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Different antihypertensive drugs as first line therapy in patients with essential hypertension[1]

Executive Summary

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Executive summary

Research question

The aim of this investigation is to find out the extent to which the benefit of antihypertensive drugs is dependent on the choice of the first-line drug in the treatment of essential hypertension.

Methods

Included in the benefit assessment were studies with patients (age at start of study ≥ 18 years) with essential (primary) arterial hypertension, defined as raised systolic blood pressure ≥ 140 mm Hg and/or diastolic blood pressure ≥ 90 mm Hg frequently occurring on different days without known cause.

The following outcomes were used in the investigation, allowing patient-relevant outcomes to be evaluated: all-cause mortality, cardiac morbidity and mortality, cerebral morbidity and mortality, vascular non-cardiac and non-cerebral morbidity and mortality, terminal kidney failure, hospitalizations, health-related quality of life and patient satisfaction, and other adverse drug effects. In order to preserve clarity and interpretability of the results and take account of patient relevance, the following outcomes were documented in detail and a meta-analysis was carried out on them: all-cause mortality, total rates of myocardial infarctions, strokes, heart failure and combined cardiovascular outcomes.

For the purposes of the report, only randomized controlled trials (RCTs) were included in the benefit assessment. Only studies with a minimum observation period of 1 year and a minimum patient population of 500 patients per comparator group or 1000 patient years per comparator group were considered. The literature search for relevant published studies was conducted in the following bibliographic databases: MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Database of Systematic Reviews (CDSR), HTA database (HTA), NHS Economic Evaluation Database (NHS-EED) and Database of Abstracts of Reviews of Effects (DARE). The citations identified through the search in bibliographic databases were assessed for relevance by 2 reviewers independently of each other on the basis of title and, if available, abstract. If questions arose during the assessment of the studies included to which answers could not be found in the publications, the relevant authors were contacted.

Data were extracted by a reviewer using standardized data extraction forms. A second reviewer checked the extraction. Discrepancies in the assessment were resolved through discussion by the reviewers.

Data on an outcome were quantitatively synthesized in a meta-analysis, provided that the contents and methods of the study data made it feasible. A model with fixed effects was used for the primary analysis. Where potential heterogeneity in individual study results was indicated, additional models were calculated with random effects.

Results

A total of 48 publications were identified as relevant to the research question, to which 16 RCTs could be allocated. All trials were randomized and conducted in parallel. A total of 9 trials had a double-blind design, whereby the VHAS[2] study was only double-blinded in the first 6 months (study duration 2 years). Six trials were conducted with an open design and a blinded outcome analysis. The study duration was between 2 and approx. 8 years. The number of participants in the trials was between 470 and 33,357 patients. This executive summary is restricted to a selection of regularly-reported, patient-relevant outcomes that are relevant to the conclusion.

Comparative trials with diuretics are available for 3 out of 4 possible drug class comparisons. In the comparison of diuretics versus *beta blockers*, 3 trials were included in the benefit assessment. There is no indication or proof of additional benefit of diuretics in the comparison with the beta blockers for any of the outcomes. Only the ALLHAT[3] trial contained results on the comparison of diuretics versus *ACE inhibitors*. In this trial there is an indication of additional benefit of diuretics on the risk of heart failure. In addition, when compared to ACE inhibitors, there is an indication of additional benefit of diuretics on the risk of stroke in the black group, but not in the non-black group. There is no indication or proof of additional benefit of diuretics for any of the other outcomes in the comparison with the ACE inhibitors. A total of 5 trials comparing diuretics with *calcium antagonists* were included in the benefit assessment. These proved the additional benefit of diuretics on the risk of heart failure. There is no indication or proof of additional benefit of diuretics for any other outcome in the comparison with the calcium antagonists. Comparative trials on diuretics and *angiotensin-II antagonists* were lacking.

Comparative trials with beta blockers are available for all 4 possible drug class comparisons. In the beta blocker versus *diuretics* comparison, 3 trials were included in the benefit assessment. In the comparison with the diuretics, there is no indication or proof of additional benefit of beta blockers for any of the outcomes. Although there are 2 trials that compare beta blockers with *ACE inhibitors*, the quality of data is unsatisfactory. In the UKPDS-39[4] trial, only patients with type 2 diabetes were studied and in the AASK[5] trial only Afro-American patients with hypertensive nephropathy. As a result, a general conclusion regarding possible

[2] Verapamil in Hypertension and Atherosclerosis Study
[3] Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
[4] UK Prospective Diabetes Study
[5] African-American Study of Kidney Disease and Hypertension

varying effects can only be made with reservations. In the comparison with ACE inhibitors, there is an indication that the quality of life under ACE inhibitor treatment is better in the black group; there is insufficient data on this outcome for the non-black group. There is no indication or proof of additional benefit of beta blockers in the comparison with ACE inhibitors for any of the other outcomes. There was only 1 trial that compared beta blockers versus *calcium antagonists*, and there is no indication or proof of additional benefit of beta blockers or calcium antagonists for any of the reported outcomes. In the comparison with *angiotensin-II antagonists*, there is an indication that, when compared to beta blockers, the angiotensin-II antagonists have an additional benefit on the mortality and heart failure outcomes in patients with diabetes mellitus; no such indications exist for non-diabetic patients. With regard to the total rate of strokes, there is an indication of additional benefit of beta blockers when compared to angiotensin-II antagonists in the black group; in the non-black group, however, there is an indication of additional benefit of angiotensin-II antagonists on the rate of strokes.

Comparative trials with ACE inhibitors are available for 3 out of 4 possible drug class comparisons. Results from the comparison of ACE inhibitors versus *diuretics* were only found in the ALLHAT trial. There is an indication of additional benefit of diuretics on the risk of heart failure. In addition, there is an indication of additional benefit of diuretics when compared to ACE inhibitors on the risk of stroke in the black group, but this indication is not present in the non-black group. There is no indication or proof of additional benefit of diuretics in the comparison with ACE inhibitors for any of the other outcomes. Although there are 2 trials that compare ACE inhibitors with *beta blockers*, the quality of data is unsatisfactory. In the UKPDS-39 trial, only patients with type 2 diabetes were studied and in the AASK trial only Afro-American patients with hypertensive nephropathy. As a result, a general conclusion regarding possible varying effects can only be made with reservations. In the comparison with beta blockers, there is an indication that the quality of life under ACE inhibitor treatment is better in the black group; there is insufficient data on this outcome for the non-black group. There is no indication or proof of additional benefit of ACE inhibitors in the comparison with beta blockers for any of the other outcomes. For the comparison of ACE inhibitors versus *calcium antagonists*, 3 trials could be included in the benefit assessment. In the comparison with calcium antagonists, there is proof of additional benefit of ACE inhibitors on the risk of heart failure. With regard to the risk of stroke, there is an indication of additional benefit of calcium antagonists in women of both ethnic groups (black and non-black group) and in black men. In patients with diabetes mellitus, there is an indication of additional benefit of ACE inhibitors on the risk of heart attack. In the comparison with calcium antagonists, there is no indication or proof of additional benefit of ACE inhibitors for any of the other outcomes. There was a lack of comparative trials on ACE inhibitors and *angiotensin-II antagonists*.

Comparative trials with calcium antagonists are available for all 4 possible drug class comparisons. In the calcium antagonists versus *diuretics* comparison, a total of 5 trials could

be included in the benefit assessment. They provided proof of additional benefit of diuretics on the occurrence of heart failure. There is no indication or proof of additional benefit of calcium antagonists in the comparison with the diuretics for any of the other outcomes. There was only 1 trial that compared calcium antagonists versus *beta blockers*, and there is no indication or proof of additional benefit of beta blockers or calcium antagonists for any of the reported outcomes. For the comparison of calcium antagonists versus *ACE inhibitors*, 3 trials could be included in the benefit assessment. In the comparison with ACE inhibitors, there is proof of additional benefit of ACE inhibitors on the risk of heart failure. With regard to the risk of stroke, there is an indication of additional benefit of calcium antagonists in women of both ethnic groups (black and non-black group) and in black men. In patients with diabetes mellitus, there is an indication of additional benefit of ACE inhibitors on the risk of heart attack. In the comparison with ACE inhibitors, there is no indication or proof of additional benefit of calcium antagonists for any of the other outcomes. For the comparison of calcium antagonists versus *angiotensin-II antagonists*, 2 trials were included. There is an indication of additional benefit of calcium antagonists on the total rate of myocardial infarctions. In contrast, there is an indication of additional benefit of angiotensin-II antagonists on the total rate of heart failure. In the comparison with the angiotensin-II antagonists, there is no indication or proof of additional benefit of calcium antagonists for any of the other outcomes.

Direct comparative trials on angiotensin-II antagonists that were included in the benefit assessment were found for 2 out of 4 possible comparisons. Comparative trials on angiotensin-II antagonists and *diuretics* were lacking. In the comparison with *beta blockers*, there is an indication that the angiotensin-II antagonists have an additional benefit on mortality and heart failure outcomes in patients with diabetes mellitus; no such indications exist for non-diabetic patients. With regard to the total rate of strokes, there is an indication of additional benefit of beta blockers when compared to angiotensin-II antagonists in the black group; in the non-black group, however, there is an indication of additional benefit of angiotensin-II antagonists on the rate of strokes. Comparative trials on angiotensin-II antagonists and *ACE inhibitors* were lacking. For the comparison of angiotensin-II antagonists versus *calcium antagonists*, 2 trials were included in the benefit assessment. There is an indication of additional benefit of calcium antagonists on the total rate of myocardial infarctions. In contrast, there is an indication of additional benefit of angiotensin-II antagonists on the total rate of heart failure. In the comparison with the angiotensin-II antagonists, there is no indication or proof of additional benefit of calcium antagonists for any of the other outcomes.

Regarding the incidence of diabetes, the data display an indication of a positive effect in favour of calcium antagonists when compared to diuretics, in favour of angiotensin-II antagonists when compared to beta blockers and calcium antagonists, and in the black group in favour of ACE inhibitors when compared to beta blockers. It is not possible to derive an additional benefit or harm from these results, particularly as they simply record changes in laboratory values. Furthermore, patients who developed diabetes mellitus while receiving

diuretics during the course of the trial did not appear to be at any greater risk – at least during the trial – from a serious patient-relevant outcome. Corresponding data on beta blockers are lacking.

In general, there were flaws in the data regarding the total number of adverse events, severe adverse events and events linked to the therapy. Overall, it is not possible to derive a generally superior side effect profile from any of the drug classes investigated. In the main, the adverse side effects of the drugs concerned are reversible.

Conclusions from the overview of the trials

Diuretics are the only drug class not inferior to any other drug class in reducing hypertension complications, and in individual aspects display advantages when compared to ACE inhibitors and calcium antagonists. However, the data from direct comparative trials with all other 4 drug classes were not available for all drug classes and research questions. Investigations on diuretics and calcium antagonists were considered the best.

In the overall results, diuretics can generally be considered the first-line therapy when addressing the research question of this report, allowing for individual patient anomalies such as comorbidities and age.

In addition, the following conclusions can be drawn from the available data:

For diuretics, comparative trials were available for all drug classes investigated in this report except for angiotensin-II antagonists (a total of 9 comparisons from 8 trials). The diuretics used in the trials were bendroflumethiazide, chlorthalidone, co-amilozide and hydrochlorothiazide.

- In the comparison with beta blockers, there is no indication of additional benefit of either of the drug classes.

- In the comparison with ACE inhibitors, there is an indication from one trial of an additional benefit on the risk of heart failure. In addition, there is an indication of additional benefit of diuretics when compared to ACE inhibitors on the risk of stroke in the black group, but this indication is not present in the non-black group.

- In the comparison with calcium antagonists, there is proof of additional benefit of diuretics on the risk of heart failure.

For *beta blockers*, trials on all drug classes investigated in this report were included (a total of 7 trials). The beta blockers used in the trials were atenolol, metoprolol and propanolol.

- In the comparison with diuretics, there is no indication of additional benefit of either of the drug classes.

- In the comparison with ACE inhibitors, there is an indication of higher quality of life under ACE inhibitor treatment in the black group, but there are insufficient data on this outcome for the non-black group.

- In the comparison with calcium antagonists, there is no indication of additional benefit of either of the drug classes.

- In the comparison with angiotensin-II antagonists, there is an indication that the angiotensin-II antagonists have an additional benefit when compared to beta blockers on the mortality and heart failure outcomes in patients with diabetes mellitus; no such indication exists for non-diabetic patients. With regard to the total rate of strokes, there is an indication of additional benefit of beta blockers when compared to angiotensin-II antagonists in the black group; in the non-black group, however, there is an indication of additional benefit of angiotensin-II antagonists on the rate of strokes.

For *ACE inhibitors*, comparative trials were available on all drug classes investigated in this report except for angiotensin-II antagonists (a total of 6 comparisons from 5 trials). The ACE inhibitors used in the trials were captopril, enalapril, imidapril, lisinopril and ramipril.

- In the comparison with diuretics, there is an indication that the diuretics have an additional benefit on the risk of heart failure. In addition, in the black group, there is an indication of additional benefit of diuretics on the risk of stroke, but this indication is not present in the non-black group.

- In the comparison with beta blockers, there is an indication of higher quality of life under ACE-inhibitor treatment in the black group, but there are insufficient data on this outcome for the non-black group.

- In the comparison with calcium antagonists, there is proof of additional benefit of ACE inhibitors on the risk of heart failure. With regard to the risk of stroke, in contrast, there is an indication of additional benefit of calcium antagonists in women of both ethnic groups (black and non-black group) and in black men. In patients with diabetes mellitus, there is an indication of additional benefit of ACE inhibitors on the risk of myocardial infarction.

For *calcium antagonists* comparative trials were available on all drug classes investigated in this report (a total of 11 comparisons from 10 trials). The calcium antagonists used in the trials were amlodipine, isradipine, lacidipine, nifedipine, nisoldipine, nitrendipine and verapamil.

- In the comparison with diuretics, the additional benefit of diuretics is proven on the risk of heart failure.

- In the comparison with beta blockers, there is no indication of additional benefit of either of the drug classes.

- In the comparison with ACE inhibitors, there is proof of additional benefit of ACE inhibitors on the risk of heart failure. With regard to the risk of stroke, in contrast, there is an indication of additional benefit of calcium antagonists in women of both ethnic groups (black and non-black group) and in black men. In patients with diabetes mellitus, there is an indication of additional benefit of ACE inhibitors on the risk of myocardial infarction.

- In the comparison with angiotensin-II antagonists, there is an indication of additional benefit of calcium antagonists on the risk of myocardial infarction. In contrast, there is an indication of additional benefit of angiotensin-II antagonists on the risk of heart failure.

For the *angiotensin-II antagonists* there were a total of 3 direct comparative trials. There were no comparative trials with diuretics or ACE inhibitors. The angiotensin-II antagonists used in the trials were eprosartan, losartan and valsartan.

- In the comparison with beta blockers, there is an indication that the angiotensin-II antagonists have an additional benefit on the mortality and heart failure outcomes in patients with diabetes mellitus; no such indication exists for non-diabetic patients. With regard to the total rate of strokes, there is an indication of additional benefit of beta blockers when compared to angiotensin-II antagonists in the black group; in the non-black group, however, there is an indication of additional benefit of angiotensin-II antagonists on the rate of strokes.

- In the comparison with calcium antagonists, there is an indication of additional benefit of calcium antagonists on the risk of myocardial infarction. In contrast, there is an indication of additional benefit of angiotensin-II antagonists on the risk of heart failure.

Regarding the incidence of diabetes, the data display an indication of a positive effect in favour of calcium antagonists when compared to diuretics, in favour of angiotensin-II antagonists when compared to beta blockers and calcium antagonists, and in the black group in favour of ACE inhibitors when compared to beta blockers. However, it is not possible to derive an additional benefit or harm from these results, particularly as they simply record changes in laboratory values. Furthermore, patients who developed diabetes mellitus while receiving diuretics during the course of the trial did not appear to be at any greater risk – at least during the trial – from a serious patient-relevant outcome. Corresponding data on beta blockers are lacking.

Conclusions

Diuretics are the only drug class not inferior to any other drug class in reducing hypertension complications and in individual aspects display additional benefit when compared to other antihypertensive drugs. In the overall results, therefore, diuretics can generally be considered the first-line therapy when considering the research question of this report.

Keywords: ACE inhibitors, angiotensin-II antagonists, antihypertensive drugs, beta blockers, calcium antagonists, diuretics, high blood pressure, hypertension, systematic review

The full report (in German) is available on www.iqwig.de/index.388.html