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Meta-analysis by Psaty BM et. al. in 1997 concluded that beta-blockers should be the first line therapy together with diuretics

The same authors, in the same journal in 2003 published an updated meta-analysis concluded that "for uncomplicated hypertension, beta-blockers should be considered a second-line antihypertensive agent." despite the fact that there has been no new outcome trials in hypertension with beta-blockers

Psaty BM. JAMA 1997;277: 739–745.

Psaty BM. JAMA 2003;289:2534–2544.

Systematic review of antihypertensive therapies: Does the evidence assist in choosing a first-line drug?

James M. Wright, MD, PhD; Cheng-Han Lee, BSc;
G. Keith Chambers, MD

Interpretation: Low-dose thiazide therapy can be prescribed as the first-line treatment of hypertension with confidence that the risk of death, coronary artery disease and stroke will be reduced. The same cannot be said for high-dose thiazide therapy, β-blockers, calcium-channel blockers or ACE inhibitors.

CMAJ • JULY 13, 1999; 161 (1)

The incidence of total cardiovascular events was lower in the thiazide group. Low-dose thiazide therapy can be prescribed as the first-line treatment of hypertension with confidence that the risk of death, coronary artery disease and stroke will be reduced. The same cannot be said for high-dose thiazide, BB, CCB or ACEI

Lancet 2004; 364: 1684–89

Bo Carlberg, Ola Samuelsson, Lars Hjalmar Lindholm

Interpretation

Our results cast doubts on atenolol as a suitable drug for hypertensive patients. Moreover, they challenge the use of atenolol as a reference drug in outcome trials in hypertension.

Articles

Atenolol in hypertension: is it a wise choice?

Bo Carlberg, Ola Samuelsson, Lars Hjalmar Lindholm

Summary

Background Atenolol is one of the most widely used β blockers clinically, and has often been used as a reference drug in randomised controlled trials of hypertension. However, questions have been raised about atenolol as the best reference drug for comparisons with other antihypertensives. Thus, our aim was to systematically review the effect of atenolol on cardiovascular morbidity and mortality in hypertensive patients.

Methods Reports were identified through searches of *The Cochrane Library*, MEDLINE, relevant textbooks, and by personal communication with established researchers in hypertension. Randomised controlled trials that assessed the effect of atenolol on cardiovascular morbidity or mortality in patients with primary hypertension were included.

Findings We identified four studies that compared atenolol with placebo or no treatment, and five that compared atenolol with other antihypertensive drugs. Despite major differences in blood pressure lowering, there were no outcome differences between atenolol and placebo in the four studies, comprising 6825 patients, who were followed up for a mean of 4·6 years: on all-cause mortality (relative risk 1·01 [95% CI 0·89–1·15]), cardiovascular mortality (0·99 [0·85–1·18]), or myocardial infarction (0·99 [0·85–1·19]). The risk of stroke, however, tended to be lower in the atenolol than in the placebo group (0·85 [0·72–1·01]). When atenolol was compared with other antihypertensives, there were no major differences in blood pressure lowering between the treatment arms. Our meta-analysis showed a significantly higher mortality (1·13 [1·02–1·25]) with atenolol treatment than with other active treatment, in the five studies comprising 17 671 patients who were followed up for a mean of 4·6 years. Moreover, cardiovascular mortality also tended to be higher with atenolol treatment than with other antihypertensive treatment. Stroke was also more frequent with atenolol treatment.

Interpretation Our results cast doubts on atenolol as a suitable drug for hypertensive patients. Moreover, they challenge the use of atenolol as a reference drug in outcome trials in hypertension.

Introduction

β blockers have long been considered to be well documented first-line drugs in the treatment of hypertension.[1] Moreover, atenolol is one of the most widely used β blockers clinically, and it has often been used as a reference drug in randomised controlled trials of hypertension.[2–4] Questions have been raised about β blockers as first-line treatment options in hypertension.[5] In the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial, losartan was shown to be more effective than atenolol in hypertensive patients with left ventricular hypertrophy.[6] Whether the result of the LIFE study was caused by a beneficial effect of losartan or a weak effect of atenolol on cardiovascular disease, or both, has been debated.[7] The effect of atenolol after myocardial infarction has also been questioned.[8] Hence, the aim of our investigation was to systematically review the effect of atenolol on cardiovascular morbidity and mortality in hypertensive individuals.

Methods

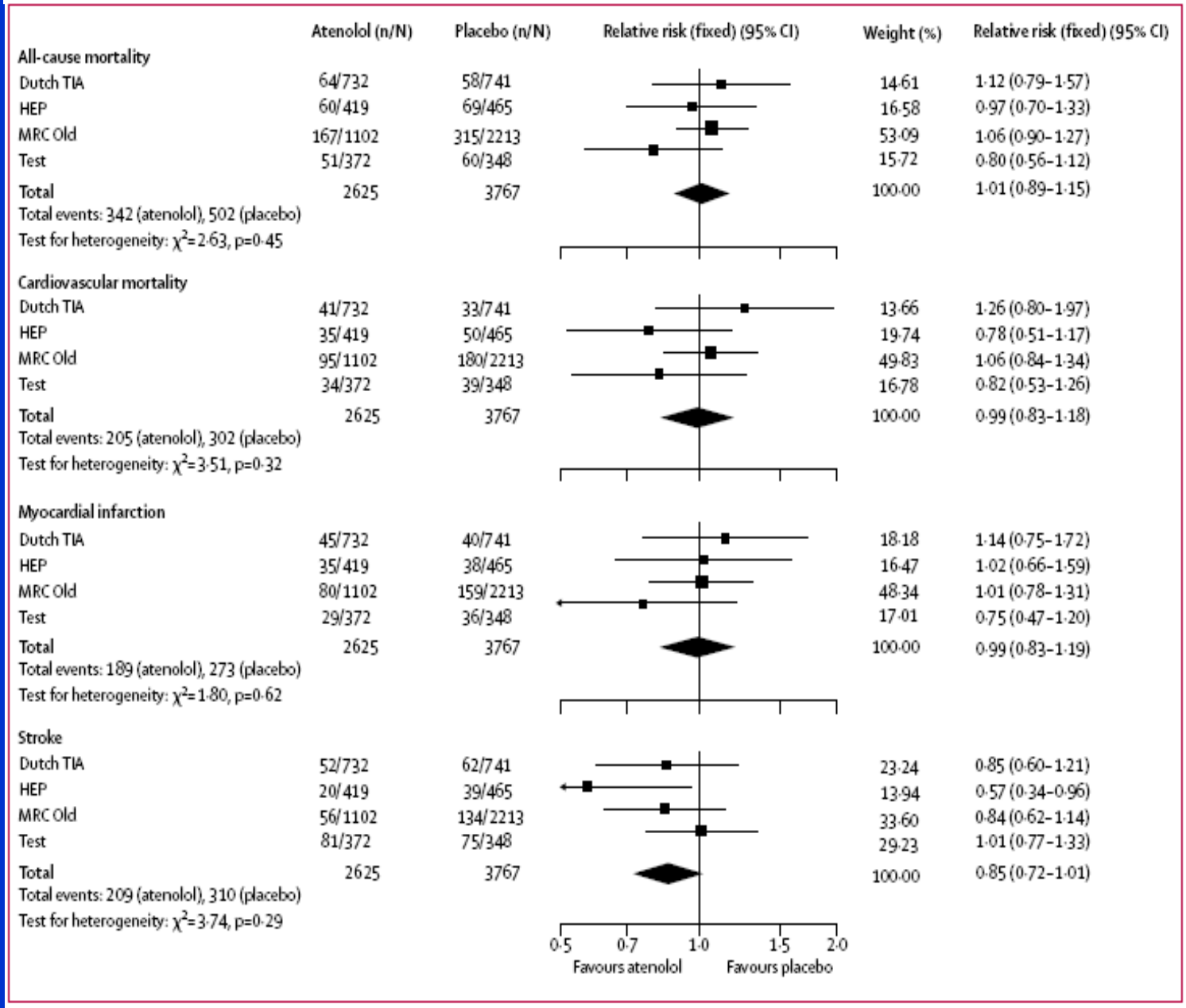
We reviewed randomised controlled trials that assessed the effect of atenolol on cardiovascular morbidity or mortality in patients with primary hypertension. Studies were identified though searching of *The Cochrane Library*, MEDLINE, textbooks, and by personal communication with established researchers in hypertension. The following keywords were used in the database search: atenolol (MESH) OR atenolol "text" AND cerebrovascular disorders (MESH) OR myocardial infarction (MESH); atenolol AND systematic; beta-blocker AND hypertension AND systematic.

The eligibility criteria for inclusion in the meta-analysis were: (1) primary hypertension, (2) randomised, controlled trial, (3) predefined criteria of myocardial infarction, stroke, and cardiovascular death, and (4) atenolol alone as the first-line drug in one of the treatment arms. Data from the studies that fulfilled the criteria were entered into the Cochrane Collaboration Review manager package (RevMan 4.2). Heterogeneity between the studies was assessed with χ^2 test and the chosen summary statistic variable was the reduction in relative risk.

Results

17 randomised controlled trials were identified in which atenolol was used in one of the treatment arms of hypertension (panel). Five studies were excluded since atenolol was one of two or more drug alternatives in the same treatment arm.[9–13] One was excluded since it compared multidrug strategies rather than individual agents.[14] Three studies were excluded since atenolol was an add-on drug.[15–17]

Outcome data for atenolol versus placebo or no treatment



Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

Summary

Background: β blockers have been used widely in the treatment of hypertension and are recommended as first-line drugs in hypertension guidelines. However, a preliminary analysis has shown that atenolol is not very effective in hypertension. We aim to substantially enlarge the data on atenolol and analyse the effect of different β blockers.

Methods: The Cochrane Library and PubMed were searched for β blocker treatment in patients with primary hypertension. Data were then entered into the Cochrane Collaboration Review Manager package and were summarised in meta-analyses. 13 randomised controlled trials (n=105 951) were included in a meta-analysis comparing treatment with β blockers with other antihypertensive drugs. Seven studies (n=27 433) were included in a comparison of β blockers and placebo or no treatment.

Findings: The relative risk of stroke was 16% higher for β blockers (95% CI 4–30%) than for other drugs. There was no difference for myocardial infarction. When the effect of β blockers was compared with that of placebo or no treatment, the relative risk of stroke was reduced by 19% for all β blockers (7–29%), about half that expected from previous hypertension trials. There was no difference for myocardial infarction or mortality.

Interpretation: In comparison with other antihypertensive drugs, the effect of β blockers is less than optimum, with a raised risk of stroke. Hence, we believe that β blockers should not remain first choice in the treatment of primary hypertension and should not be used as reference drugs in future randomised controlled trials of hypertension.

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Introduction

For three decades, β blockers have been widely used in the treatment of hypertension and are still recommended as first-line drugs in hypertension guidelines.[1,2] Moreover, after myocardial infarction and in patients with heart failure, treatment with β blockers prevents re-infarction, hospitalisation for heart failure, and premature death.[3,4] The effect of β blockers as a treatment for primary hypertension has been challenged.[5,6] A preliminary analysis has shown that atenolol is not very effective in hypertension.[6] To avoid unnecessary harm to patients, the role of other β blockers needs to be investigated. Here, we substantially enlarge the data on atenolol and analyse the effect of different β blockers on stroke, myocardial infarction, and mortality of all causes (n=127 879).

Methods

The eligibility criteria for inclusion in the present meta-analyses were: randomised controlled trial; treatment of primary hypertension; β blocker as first-line antihypertensive drug in at least 50% of all patients in one treatment group; and outcome data for all-cause mortality, cardiovascular morbidity, or both. Data were then entered into the Cochrane Collaboration review manager programme (RevMan version 4.2). Heterogeneity between the studies was assessed with χ^2 test and the chosen summary statistic variable was the reduction in relative risk (RR). When the p value for heterogeneity in any analysis was less than 0·10, the random model was used for calculations.

The studies were analysed in two main groups: studies comparing β blockers with other drugs in primary hypertension, and those comparing β blockers with placebo or no treatment. Data were analysed for all β blockers and for three subgroups: non-atenolol β blockers; mixed β blockers and diuretics when more than 50% of patients started on a β blocker; and atenolol. Data in all groups are provided for stroke, myocardial infarction, and death from all causes. Heart failure was not included since many trials did not have adequate data.

Search strategy and selection criteria

Initially, the Cochrane Library and PubMed were searched for systematic reviews of β blocker treatment in hypertensive patients (("adrenergic β antagonists" [MeSH Terms] OR "adrenergic β antagonists" [Pharmacological Action] OR β blocker [Text Word]) AND ("hypertension" [MeSH Terms] OR hypertension [Text Word]) AND ("classification" [MeSH Terms] OR systematic [Text Word])) or (("adrenergic β antagonists" [MeSH Terms] OR "adrenergic β antagonists" [Pharmacological Action] OR beta blocker [Text Word]) AND ("hypertension" [MeSH Terms] OR hypertension [Text Word]); limited to meta-analysis).

Thereafter, PubMed was searched for randomised controlled clinical trials (RCTs): ("hypertension" [MeSH Terms] OR hypertension [Text Word]) AND ("adrenergic β antagonists" [MeSH Terms] OR "adrenergic β antagonists" [Pharmacological Action] OR beta blocker [Text Word]) AND (("cerebrovascular disorders" [MeSH Terms] OR Cerebrovascular disorders [Text Word]) OR ("myocardial infarction" [MeSH Terms] OR myocardial infarction [Text Word])). Finally, we included the recently published ASCOT-BPLA trial[16] in the analyses.

Should BB remain first choice in the treatment of primary hypertension?

13 randomized controlled trials (n=105951) were included in a meta-analysis comparing treatment with BB with other antihypertensive drugs.

Seven studies (n=27433) were included in a comparison of BB and placebo or no treatment.

The relative risk of stroke was 16% higher for BB than for other drugs.

Lancet 2005; 366: 1545-53

Should β blockers remain first choice in the treatment of primary hypertension? A meta-analysis

Lars Hjalmar Lindholm, Bo Carlberg, Ola Samuelsson

Summary

Background: β blockers have been used widely in the treatment of hypertension and are recommended as first-line drugs in hypertension guidelines. However, a preliminary analysis has shown that atenolol is not very effective in hypertension. We aim to substantially enlarge the data on atenolol and analyse the effect of different β blockers.

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Findings: The relative risk of stroke was 16% higher for β blockers (95% CI 4–30%) than for other drugs. There was no difference for myocardial infarction. When the effect of β blockers was compared with that of placebo or no treatment, the relative risk of stroke was reduced by 19% for all β blockers (7–29%), about half that expected from previous hypertension trials. There was no difference for myocardial infarction or mortality.

Interpretation: In comparison with other antihypertensive drugs, the effect of β blockers is less than optimum, with a raised risk of stroke. Hence, we believe that β blockers should not remain first choice in the treatment of primary hypertension and should not be used as reference drugs in future randomised controlled trials of hypertension.

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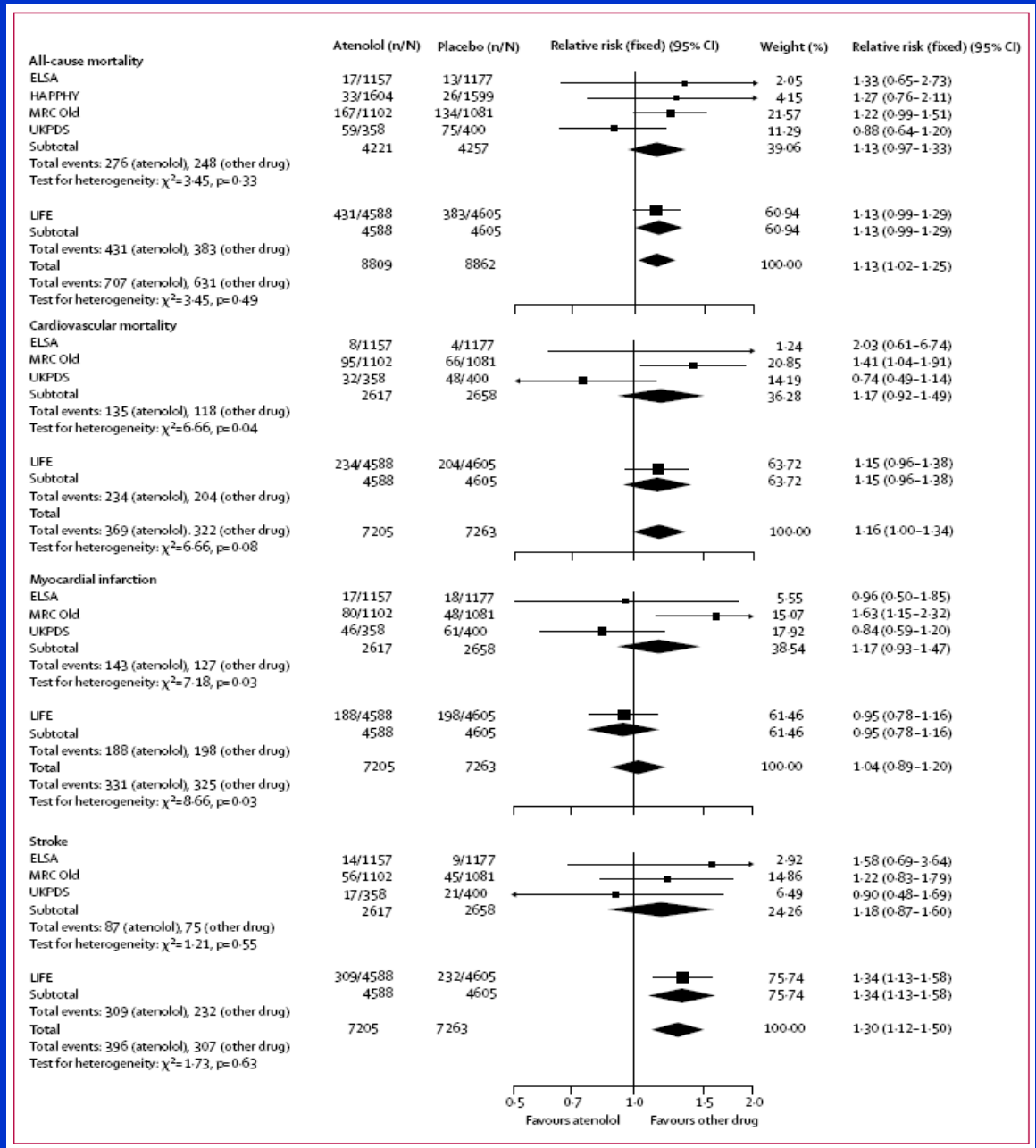
Outcome data for atenolol versus other antihypertensives

(95% CI)



Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial

*Björn Dahlöf, Peter S Sever, Neil R Poulter, Hans Wedel, D Gareth Beevers, Mark Caulfield, Rory Collins, Sverre E Kjeldsen, Arni Kristinsson, Gordon T McInnes, Jesper Mehlsen, Markku Nieminen, Eoin O'Brien, Jan Östergren, for the ASCOT investigators**

Summary

Background The apparent shortfall in prevention of coronary heart disease (CHD) noted in early hypertension trials has been attributed to disadvantages of the diuretics and β blockers used. For a given reduction in blood pressure, some suggested that newer agents would confer advantages over diuretics and β blockers. Our aim, therefore, was to compare the effect on non-fatal myocardial infarction and fatal CHD of combinations of atenolol with a thiazide versus amlodipine with perindopril.

Methods We did a multicentre, prospective, randomised controlled trial in 19 257 patients with hypertension who were aged 40–79 years and had at least three other cardiovascular risk factors. Patients were assigned either amlodipine 5–10 mg adding perindopril 4–8 mg as required (amlodipine-based regimen; n=9639) or atenolol 50–100 mg adding bendroflumethiazide 1·25–2·5 mg and potassium as required (atenolol-based regimen; n=9618). Our primary endpoint was non-fatal myocardial infarction (including silent myocardial infaction) and fatal CHD. Analysis was by intention to treat.

Findings The study was stopped prematurely after 5·5 years' median follow-up and accumulated in total 106 153 patient-years of observation. Though not significant, compared with the atenolol-based regimen, fewer individuals on the amlodipine-based regimen had a primary endpoint (429 *vs* 474; unadjusted HR 0·90, 95% CI 0·79–1·02, p=0·1052), fatal and non-fatal stroke (327 *vs* 422; 0·77, 0·66–0·89, p=0·0003), total cardiovascular events and procedures (1362 *vs* 1602; 0·84, 0·78–0·90, p<0·0001), and all-cause mortality (738 *vs* 820; 0·89, 0·81–0·99, p=0·025). The incidence of developing diabetes was less on the amlodipine-based regimen (567 *vs* 799; 0·70, 0·63–0·78, p<0·0001).

Interpretation The amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen. On the basis of previous trial evidence, these effects might not be entirely explained by better control of blood pressure, and this issue is addressed in the accompanying article. Nevertheless, the results have implications with respect to optimum combinations of antihypertensive agents.

Interpretation: The amlodipine-based regimen prevented more major cardiovascular events and induced less diabetes than the atenolol-based regimen.

- A number of studies have indicated that beta-blockers as a class are not as effective as other antihypertensive drug classes in the prevention of cardiovascular events, and several meta-analyses of major clinical trials in hypertension, most notably by Prof. Lars H. Lindholm and Franz H. Messerli have concluded that beta blockers should not be used as first-line therapy in primary hypertension

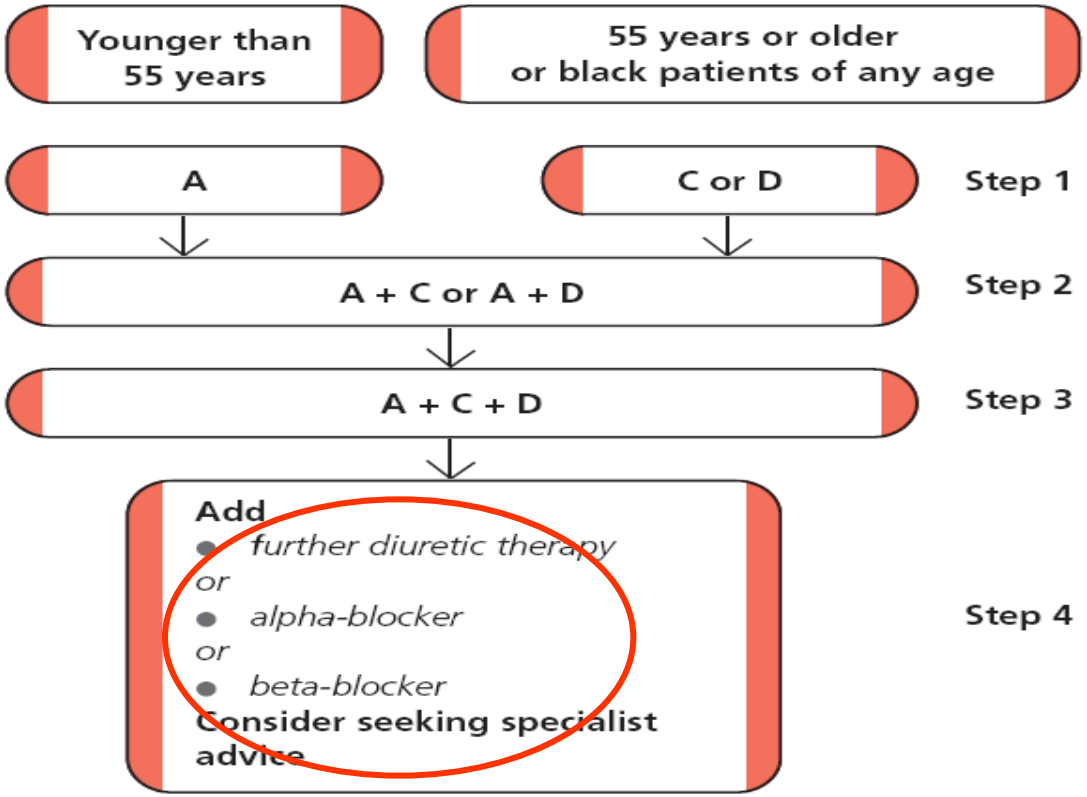
- The guidelines for the management of hypertension in the United Kingdom were recently updated, removing beta-blockers as initial therapy for hypertension in patients without compelling indications.

BHS-NICE Guideline 2006

Choosing drugs for patients newly diagnosed with hypertension

Abbreviations:
A = ACE inhibitor
(consider angiotensin-II receptor antagonist if ACE intolerant)
C = calcium-channel blocker
D = thiazide-type diuretic

Black patients are those of African or Caribbean descent, and not mixed-race, Asian or Chinese patients



BHS

NHS National Institute for Health and Clinical Excellence

AJH 2003; 16:870–873

Brief Communications

β-Blockers in Hypertension—The Emperor Has No Clothes: An Open Letter to Present and Prospective Drafters of New Guidelines for the Treatment of Hypertension

Franz H. Messerli, D. Gareth Beevers, Stanley S. Franklin,
and Thomas G. Pickering

Clearly, the time has come to admit that the emperor has no clothes

and

That beta –blockers should no longer be considered appropriate as first-line therapy in the treatment of uncomplicated hypertension.

The Emperor's New Clothes

Hans Christian Andersen fairy tale

The emperor was parading through the streets of the city to show off to an admiring crowd his celebrated "new clothes." Suddenly a small child cried out, "But the Emperor has nothing on!" And the Emperor stiffened for he knew it was true. "Nonetheless," he thought, "the procession must go on." And so he continued to walk, holding himself more proudly than ever while the chamberlains held up a train made of cloth that had never been there at all!"

THANK YOU