA is an extension of meta-analysis to compare more than two treatments and is essential to make coherent decisions when multiple treatments are available (Dias, Sutton, Ades, & Welton, 2013). They allow the comparison of treatments that have not been directly compared in head-to-head trials, thereby making it possible to rank all the treatments, and to pool all the available evidence (Caldwell, Ades, & Higgins, 2005). One NMA concluded that is no or just little difference between commonly used blood pressure lowering agents in the prevention of cardiovascular disease in the general hypertensive population (Fretheim et al., 2012). Recently, an NMA compared the effectiveness of antihypertensive drugs in patients with diabetes (Wu et al., 2013) and authors concluded that only ACE inhibitors had a renoprotective effect, but no statistically significant difference in total mortality was observed. However, the authors included patients with both type 1 and type 2 diabetes, and patients without established hypertension, which may have influenced the results. We believe it is more clinically relevant to analyze the efficacy of antihypertensive agents on hard outcomes—total mortality and cardiovascular mortality—in a more homogeneous and prevalent population of patients with type 2 diabetes and hypertension. Therefore, the aim of this study is to analyze the effects of each of the main antihypertensive drug classes used alone or in combination in hypertensive patients with type 2 DM on total and cardiovascular (CV) mortality by using NMA.

2. Materials and methods

The protocol for this network meta-analysis is registered in international prospective register of systematic reviews (PROSPERO) and available from www.crd.york.ac.uk/NIHR_PROSPERO with registration number CRD42012001702.

2.1. Data sources and search

We searched MEDLINE, EMBASE, Clinical Trials and Cochrane Library from 1950 to November, 2012 using the Medical Subject Heading terms type 2 diabetes and hypertension or each drug by name of the defined antihypertensive classes defined [thiazide diuretics, betablockers, calcium channel blockers (CCBs), angiotensin converting enzyme inhibitors (ACEi), and angiotensin receptor blockers (ARBs)] and a validated filter to identify randomized clinical trials (Robinson & Dickersin, 2002), reporting cardiovascular events or death (detailed search strategy is described in supplemental material). We searched also abstracts from major cardiology, nephrology and endocrinology meetings. A manual search was also performed through references of reviews, previous meta-analysis and key articles. All potential eligible trials were considered for review regardless of the primary outcome or language.

2.2. Study selection

Trials were considered for inclusion if they were conducted in hypertensive adults older than 18 years with type 2 DM, compared the effects of one of the classes, or combinations of classes, of antihypertensive agents with another or placebo, had at least 12 months of follow up and reported incidence of cardiovascular or total mortality. Studies not designed for the treatment of hypertension were eligible if more than 95% of patients included had hypertension. The definitions of hypertension were the ones defined in each study based on contemporary recommendations when studies were planned. Two independent investigators (LRR and LPK) selected potentially eligible studies based on titles and abstracts and these were retrieved for full-text evaluation. Disagreements were resolved by a third investigator (CBL).

2.3. Data extraction, and quality assessment

Studies that met inclusion criteria were included and two investigators extracted information on: study design, intervention and control group, number of participants, trial duration, drug class and dose of the antihypertensive agent used, age, sex distribution, cardiovascular risk factors such as total, HDL and LDL cholesterol, creatinine, HbA1c, baseline arterial blood pressure (BP), smoking habit and urinary albumin excretion rate as well as outcome data for myocardial infarction, stroke and death. Any discrepancies between data extracted were discussed and a consensus was reached. Whenever necessary, authors were contacted in order to obtain additional needed data. Quality of trials and risk of bias were assessed using recommendations from Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) and quality of the evidence was assessed using Grading of Recommendations Assessment, Development and Evaluation (GRADE) system (Guyatt et al., 2011; Guyatt et al., 2013; Liberati et al., 2009).

2.4. Data synthesis and analysis

Analyzed outcomes were mortality from all causes and cardiovascular mortality defined as death due to fatal cardiac events or stroke were recorded.

Data from all the publications were entered into a computerized spreadsheet (Microsoft Excel) and NMA models were estimated using Bayesian Markov Chain Monte Carlo simulation implemented in the freely available Bayesian software WinBUGS (Medical Research Council Biostatistics Unit, Cambridge, United Kingdom; www.mrc-bsu.cam.ac.uk/bugs). WinBUGS model used is available on Supplemental Material. For the mortality outcomes we modeled the log-hazard ratio of events over time, assuming proportional hazards, and report posterior median hazard ratios (HR) with 95% credible intervals (95% CrIs) that are the Bayesian equivalent to confidence intervals. For the blood pressure outcomes we modeled the mean differences in blood pressure at the follow-up time (Dias et al., 2013; Welton, Sutton, Cooper, Abrams, & Ades, 2012), and report posterior median differences with 95% CrIs. The specific code and data structure used are available from the authors on request. We also assessed the probability that each antihypertensive class is ranked as the 1st best, 2nd best, 3rd best through to worst treatment in reducing cardiovascular and total mortality using placebo as the reference treatment.

We assessed model fit of fixed and random effects models using the posterior mean of the residual deviance (Dias et al., 2013; Welton et al., 2012). Statistical heterogeneity of the NMA was evaluated comparing the deviance information criteria (DIC) between fixed and random effect models (see Supplemental Material for details). We decided to use the more conservative random effects (RE) model since there was an a priori expectation that there would be heterogeneity in the evidence as different treatments were combined into single

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