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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: 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: 27 studies, comprising 49418 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. 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.

Key words: Type 2 diabetes, Hypertension, antihypertensive drugs, mortality

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 [1,2]. Hypertension increases 7.2 times the risk of death in patients with DM, especially due to cardiovascular disease [3].

Treatment of hypertension in patients with type 2 DM diminishes the risk of micro- and macrovascular outcomes. In United Kingdom Prospective Diabetes Study (UKPDS), intensive control of hypertension reduced diabetes related deaths, stroke, and microvascular complications, especially diabetic retinopathy [4].

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 [5]. 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 [6,7]. NMA are an extension of meta-analysis to compare more than two treatments and are essential to make coherent decisions when multiple treatments are available [8]. 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 [9]. 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 [10]. Recently, a NMA compared the effectiveness of antihypertensive drugs in patients with diabetes [11] 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 [12], 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 [13-15].

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 [8, 16], 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 [8, 16].]. 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 classes. NMA assumes that the network is consistent [8]. Consistency was assessed using the node-split method, where results based on direct and indirect evidence for all pairs of treatments are compared [17]. When a significant inconsistency was found ($p<0.05$), the first step was to search for clinical differences in the included trials that may explain the inconsistency and exclusion of any trials if there is a clinical rationale to do so [18,19]. If we did not find any important clinical aspect that could justify exclusion of the trial, then a cross-validation analysis was performed. This analysis predicts the expected number of events (mortalities) in a trial with the same number of patients and number of control events, as the original trial under consideration, given the evidence (direct and indirect, when available) from the remaining network. This result is then compared to the original finding of the trial giving a p-value that is interpreted as the probability of observing such a result in a trial given all the other evidence. With this analysis it is possible to evaluate if the observed outcomes in the original trial could be predicted from the variability in the other trials (p-value not significant), or if the trial was an outlier (p-value significant) [20, 21].

3. RESULTS

The search retrieved 10692 studies and 10459 were excluded based on title and abstracts. Of the 233 reports assessed for full text analysis, five could not be translated and were excluded, and 30 fulfilled the inclusion criteria (Figure 1). For three studies, outcomes were described in two different publications, so there were 27 different trials included [22-51).

3.1. Studies characteristics

Details of the included trials are described in Table 1. The included studies compared 9 types of antihypertensive treatments (Figure S1). There were 3 trials [30, 33, 40] that compared an active treatment to conventional treatment that could be a diuretic and/or a betablocker at physician discretion. These groups were included as a separate class coded as diuretic and/or betablocker. Six trials included at least one arm that was randomized to a combination of two drugs of different classes. These arms were coded as different categories of treatments and analyzed in separate as a treatment strategy comparing then with the other drug and combination classes.

Risk of bias in the trials is described in Table S1 in supplemental material. All studies were randomized, however in ten we could not define the method used for randomization and, therefore, its concealment. Eleven trials were not double blinded; however in all but 2 trials the outcome evaluators were blinded. . From the 21 studies included in cardiovascular mortality analysis, 16 had all events adjudicated by an independent committee. The other 5 trials do not describe if outcomes were adjudicated and, in 3 of these, the events of death were described in adverse event section. In 9 trials, the study describes clearly a standardized method for blood pressure measurement. Six trials describes that clinical assessments including blood pressure were conducted according to the study protocol. Only in one case, there is no information regarding blood pressure measurement technique. According to GRADE system, the quality of the evidence was considered moderate (Supplemental Table S2). Model fit evaluation is detailed in Table S3 in supplemental material.

3.2. Overall mortality

Overall mortality was reported in 25 trials (27 publications) comprising 48171 patients with 5647 deaths and comparing 9 different treatments. Results of RE NMA analysis did not show evidence of difference between classes of antihypertensives regarding total mortality in comparison to placebo (Figure 2A). The posterior median of overall heterogeneity was 0.12 (95% CI 0.007 to 0.30). A borderline effect in reduction of total mortality was observed with the combinations of ACEi plus CCB and ACEi plus thiazide compared to placebo or to treatment with diuretic and/or betablocker (Table 2). There was evidence of inconsistency in this model related to comparison of treatment with betablocker *vs* ARB. The only trial comparing these treatments was LIFE (Losartan Intervention For Endpoint Reduction) study. No clinical reasons were identified that set this trial apart from the others so a predictive cross-validation was carried out, under a RE model. According to this analysis, the number of events predicted for patients on ARBs treatment would be 111 (95% CrI 75 to 159) and the observed number of events was 63 (p = 0.0056), suggesting that LIFE was an outlier for this outcome. The analysis was performed excluding the LIFE trial and results are similar except that there was an evidence of effect of the combinations of ACEi plus CCB and ACEi plus thiazide compared to placebo in reduction of mortality (median HR, 95% CrI: 0.324, 0.086 – 0.986 and 0.32, 0.082 – 0.998, respectively).

3.3. Cardiovascular mortality

Cardiovascular mortality was described in 21 trials (24 publications) comprising 32101 patients with 1306 deaths due to cardiovascular events and comparing 9 treatments. Results of the RE NMA analysis showed that the combination of ACEi plus CCB had a lower CV mortality in comparison to placebo (median HR, 95% CrI: 0.16, 0.01 to 0.82), betablocker (0.20, 0.024 to 0.98), CCB alone (0.21, 0.02 to 0.97), ARB (0.18, 0.02 to 0.91) and treatment with diuretic and/or betablocker (0.18, 0.02 to 0.91) (Figure 2B and Table 2). The posterior median of overall heterogeneity was 0.39 (95% CI 0.11 to 0.83). All the other classes had similar CV mortality when compared to each other (Table 2). In this model, there was evidence of inconsistency related to comparison of treatment with placebo *vs.* ARB. The only trial that directly compared these treatments was ORIENT (Olmesartan Reducing Incidence of Endstage renal disease in diabetic Nephropathy Trial). In this trial, unexpectedly, the number of cardiovascular deaths was higher in the active treatment than in placebo (10/282 *vs.* 3/284). A predictive cross-validation analysis was carried out which predicted 6 events in patients treated with ARBs (95% CrI 0 to 9) while the observed number of events in the ORIENT trial was 10 (p = 0.01). This suggests that this trial is an outlier for this outcome, given the remaining trials and an analysis was also performed excluding it. In this analysis, the combination of ACEi plus CCB was also the only treatment with evidence of benefit in reduction of CV mortality, but this effects was observed only when compared to placebo (0.14, 0.01 to 0.70), CCB alone (0.21, 0.02 to 0.97) and treatment with diuretic and/or betablocker (0.18, 0.002 to 0.91).

3.4. Ranking of efficacy in reduction of mortality

The distribution of probabilities of each treatment being ranked at each of the possible 9 positions for the model including all trials is shown in Supplemental Figure S2. Combinations of ACEi plus CCB and ACE plus diuretic were the most efficacious treatments being more frequently ranked as first or second best treatments in reducing both total and cardiovascular mortality. Cumulative frequency of being ranked into the three most efficacious treatments in reducing total mortality were: ACEi plus CCB 95.9%, ACEi plus diuretic 95.1%, ARB 47.5%, ACEi 23.7%, thiazides 10.5%, betablockers 8.7% and CCBs 7.9%. Cumulative frequency of being ranked into the three most efficacious treatments in reducing cardiovascular mortality were: ACEi plus CCB 97.1%, ACEi plus diuretic 91.1%, ACEi 30.2%, thiazides 27.8%, betablockers 14.4%, CCBs 11.3%, ARB 9.7%,.

3.5. End-of-study blood pressure

Considering that the benefit associates with an individual antihypertensive agent could be solely due to its effect on BP reduction, we also analyzed the effects of each antihypertensive drug class in the end of study blood pressure for the trials included in the analysis of total and cardiovascular mortality. We were able to extract data about final systolic and diastolic blood pressure in diabetic patients in 16 of these studies comparing 7 classes of treatment (classes not included due to lack of data were: diuretic and/or betablocker and ACEi plus diuretic). Results of NMA analysis showed that, compared to placebo, the combination of ACEi plus CCB had lower final systolic and diastolic blood pressure levels (median difference, 95% CrI: -4.97, -8.60 to -1.50 and -3.50, -5.62 to -1.41, respectively) as well as ARB (-3.34, -5.96 to -0.73 and -1.56, -3.09 to -0.04, respectively) (Supplemental Figure S3). Compared to other active treatments, combination of ACEi and CCB had lower end of trial systolic and diastolic blood pressure in comparison to ACEi (-3.97, -6.77 to -1.27 and -2.67, -4.31 to -1.03 mmHg, respectively). In addition, ACEi in combination with CCB had lower diastolic blood pressure levels in comparison to thiazide and CCBs (-2.43, -4.66 to -0.21 and -1.87, -3.58 to -0.17, respectively) (Table 3).

The probability of each class being ranked as the 1st best, 2nd best, 3rd best through to the least effective treatment in reducing end of study blood pressure levels is shown in Supplemental Figure S4.

4. DISCUSSION

In the present meta-analysis on hypertensive patients with type 2 DM, we did not observe benefits in reduction on total and CV mortality of any class of a single antihypertensive in comparison to placebo or other classes. Combination of ACEi plus CCB had lower CV mortality in comparison to other classes, and this was also the treatment that most consistently achieved both lower systolic and diastolic end of study blood pressure.

The results presented here are in accordance with findings from UKPDS which showed a significant reduction of 12% in total mortality with a 10 mmHg reduction in blood pressure but did not find differences in treatments with captopril or atenolol, suggesting that blood pressure reduction is more important than the selection of a specific drug class [4, 22, 52]. Thus, the benefit on CV mortality observed with combination of ACEi plus CCB may be related to lower blood pressure values

achieved by this strategy. However, we have to take into account that this analysis was conducted only in the trials that were included in the mortality analysis, therefore it is not a comprehensive NMA of the antihypertensive effect of these classes.

Other meta-analyses have evaluated the effects of antihypertensive treatment in the prevention of cardiovascular events. A previous NMA found small or no differences among antihypertensive drug classes in hypertensive patients [10]. A direct meta-analysis comparing antihypertensive treatment in diabetic patients did not show differences between ACEi and CCB or any of these classes and conventional treatment with diuretic or betablocker in mortality, and, besides, this study did not include analysis of the efficacy of ARBs and diuretics or betablockers separately [7]. In a previous published NMA [11], ACE inhibitors were considered superior to the other agents in patients with diabetes only regarding the outcome of doubling serum creatinine, and there was no significant effect on total mortality. In our study we observed an evidence of effect on cardiovascular mortality of the combination ACEi + CCB, and in treatment ranking this combination has the highest probability to be the most effective treatment for reduction both total and cardiovascular mortality. Althoug the HR estimate for this treatment is quite low, it is important to note that credible intervals are wide.

Probably we were able to observe this effect because we included only type 2 diabetic patients with hypertension, who have a well-known risk for cardiovascular mortality [2]. Moreover, the reduction in blood pressure was more evident with the combination ACEi + CCB.

The strength of the meta-analysis presented here is the number of included patients and events and the fact that we analyzed mortality outcomes only and not surrogate endpoints. Another advantage of this study is the use of a NMA method to evaluate the effects of the different antihypertensive drug classes relative to each other in a coherent way. This analysis has limitations. NMA method takes into account several statistical assumptions that can not be verified and could introduce bias. However, bias is not expected to act exclusively in one particular direction and NMA method is considered essential to make comparisons when multiple treatments are available [53]. Like in other multiple comparisons, these conclusions must be interpreted with caution and proper clinical judgment. For several trials, we had no details of baseline characteristics of patients, in order to estimate a baseline cardiovascular risk to use in the analysis as a correction factor. In addition, data about initial and/or final blood pressure was not available for some of the trials, precluding its inclusion as a covariate in a

metaregression and allowing only the evaluation of the effect of antihypertensive drug classes on blood pressure as a separate analysis. These two factors would be particularly important in the analysis in order to correct for potential confounding factors between studies. The different treatment and even placebo arms may have received additional drugs as rescue therapy during the trials and this fact could explain the lack of difference in end of trial blood pressure of most antihypertensive drug classes compared to placebo in the network analysis. This is an important potential confounding factor in meta-analysis of these trials as it could minimize the effects of each randomized drug class that was being evaluated in individual trials. We included three trials that used diuretic or betablocker at the discretion of the physician and outcomes for these patients were grouped as described by Fretheim et al [10]. As this is not one drug class nor exactly a combination, the results of these comparisons were not considered clinically significant. Moreover, we included data from subgroup of patients with diabetes of larger trials that included non diabetic patients in the original randomized sample and studies were health care providers and/or patients were not blinded.

There was also some evidence of conflict between direct and indirect evidence in our models and there is controversy about what is the best strategy to deal with it [18,19]. In the analysis of overall mortality, the LIFE study was considered an outlier due to a higher than predicted number of deaths in atenolol group. Regarding cardiovascular mortality, the same unexpected result was found in olmesartan group in the ORIENT trial and there was also evidence to suggest that this trial may be an outlier, given the remaining evidence. Other studies had also suggested a worse outcomes with use of olmesartan [54, 55]. Nevertheless, the results in this meta-analysis did not change in essence if the LIFE and ORIENT trials are not included in the total and cardiovascular mortality analyses, respectively.

In conclusion, our results did not demonstrate a benefit of one class of a single antihypertensive over another in reduction of mortality in patients with type 2 diabetes and hypertension. A combination of drugs, ACEi plus CCB, appeared more effective in reducing CV mortality. We hypothesise that maybe the benefits of this drug combination may be mediated by its apparent better efficacy in blood pressure reduction rather than an effect of the specific antihypertensive agents.

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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J.L.G. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf and declare have no competing interests relevant to this work. SD has received payment for her institution from Quintiles for consultancy, and from Novartis, Pfizer and Oxford outcomes for development of educational presentations. JLG has served on boards for Bristol-Myers Squibb, GlaxoSmithKline, Novo Nordisk, Sanofi-Aventis, and Eli Lilly, and has received payment for the development of educational presentations for Bristol-Myers Squibb, Novo Nordisk, and Eli Lilly.

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Table 1: Details of the included trials.

Author	Study	Year	Follow up (years)	Mean age (years)	DM duration (years)	Lost to follow up (%)	Study/drug discon-tinuation (%) [§]	Groups	Mean Initial BP - mmHg (SD)	Mean Final BP - mmHg (SD)	Total deaths (events/n)	CV deaths (events/n)
Bakris	INVEST (DM subgroup)	2004	5	66	-	2.52 *	9.28 *	Verapamil SR	151.1/85.5 (19.6/12.2)	-	370/3169	190/3169
								Atenolol	150.5/85.4 (19.8/12.1)		355/3231	161/3231
Barnett	DETAIL	2004	5	60.57	8	0.71	28.57	Telmisartan	152.6/85.4 (16.6/8.8)	-	6/120	3/120
								Enalapril	151.6/85.9 (15.8/7.8)		6/130	2/130
Berl and Lewis	IDNT	2003	4.5	58.9	-	0.64	24.55	Ibesartan	160/87 (20/11)	140/77 (-/-)	87/579	52/579
								Amlodipine	159/87 (19/11)	141/77 (-/-)	83/567	37/567
								Placebo	158/87 (20/11)	144/80 (-/-)	93/569	46/569
Brenner	RENAAL	2001	4	60	-	-	29.28	Losartan	152/82 (19/10)	140/74 (-/-)	158/751	-
								Placebo	153/82 (20/11)	142/74 (-/-)	155/762	
Curb	SHEP (DM subgroup)	1996	5	70.35	-	-	-	Chlorthalidone	170.2/76.9 (9.2/8.9)	-	39/283	-
								Placebo	170.2/74.8 (9.2/10)		48/300	
Estacio	ABCD	1998	5	57.45	8.6	-	52.55	Nisoldipine	155/98 (19/7)	-	18/235	11/235
								Enalapril	156/98 (17/7)		14/235	6/235
Fogari		2002	4	62.52	8.76	-	4.74	Amlodipine	160.4/99.3 (14.4/7.1)	140.4/86.5 (10.1/5.4)	4/103	2/103
								Fosinopril	159.5/99.1 (13.3/6.7)	142.3/87.3 (10.4/5.6)	3/102	2/102
								Amlodipine + fosinopril	161.1/99.4 (16.2/6.6)	132.4/82.3 (9.9/5.1)	2/104	1/104
Hansson	NORDIL	2000	5	-	-	0.48 *	14.93 *	Diltiazem	-	-	28/351	15/351
								Diuretic and/or betablocker			26/376	13/376

Imai	ORIENT	2011	4.5	59.15	-	-	24.2	Olmesartan	141.7/77.8 (17/10.4)	131.8/72.2 (-/-)	19/282	10/282
								Placebo	140.8/77.2 (18/10.6)	136.6/73.6 (-/-)	20/284	3/284
Lindholm	LIFE (DM subgroup)	2002	5.5	67.4	-	0.33	5.36	Losartan	176/97 (14/9)	146/79 (17/11)	63/586	38/586
								Atenolol	177/96 (14/10)	148/79 (19/11)	104/609	61/609
Lindholm	STOP-2 (DM subgroup)	2000	2	75.8	-	-	-	Diuretics and/or Betablocker	195/97 (-/-)	161.3/81.2 (-/-)	67/253	45/253
								Calcium antagonist	196/97 (-/-)	161.8/79.1 (-/-)	50/231	33/231
								ACEi	196/96 (-/-)	161.8/80.3 (-/-)	56/235	39/235
Mancia	INSIGHT (DM subgroup)	1993	4	65.54	-	2.36 *	34.14 *	Nifedipine	174.7/98.2 (15.8/9.2)	161.3/81.9 (16.1/9.4)	44/649	19/649
								Hydrochlorothiazide + amiloride	175.7/9737 (15.1/9.1)	143.6/82.4 (17/9.7)	59/653	19/653
Marre	NESTOR	2004	1	59.98	8.23	-	11.25	Indapamide	161.1/94 (10.8/6.9)	137.3/81 (12/8.1)	2/284	2/284
								Enalapril	160.2/93.5 (10.8/6.1)	139.3/81.4 (14.3/7.9)	1/286	1/286
Muramatsu	NAGOYA HEART	2012	4.5	63	-	2.61	-	Valsartan	145/82 (18/13)	131/73 (-/-)	22/575	-
								Amlodipine	144/81 (19/13)	132/74 (-/-)	16/575	
Nakao	CASE-J (DM subgroup)	2010	4	64	-	2.89 *	8.46 *	Candesartan	159.8/88.3 (12.9/9.9)	-	40/1011	11/1011
								Amlodipine	160/88.3 (12.5/10.3)		49/1007	15/1007
Nielsen		1997	3.5	-	-	-	25.0	Lisinopril	172/87 (22.9/13.7)	163/82 (22.9/9.1)	-	1/21
								Atenolol	174/94 (23.5/11.7)	166/84 (23.5/11.7)		3/22
Niskanen	CAPPP (DM subgroup)	2001	5.5	55.32	-	0.17	-	Captopril	163.6/97.1 (18.8/9.6)	-	20/309	9/309
								Diuretic and/or betablocker	163.3/97.3 (20.6/10.1)		34/263	15/263
Ostergren	ASCOT (DM subgroup)	2008	5	63.4	-	0.25	-	Amlodipine	164.9/92.7 (18.2/10.4)	136/75 (-/-)	245/2565	94/2565
								Atenolol	164.8/92.3 (17.9/10.3)	137/76 (-/-)	250/2572	96/2572

Parving	IRMA	2001	2	58	9.7	0.51	11.86	Ibesartan Placebo	153/90 (14/9) 153/91 (15/10)	-	3/389 1/201	-
Remuzzi	BENEDICT-A	2006	4	62.34	7.85	1.33	48.17	Trandolapril + Verapamil Trandolapril Verapamil Placebo	150.5/87.3 (13.3/8.1) 150.8/87.4 (14.8/7.7) 150.1/87.5 (13.1/7.2) 151.9/87.7 (15.4/7.6)	139/80 (10/6) 139/81 (12/6) 141/82 (10/6) 142/83 (12/6)	- 	0/300 1/301 1/303 3/300
Ruggenenti	BENEDICT-B	2011	4	62.35	9.25	3.20	47.33	Verapamil + Trandolapril Trandolapril	150.1/86.5 (16/9.5) 148.9/86.2 (16.7/9)	141/81.6 (11.5/6.4) 141.8/82.3 (12.2/6.7)	2/138 7/143	1/138 4/143
Safar and Tuomilehto	SYST-EUR (DM subgroup)	2003	5	-	-	5.05 *	-	Nitrendipine Placebo	-	-	19/278 27/269	5/278 16/269
Tatti	FACET	1998	4	63.05	10.59	1.05	23.16	Fosinopril Amlodipine	170/95 (-/-) 171/94 (-/-)	157/88 (-/-) 153/86 (-/-)	4/189 5/191	
Weber M	ACCOMPLISH (DM subgroup)	2010	3.5	67.5	-	1.02 *	30.0 *	Benazepril + amlodipine Benazepril + hydrochlorothiazide	-	131.5/72.6 (-/-) 132.7/73.7 (-/-)	141/3478 139/3468	62/3478 74/3468
Whelton	ALLHAT (DM subgroup)	2005	6	66.6	-	3.08	-	Chlortalidone Amlodipine Lisinopril	146.4/83.9 (15.5/9.9) 146.4/82.7 (15.6/10.1) 146.9/83.1 (15.5/9.9)	135/74.4 (15.6/9.7) 136.3/73.6 (15.9/10.1) 137.9/74.6 (19/11.1)	1145/5994 683/3597 674/3510	-
Yui Y	JMIC-B (DM subgroup)	2004	3	64.26	-	6.06 *	15.15 *	Nifedipine retard Imidapril or Lisinopril	147/82 (18/12) 146/81 (20/11)	138/76 (14/8) 140/78 (16/9)	2/199 5/173	1/199 3/173
	UKPDS 39	1998	9	56.15	2.64	-	-	Captopril Atenolol	159/94 (20/10) 159/93 (19/10)	144/83 (14/8) 143/81 (14/7)	75/400 59/358	48/400 32/358

507 DM = Diabetes Mellitus; BP = blood pressure; CV = cardiovascular
508 [§]excluding deaths

509 * data from the whole original sample and not only DM subgroup
510 (-) data not available

Table 2: Comparisons of the effects of antihypertensive drug classes in total and cardiovascular (CV) mortality (median Hazard Ratio (95% CrI)).

Placebo	0.85 (0.24 – 2.79)	0.81 (0.35 – 1.74)	0.78 (0.37 – 1.44)	0.72 (0.29 – 1.51)	0.89 (0.45 – 1.79)	0.90 (0.33 – 2.14)	**0.16 (0.01 – 0.82)**	0.19 (0.01 – 1.28)
0.98 (0.72 – 1.32)	**Thiazide**	0.94 (0.30 – 2.95)	0.91 (0.32 – 2.48)	0.85 (0.26 – 2.43	1.04 (0,.33 – 3.47)	1.06 (0.30 – 3.4)	0.19 (0.02 – 1.18)	0.23 (0.01 – 1.79)
0.98 (0.72 – 1.31)	1.0 (0.74 – 1.34)	**BB**	0.97 (0.55 – 1.58)	0.89 (0.45 – 1.56)	1.10 (0.58 – 2.21)	1.12 (0.48 – 2.38)	**0.20 (0.02 – 0.98)**	0.24 (0.02 – 1.53)
0.95 (0.72 – 1.20)	0.97 (0.75 – 1.20)	0.97 (0.78 – 1.17)	**CCB**	0.93 (0.53 – 1.51)	1.14 (0.67 – 2.20)	1.16 (0.59 – 2.22)	**0.21 (0.02 – 0.97)**	0.25 (0.02 – 1.54)
0.93 (0.66 – 1.23)	0.95 (0.70 – 1.20)	0.95 (0.71 – 1.20)	0.97 (0.79 – 1.18)	**ACEi**	1.23 (0.64 – 2.78)	1.24 (0.65 – 2.48)	0.23 (0.02 – 1.03)	0.27 (0.028 – 1.65)
0.89 (0.70 – 1.11)	0.90 (0.67 – 1.22)	0.90 (0.69 – 1.18)	0.93 (0.75 – 1.18)	0.95 (0.73 – 1.30)	**ARB**	1.02 (0.39 – 2.25)	**0.18 (0.02 – 0.91)**	0.21 (0.02 – 1.41)
1.18 (0.78 – 1.72)	1.20 (0.81 – 1.71)	1.20 (0.82 – 1.70)	1.24 (0.90 – 1.69)	1.26 (0.93 – 1.74)	1.32 (0.89 – 1.91)	**Diuretic ± BB**	**0.18 (0.02 – 0.91)**	0.21 (0.02 – 1.44)
0.34 (0.08 – 1.03)	0.35 (0.09 – 1.04)	0.35 (0.09 – 1.05)	0.36 (0.09 – 1.06)	0.37 (0.09 – 1.08)	0.38 (0.09 – 1.15)	**0.29 (0.07 – 0.89)**	**ACEi + CCB**	1.20 (0.44 – 3.24)
0.34 (0.08 – 1.09)	0.34 (0.08 – 1.09)	0.34 (0.08 – 1.1)	0.35 (0.08 – 1.12)	0.36 (0.09 – 1.14)	0.38 (0.09 – 1.21)	**0.28 (0.07 – 0.94)**	0.98 (0.67 – 1.46)	**ACEi + diuretic**

HR for total mortality (95% CrI) HR for CV mortality (95% CrI)

Numbers express the HR for the treatments in the lower line compared to the treatment in the upper line. In total mortality section, HR < 1 favours the line-defining treatment. In CV mortality section, HR < 1 favours the row-defining treatment. Results with evidence of benefit are in bold and underlined.

BB = betablocker, CCB = calcium channel blocker, ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker

Table 3: Comparisons of the effects of antihypertensive drug classes in end of study blood pressure (median difference mmHg (95% CrI).

Placebo	-1.07 (-3.35 to 1.17)	-1.46 (-3.59 to 0.71)	-1.63 (-3.29 to 0.01)	-0.84 (-2.66 to 0.99)	**-1.56 (-3.09 to -0.04)**	**-3.50 (-5.62 to -1.41)**
-3.38 (-7.17 to 0.41)	**Thiazide**	-0.39 (-2.66 to 1.93)	-0.56 (-2.24 to 1.12)	0.23 (-1.45 to 1.94)	-0.49 (-2.77 to 1.78)	**-2.43 (-4.66 to -0.21)**
-1.38 (-5.01 to 2.27)	1.99 (-1.84 to 5.89)	**Betablocker**	-0.16 (-1.97 to 1.55)	0.62 (-1.19 to 2.40)	-0.10 (-2.12 to 1.85)	-2.04 (-4.34 to 0.19)
-2.19 (-5.00 to 0.57)	1.19 (-1.63 to 3.96)	-0.80 (-3.80 to 2.10)	**CCB**	0.79 (-0.40 to 2.01)	0.06 (-1.55 to 1.68)	**-1.87 (-3.58 to -0.17)**
-1.00 (-4.08 to 2.03)	2.37 (-0.41 to 5.17)	0.37 (-2.71 to 3.41)	1.18 (-0.78 to 3.16)	**ACEi**	-0.73 (-2.59 to 1.10)	**-2.67 (-4.31 to -1.03)**
-3.34 (-5.96 to -0.73)	0.04 (-3.77 to 3.81)	-1.95 (-5.30. to 1.34)	-1.14 (-3.85 to 1.56)	-2.32 (-5.41 to 0.75)	**ARB**	-1.93 (-4.12 to 0.24)
-4.97 (-8.60 to -1.50)	-1.59 (-5.37 to 2.05)	-3.59 (-7.54 to 0.16)	-2.78 (-5.73 to 0.02)	**-3.97 (-6.77 to -1.27)**	-1.64 (-5.37 to 1.97)	**ACEi + CCB**

Systolic blood pressure Diastolic blood pressure

Numbers express the difference in end of study blood pressure for the treatment in the lower line related to the treatment in the upper line. In systolic blood pressure line, median differences < 0 favours line-defining treatment. In diastolic blood pressure section, median differences < 0 favours row-defining treatment. Results with evidence of benefit are in bold and underlined.

CCB = calcium channel blocker, ACEi = angiotensin-converting enzyme inhibitor, ARB = angiotensin receptor blocker

Figure 1: Flowchart of study selection process

Figure 2 Hazard Ratio for total mortality (A) and cardiovascular mortality (B) considering placebo as reference treatment.

CCB = calcium channel blocker, ACEI = angiotensin converting enzyme inhibitor, ARB = angiotensin receptor blocker, BB = betablocker

Vertical line represents the no effect line. X-axis represents the Hazard ratio