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**CLASSES OF ANTIHYPERTENSIVE AGENTS AND MORTALITY IN HYPERTENSIVE PATIENTS
WITH TYPE 2 DIABETES – NETWORK META-ANALYSIS OF RANDOMIZED TRIALS**

Luciana R. Remonti MD ^a, Sofia Dias PhD ^b, Cristiane B. Leitão MD ^a, Caroline K. Kramer MD ^c, Lucas P. Klassman ^a, Nicky J. Welton PhD ^b, A. E. Ades PhD ^b, Jorge L. Gross MD ^a.

^aDiabetes and Endocrinology Meta-Analysis (DEMA) group, Endocrinology Division,
Hospital de Clínicas de Porto Alegre, Ramiro Barcelos, 2350, Porto Alegre, Brazil

^bSchool of Social and Community Medicine, University of Bristol, Canynge Hall
39 Whatley Road, Bristol, UK

^c Invited researcher, Division of Endocrinology, University of Toronto, 200 Elizabeth
Street, Toronto, Canada

Corresponding author:

Luciana Reck Remonti

Diabetes and Endocrinology Meta-Analysis group, Endocrinology Division, Hospital de
Clínicas de Porto Alegre, Brazil

R. Ramiro Barcelos, 2350 – building 12 – fourth floor – Porto Alegre – RS – Brazil

Postal Code 90035 – 901

Phone: + 55 51 33598127 / Fax: + 55 51 33598777

Email: lucianalreck@gmail.com

23 Abstract

24 **Aims:** to evaluate the effects of antihypertensive drug classes in mortality in patients with
25 type 2 diabetes.

26 **Methods:** MEDLINE, EMBASE, Clinical Trials and Cochrane Library were searched for
27 randomized trials comparing thiazides, beta-blockers, calcium channel blockers (CCBs),
28 angiotensin-converting inhibitors (ACEi) and angiotensin-receptor blockers (ARBs), alone
29 or in combination for hypertension treatment in patients with type 2 diabetes. Outcomes were
30 overall and cardiovascular mortality. Network Meta-Analysis was used to obtain pooled
31 effect estimate.

32 **Results:** 27 studies, comprising 49418 participants, 5647 total and 1306 cardiovascular
33 deaths were included. No differences in total or cardiovascular mortality were observed with
34 isolated antihypertensive drug classes compared to each other or placebo. ACEi and CCB
35 combination showed evidence of reduction in cardiovascular mortality comparing to placebo
36 (median HR, 95% Credibility Intervals: 0·16, 0·01-0·82), betablockers (0·20, 0·02-0·98),
37 CCBs (0·21, 0·02-0·97) and ARBs (0·18, 0·02-0·91). In included trials, this combination was
38 the treatment that most consistently achieved both lower systolic and diastolic end of study
39 blood pressure.

40 **Conclusions:** There is no benefit of a single antihypertensive class in reduction of mortality
41 in hypertensive patients with type 2 diabetes. Reduction of cardiovascular mortality observed
42 in patients treated with ACEi and CCB combination may be related to lower blood pressure
43 levels.

44 **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 (Olmесartan 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

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

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

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

265 The strength of the meta-analysis presented here is the number of included patients and events and the
 266 fact that we analyzed mortality outcomes only and not surrogate endpoints. Another advantage of this
 267 study is the use of a NMA method to evaluate the effects of the different antihypertensive drug classes
 268 relative to each other in a coherent way. This analysis has limitations. NMA method takes into
 269 account several statistical assumptions that can not be verified and could introduce bias. However,
 270 bias is not expected to act exclusively in one particular direction and NMA method is considered
 271 essential to make comparisons when multiple treatments are available [53]. Like in other multiple
 272 comparisons, these conclusions must be interpreted with caution and proper clinical judgment. For
 273 several trials, we had no details of baseline characteristics of patients, in order to estimate a baseline
 274 cardiovascular risk to use in the analysis as a correction factor. In addition, data about initial and/or
 275 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. Funding by Conselho Nacional de Pesquisas (CNPq) grant n° 307015/2010-6 and Fundo de Incentivo à Pesquisa e Eventos (FIPE) n° 12-0093. The funding source had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors revised and approved the final version of the manuscript.

324 REFERENCES

- 325 1. Vijan S, Hayward RA. Treatment of hypertension in type 2 diabetes mellitus: blood pressure
326 goals, choice of agents, and setting priorities in diabetes care. *Ann Intern Med* 2003; 138:593–602.
- 327 2. Ferrannini E, Cushman WC. Diabetes and hypertension: the bad companions. *Lancet* 2012;
328 380:601–10.
- 329 3. Bakris GL, Sowers JR. ASH position paper: treatment of hypertension in patients with
330 diabetes-an update. *J Clin Hypertens (Greenwich)* 2008; 10:707–13.
- 331 4. Tight blood pressure control and risk of macrovascular and microvascular complications in
332 type 2 diabetes: UKPDS 38. UK Prospective Diabetes Study Group. *BMJ* 1998; 317:703–13.
- 333 5. Standards of medical care in diabetes – 2014. *Diabetes Care* 2014; 37(suppl 1):S14–S80.
- 334 6. Wright JM, Musini VM. First-line drugs for hypertension. *Cochrane Database Syst Rev*
335 2009; 8(3): DOI: 10.1002/14651858.CD001841.pub2.
- 336 7. Turnbull F, Neal B, Algert C, Chalmers J, Chapman N, Cutler J, Woodward M, MacMahon S
337 for the Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood
338 pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes
339 mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med* 2005;
340 165:1410–19.
- 341 8. Dias S, Sutton AJ, Ades AE, Welton NJ. A Evidence synthesis for decision making 2: a
342 Generalized Linear Modeling Framework for Pairwise and Network Meta-analysis of Randomized
343 Controlled Trials. *Med Decis Making* 2013; 33(5):607-17.
- 344 9. Caldwell DM, Ades AE, Higgins JP. Simultaneous comparison of multiple treatments:
345 combining direct and indirect evidence. *BMJ* 2005; 331:897–900.
- 346 10. Fretheim A, Odgaard-Jensen J, Brørs O, Madsen S, Njølstad I, Norheim OF, Svilaas A,
347 Kristiansen IS, Thürmer H, Flottorp S. Comparative effectiveness of antihypertensive medication for
348 primary prevention of cardiovascular disease: systematic review and multiple treatments meta-
349 analysis. *BMC Med* 2012; 10:33.
- 350 11. Wu HY, Huang JW, Lin HJ, Liao WC, Peng YS, Hung KY, Wu KD, Tu YK, Chien KL.
351 Comparative effectiveness of renin-angiotensin system blockers and other antihypertensive drugs in

- 352 patients with diabetes: systematic review and bayesian network meta-analysis. *BMJ* 2013; 347:f6008;
 353 doi: 10.1136/bmj.f6008.
- 354 12. Robinson KA, Dickersin K. Development of a highly sensitive search strategy for the
 355 retrieval of reports of controlled trials using PubMed. *Int J Epidemiol* 2002; 31:150–3.
- 356 13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M,
 357 Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and
 358 meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann*
 359 *Intern Med* 2009; 151:W65–94.
- 360 14. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, Atkins D, Kunz R,
 361 Montori V, Jaeschke R, Rind D, Dahm P, Akl EA, Meerpohl J, Vist G, Berliner E, Norris S, Falck-
 362 Ytter Y, Schünemann HJ. GRADE guidelines 11-making an overall rating of confidence in effect
 363 estimates for a single outcome and for all outcomes. *J Clin Epidemiol* 2013; 66:151–7.
- 364 15. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P,
 365 Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA,
 366 Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence--publication bias. *J Clin*
 367 *Epidemiol* 2011; 64:1277–82.
- 368 16. Welton NJ, Sutton AJ, Cooper NJ, Abrams KR, Ades AE. *Evidence Synthesis for Decision*
 369 *Making in Healthcare*. Chichester: Ed. Wiley; 2012.
- 370 17. Dias S, Welton NJ, Caldwell DM, Ades AE. Checking consistency in mixed treatment
 371 comparison meta-analysis. *Stat Med* 2010; 29:932–44.
- 372 18. Higgins JPT, Jackson D, Barrett JK, Lu G, Ades AE, White IR. Consistency and
 373 inconsistency in network meta-analysis: concepts and models for multi-arm studies. *Res Syn Meth*
 374 2012; 3:98-110.
- 375 19. Dias S, Welton NJ, Sutton AJ, Caldwell DM, Lu G, Ades AE. NICE DSU Technical Support
 376 Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials.
 377 Available from <http://www.nicesdu.org.uk>. 2011; last updated April 2012.
- 378 20. Dias S, Sutton AJ, Welton NJ, Ades AE. NICE DSU Technical Support Document 3:
 379 Heterogeneity: subgroups, meta-regression, bias and bias-adjustment. Available from
 380 <http://www.nicesdu.org.uk>. 2011; last updated April 2012.

- 381 21. Madan J, Stevenson MD, Cooper KL, Ades AE, Whyte S, Akehurst R. Consistency between
382 direct and indirect trial evidence: is direct evidence always more reliable? *Value Health* 2011;
383 14:953–60.
- 384 22. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular
385 complications in type 2 diabetes: UKPDS 39. UK Prospective Diabetes Study Group. *BMJ* 1998;
386 317:713–20.
- 387 23. Bakris GL, Gaxiola E, Messerli FH, Mancia G, Erdine S, Cooper-DeHoff R, Pepine CJ.
388 Clinical outcomes in the diabetes cohort of the INternational VERapamil SR-Trandolapril study.
389 *Hypertension* 2004; 44:637–42.
- 390 24 Barnett AH, Bain SC, Bouter P, Karlberg B, Madsbad S, Jervell J, Mustonen J; Diabetics
391 Exposed to Telmisartan and Enalapril Study Group. Angiotensin-receptor blockade versus converting-
392 enzyme inhibition in type 2 diabetes and nephropathy. *N Engl J Med* 2004; 351:1952–61.
- 393 25. Berl T, Hunsicker LG, Lewis JB, Pfeffer MA, Porush JG, Rouleau JL, Drury PL, Esmatjes E,
394 Hricik D, Parikh CR, Raz I, Vanhille P, Wiegmann TB, Wolfe BM, Locatelli F, Goldhaber SZ, Lewis
395 EJ; Irbesartan Diabetic Nephropathy Trial. Collaborative Study Group. Cardiovascular Outcomes in
396 the Irbesartan Diabetic Nephropathy Trial of Patients with Type 2 Diabetes and Overt Nephropathy.
397 *Ann Intern Med* 2003; 138:542–9.
- 398 26. Brenner BM, Cooper ME, de Zeeuw D, Keane WF, Mitch WE, Parving HH, Remuzzi G,
399 Snapinn SM, Zhang Z, Shahinfar S; RENAAL Study Investigators. Effects of losartan on renal and
400 cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;
401 345:861–9.
- 402 27. Curb JD, Pressel SL, Cutler JA, Savage PJ, Applegate WB, Black H, Camel G, Davis BR,
403 Frost PH, Gonzalez N, Guthrie G, Oberman A, Rutan GH, Stamler J. Effect of diuretic-based
404 antihypertensive treatment on cardiovascular disease risk in older diabetic patients with isolated
405 systolic hypertension. Systolic Hypertension in the Elderly Program Cooperative Research Group.
406 *JAMA* 1996; 276:1886–92.
- 407 28. Estacio RO, Jeffers BW, Hiatt WR, Biggerstaff SL, Gifford N, Schrier RW. The effect of
408 nisoldipine as compared with enalapril on cardiovascular outcomes in patients with non-insulin-
409 dependent diabetes and hypertension. *N Engl J Med* 1998; 338:645–52.

- 410 29. Fogari R, Preti P, Zoppi A, Rinaldi A, Corradi L, Pasotti C, Poletti L, Marasi G, Derosa G,
411 Mugellini A, Voglini C, Lazzari P. Effects of amlodipine fosinopril combination on microalbuminuria
412 in hypertensive type 2 diabetic patients. *Am J Hypert* 2002; 15:1042–9.
- 413 30. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, Lanke J,
414 de Faire U, Dahlöf B, Karlberg BE. Randomised trial of effects of calcium antagonists compared with
415 diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic
416 Diltiazem (NORDIL) study. *Lancet* 2000; 356:359–65.
- 417 31. Imai E, Chan JC, Ito S, Yamasaki T, Kobayashi F, Haneda M, Makino H. Effects of
418 olmesartan on renal and cardiovascular outcomes in type 2 diabetes with overt nephropathy: a
419 multicentre, randomised, placebo-controlled study. *Diabetologia* 2011; 54:2978–86.
- 420 32. Lewis EJ, Hunsicker LG, Clarke WR, Berl T, Pohl MA, Lewis JB, Ritz E, Atkins RC, Rohde
421 R, Raz I; Collaborative Study Group. Renoprotective effect of the angiotensin-receptor antagonist
422 irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001; 345:851–60.
- 423 33. Lindholm LH, Hansson L, Ekblom T, Dahlöf B, Lanke J, Linjer E, Scherstén B, Wester PO,
424 Hedner T, de Faire U. Comparison of antihypertensive treatments in preventing cardiovascular events
425 in elderly diabetic patients: results from the Swedish Trial in Old Patients with Hypertension-2. STOP
426 Hypertension-2 Study Group. *J Hypertens* 2000; 18:1671–75.
- 427 34. Lindholm LH, Ibsen H, Dahlöf B, Devereux RB, Beevers G, de Faire U, Fyhrquist F, Julius
428 S, Kjeldsen SE, Kristiansson K, Lederballe-Pedersen O, Nieminen MS, Omvik P, Oparil S, Wedel H,
429 Aurup P, Edelman J, Snapinn S; LIFE Study Group. Cardiovascular morbidity and mortality in
430 patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study
431 (LIFE): a randomised trial against atenolol. *Lancet* 2002; 359:1004–10.
- 432 35. Mancia G, Brown M, Castaigne A, de Leeuw P, Palmer CR, Rosenthal T, Wagener G,
433 Ruilope LM; INSIGHT. Outcomes with nifedipine GITS or Co-amlozide in hypertensive diabetics
434 and nondiabetics in Intervention as a Goal in Hypertension (INSIGHT). *Hypertension* 2003;
435 41:431–36.
- 436 36. Marre M, Puig JG, Kokot F, Fernandez M, Jermendy G, Opie L, Moyseev V, Scheen A,
437 Ionescu-Tirgoviste C, Saldanha MH, Halabe A, Williams B, Mion Júnior D, Ruiz M, Hermansen K,
438 Tuomilehto J, Finizola B, Gallois Y, Amouyel P, Ollivier JP, Asmar R. Equivalence of indapamide

- 439 SR and enalapril on microalbuminuria reduction in hypertensive patients with type 2 diabetes: The
 440 NESTOR study. *J Hypertens* 2004; 22:1613–22.
- 441 37. Muramatsu T, Matsushita K, Yamashita K, Kondo T, Maeda K, Shintani S, Ichimiya S, Ohno
 442 M, Sone T, Ikeda N, Watarai M, Murohara T; NAGOYA HEART Study Investigators. Comparison
 443 between valsartan and amlodipine regarding cardiovascular morbidity and mortality in hypertensive
 444 patients with glucose intolerance: NAGOYA HEART study. *Hypertension* 2012; 59:580–6.
- 445 38. Nakao K, Hirata M, Oba K, Yasuno S, Ueshima K, Fujimoto A, Ogihara T, Saruta T; CASE-J
 446 Trial Group. Role of diabetes and obesity in outcomes of the candesartan antihypertensive survival
 447 evaluation in Japan (CASE-J) trial. *Hypertens Res* 2010; 33:600–6.
- 448 39. Nielsen FS, Rossing P, Gall MA, Skott P, Smidt UM, Parving HH. Long-term effect of
 449 lisinopril and atenolol on kidney function in hypertensive NIDDM subjects with diabetic nephropathy.
 450 *Diabetes* 1997; 46:1182–8.
- 451 40. Niskanen L, Hedner T, Hansson L, Lanke J, Niklason A. Reduced cardiovascular morbidity
 452 and mortality in hypertensive diabetic patients on first-line therapy with an ACE inhibitor compared
 453 with a diuretic/beta-blocker-based treatment regimen: a subanalysis of the Captopril Prevention
 454 Project. *Diabetes Care* 2001; 24:2091–96.
- 455 41. Ostergren J, Poulter NR, Sever PS, Dahlöf B, Wedel H, Beevers G, Caulfield M, Collins R,
 456 Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E; ASCOT investigators.
 457 The Anglo-Scandinavian Cardiac Outcomes Trial: blood pressure-lowering limb: effects in patients
 458 with type II diabetes. *J Hypertens* 2008; 26:2103–11.
- 459 42. Parving HH, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P. The effect of
 460 irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med*
 461 2001; 345:870–8.
- 462 43. Remuzzi G, Macia M, Ruggenenti P. Prevention and treatment of diabetic renal disease in
 463 type 2 diabetes: The BENEDICT study. *J Am Soc Nephrol* 2006; 17(4 suppl. 2):S90–S7.
- 464 44. Ruggenenti P, Fassi A, Ilieva A, Iliev IP, Chiurciu C, Rubis N, Gherardi G, Ene-Iordache B,
 465 Gaspari F, Perna A, Cravedi P, Bossi A, Trevisan R, Motterlini N, Remuzzi G; BENEDICT-B Study
 466 Investigators. Effects of verapamil added-on trandolapril therapy in hypertensive type 2 diabetes
 467 patients with microalbuminuria: The BENEDICT-B randomized trial. *J Hypertens* 2011; 29:207–16.

- 468 45. Safar M, Thijs L, Staessen JA. Syst-Eur Trial: Benefits of nitrendipine in the type 2 diabetic
469 hypertensive patients. *Arch Mal Coeur et des Vaiss* 2003; 96:768–71.
- 470 46. Tatti P, Pahor M, Byington RP, Di Mauro P, Guarisco R, Strollo G, Strollo F. Outcome
471 results of the Fosinopril Versus Amlodipine Cardiovascular Events Randomized Trial (FACET) in
472 patients with hypertension and NIDDM. *Diabetes Care* 1998; 21:597–603.
- 473 47. Tuomilehto J, Rastenyte D, Birkenhäger WH, Thijs L, Antikainen R, Bulpitt CJ, Fletcher AE,
474 Forette F, Goldhaber A, Palatini P, Sarti C, Fagard R. Effects of calcium-channel blockade in older
475 patients with diabetes and systolic hypertension. Systolic Hypertension in Europe Trial Investigators.
476 *N Engl J Med* 1999; 340:677–84.
- 477 48. Weber MA, Bakris GL, Jamerson K, Weir M, Kjeldsen SE, Devereux RB, Velazquez EJ,
478 Dahlöf B, Kelly RY, Hua TA, Hester A, Pitt B; ACCOMPLISH Investigators. Cardiovascular events
479 during differing hypertension therapies in patients with diabetes. *J Am Coll Cardiol* 2010; 56:77–85.
- 480 49. Whelton PK, Barzilay J, Cushman WC, Davis BR, Iamathi E, Kostis JB, Leenen FH, Louis
481 GT, Margolis KL, Mathis DE, Moloo J, Nwachuku C, Panebianco D, Parish DC, Pressel S, Simmons
482 DL, Thadani U; ALLHAT Collaborative Research Group. Clinical outcomes in antihypertensive
483 treatment of type 2 diabetes, impaired fasting glucose concentration, and normoglycemia:
484 Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch*
485 *Intern Med* 2005; 165:1401–9.
- 486 50. Yui Y, Sumiyoshi T, Kodama K, Hirayama A, Nonogi H, Kanmatsuse K, Origasa H, Iimura
487 O, Ishii M, Saruta T, Arakawa K, Hosoda S, Kawai C. Nifedipine retard was as effective as
488 angiotensin converting enzyme inhibitors in preventing cardiac events in high-risk hypertensive
489 patients with diabetes and coronary artery disease: the Japan Multicenter Investigation for
490 Cardiovascular Diseases-B (JMIC-B) subgroup analysis. *Hypertens Res* 2004; 27:449–56.
- 491 51. Ruggerenti P, Fassi A, Ilieva AP, Bruno S, Iliev IP, Brusegan V, Rubis N, Gherardi G,
492 Arnoldi F, Ganeva M, Ene-Iordache B, Gaspari F, Perna A, Bossi A, Trevisan R, Dodesini AR,
493 Remuzzi G; Bergamo Nephrologic Diabetes Complications Trial (BENEDICT) Investigators.
494 Preventing microalbuminuria in type 2 diabetes. *N Engl J Med* 2004; 351:1941–51.
- 495 52. Adler AI, Stratton IM, Neil HA, Yudkin JS, Matthews DR, Cull CA, Wright AD, Turner RC,
496 Holman RR. Association of systolic blood pressure with macrovascular and microvascular

- 497 complications of type 2 diabetes (UKPDS 36): prospective observational study. BMJ 2000;
498 321:412–9.
- 499 53. Caldwell DM, Ades AE, Higgins JPT. Simultaneous comparison of multiple treatments:
500 combining direct and indirect evidence. BMJ 2005; 331:897–900.
- 501 54. Haller H, Ito S, Izzo JL, Jr., Januszewicz A, Katayama S, Menne J, Investigators RT.
502 Olmesartan for the delay or prevention of microalbuminuria in type 2 diabetes. N Engl J Med 2011;
503 364:907–17.
- 504 55. Ogawa H, Kim-Mitsuyama S, Matsui K, Jinnouchi T, Jinnouchi H, Arakawa K. Angiotensin
505 II receptor blocker-based therapy in Japanese elderly, high-risk, hypertensive patients. Am J Med
506 2012; 125:981–90.

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 discontinuation (%) [§]	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)	<u>0.16</u> (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)	<u>0.20</u> (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)	<u>0.21</u> (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)	<u>0.18</u> (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	<u>0.18</u> (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)	<u>0.29</u> (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)	<u>0.28</u> (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)	<u>-1.56</u> (-3.09 to -0.04)	<u>-3.50</u> (-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)	<u>-2.43</u> (-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)	<u>-1.87</u> (-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)	<u>-2.67</u> (-4.31 to -1.03)
<u>-3.34</u> (-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)
<u>-4.97</u> (-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)	<u>-3.97</u> (-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

531

532 **Figure 1: Flowchart of study selection process**

533

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

536 CCB = calcium channel blocker, ACEI = angiotensin converting enzyme inhibitor, ARB =

537 angiotensin receptor blocker, BB = betablocker

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