

Management of hypertension

Evidence from the Blood Pressure Lowering Treatment Trialists' Collaboration and from major clinical trials

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KEY WORDS

absolute risk, blood pressure lowering, combination therapy, management of hypertension, total cardiovascular risk

ABSTRACT

Deciding who to treat should be based on estimation of the total cardiovascular risk, not just the blood pressure (BP), so that patients with established cardiovascular disease or at high risk of cardiovascular disease should have their BP lowered even though it may be in the "normal range".

Drug treatment should build upon effective lifestyle measures. Meta-analyses from the Blood Pressure Lowering Treatment Trialists' Collaboration have shown that differences between drug classes are quite small, even across different age groups, compared to the benefits of maximizing the reduction in BP, especially the systolic pressure. The major guidelines now recommend a focus on building effective drug combinations rather than arguing about which drug to use, and they approve initiation of treatment with combinations in high risk groups. While clinical trials have demonstrated some differences in the efficacy of individual drug classes in reducing cause specific outcomes such as coronary disease, stroke or heart failure, there are still very few comparisons between drug combinations. Our own preferred combinations include angiotensin converting enzyme inhibitors (ACEI) and diuretics, which comprise my first choice for Caucasians and Asians, and angiotensin receptor blockers (ARB) which are best used with diuretics when ACEI are not tolerated. ACEI and calcium channel blockers (CCB) are also very effective and CCB and diuretics are preferred for black subjects or those with isolated systolic hypertension. Combinations to avoid in patients with uncomplicated hypertension include ACEI and β -blockers and ACEI and ARBs, since their beneficial effects are not additive.

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Received: February 21, 2009.

Accepted: February 21, 2009.

Conflict of interest: John Chalmers has received research grants from Servier, administered through the University of Sydney, as Principal Investigator for ADVANCE and PROGRESS. He has also received honoraria from Servier, Daiichi and Pfizer for speaking at Scientific Meetings in the past 3 years.

Pol Arch Med Wewn. 2009;

119 (6): 373-380

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INTRODUCTION The management of hypertension remains a much debated subject particularly when it comes to the choice of blood pressure (BP) lowering drugs. This is despite a vast body of evidence that has accumulated from randomized clinical trials as well as from observational studies and other modalities of clinical research. This is reflected in the growing length and complexity of the major guidelines which have grown from <10 pages to close to 100 pages.¹⁻³ Accordingly, we will not attempt a comprehensive review of the subject, but instead will provide a personal view focussing on 2 key decisions the practicing physician must make when faced with a patient with hypertension or with BP related disease – "Who to treat?" and "How to treat?". This paper will not deal with other important issues

such as the diagnosis and exclusion of secondary causes of hypertension, investigation and management of target organ damage, or specific regimens indicated for a variety of important groups such as the very young, the elderly, those with pregnancy hypertension, or those with renal disease or with diabetes.

Who to treat One major issue that has emerged over the past 2 decades is that serious BP related disease extends beyond populations that fit the usual definition of hypertension.⁴⁻⁶ As demonstrated by MacMahon et al. in 1990 for diastolic pressure and confirmed by others for systolic BP (SBP), the risk of stroke and coronary heart disease is strongly and continuously related to the level of BP, well into the normal range

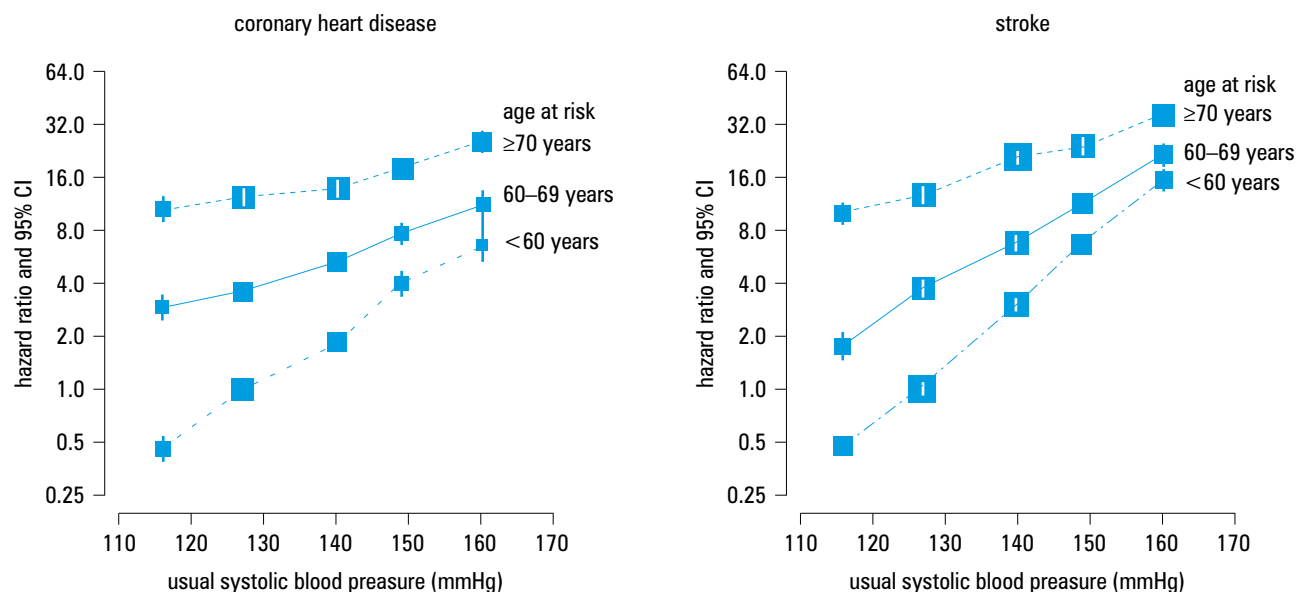


FIGURE 1 Risk of coronary heart disease and stroke against usual blood pressure by age group

Data from Asia Pacific Cohort Studies Collaboration showing continuous association of blood pressure with the incidence of coronary heart disease and stroke in 3 different age groups.⁸ Solid boxes represent estimates of relative risk of stroke; areas of the boxes are proportional to the inverse variance; vertical lines represent 95% CI. Reproduced from the Journal of Hypertension⁸ with permission from the Wolters Kluwer Health.

(FIGURE 1).^{5,7,8} The World Health Organization (WHO) Report 2002 confirmed that a substantial proportion of the burden of BP related disease extended down to a SBP of the order of 115 mmHg, which was termed “optimal” SBP,⁴ well below the usual definition of hypertension starting with a SBP above 140 mmHg.^{1–3} More recently this has been quantified to demonstrate that approximately half of the total burden of BP related disease occurs in individuals whose SBP is below 140 mmHg, and thus in the so-called “normal range” (FIGURE 2).⁶ This means that if we persist in discussing “The Treatment of Hypertension”, we ignore half of the population that might benefit from BP lowering treatment. Therefore we should address our efforts to “Blood Pressure Lowering” which will include those with normal BP, but with BP related disease.⁹

The major categories of patients who fall into this group are those with established cardiovascular disease, including those with previous stroke, heart attack, or heart failure, and those with high cardiovascular risk particularly patients with diabetes or renal disease, and patients with multiple risk factors such as raised cholesterol, smoking and advanced age.^{1–3} The evidence to support this view has come from major clinical trials that have substantiated the hypotheses based on observational studies. Thus, the HOPE (Heart Outcomes Prevention Evaluation), the PROGRESS (Perindopril Protection Against Recurrent Stroke Study) and the ADVANCE trials (Action in Diabetes and Vascular Disease: Preterax and Diamicon MR Controlled Evaluation) have clearly shown that patients with high cardiovascular risk or established cardiovascular disease benefit from BP lowering treatment, whatever their initial BP, and regardless of whether they were hypertensive or normotensive.^{10–12} For the HOPE trial this was in relation to high risk patients, predominantly those with coronary heart disease.¹⁰ For the PROGRESS trial this was for patients with cerebrovascular disease, whether stroke or

transient ischemic attack¹¹ and for ADVANCE this was for patients with type 2 diabetes.¹²

The concept of treating those with established cardiovascular disease, diabetes and renal disease at BP levels well below the standard definitions of hypertension is now widely accepted and indeed recommended by the major treatment guidelines.^{1–3} Thus, the recommendations of the Joint Task Force of the European Societies of Hypertension and Cardiology¹ clearly state that all patients should be classified in terms of their total cardiovascular risk – the absolute risk – and they set out a comprehensive scheme (FIGURE 2 of these guidelines) indicating the various BP thresholds for the initiation of treatment, that might apply to patients with different degrees of total or absolute cardiovascular risk.¹

Furthermore, the WHO and the International Society of Hypertension have produced risk tables for men and women from many different parts of the world, setting out the combinations of risk factors that will predict a range of probabilities that the individual may suffer a major cardiovascular event within 10 years.¹³ These risk tables are now available for a large number of individual countries, including Poland and all practicing clinicians who manage patients with BP related disease should use these in their daily practice.¹⁴

The importance of changing our approach is underlined by the failure of the current paradigm, “treating hypertension”, to control the burden of “hypertension”, let alone that of BP related disease. As indicated earlier, this approach only addresses half the global burden, but as the rule of halves still applies in most parts of the world, only about half of those with “hypertension” are detected, only half are treated, and only half of those treated have their BP controlled to recommended levels.^{1–3,15–17} Thus <10% of the global population that could benefit from BP lowering is treated effectively at the present time.

New approaches, founded on addressing the total burden of BP related disease need a 2-pronged

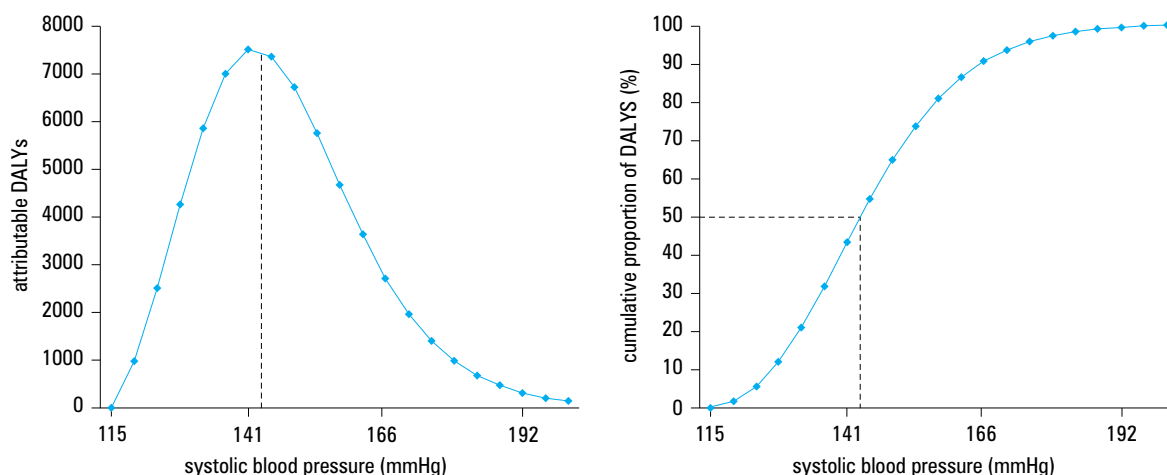


FIGURE 2 Distribution of cardiovascular disease burden attributable to blood pressure

Data from Reference 6 showing distribution of the estimated cardiovascular disease burden (in DALYs) attributable to blood pressure, by exposure levels.

approach combining a population-based preventive strategy, with a clinical treatment strategy. The population strategy should intensify non-drug (lifestyle) intervention programs that will reduce BP levels across the whole population, including measures such as reduction of dietary salt, increase in physical activity and combating overweight and obesity.

The clinical or so called “high risk” strategy plainly requires that BP lowering treatment is implemented on the basis of the individual’s total or absolute level of cardiovascular risk, not just the level of BP, and that other risk factors present are also addressed. Furthermore, this requires substantial improvement in hypertension-based efforts, including better detection, better application of current treatments and some new treatments in order to lower the pressure towards optimal levels, below the minimum targets.

How to treat While this paper will focus on the use of BP lowering drugs, it must be stressed that good control of BP is based on a foundation of effective lifestyle measures including attention to body weight, exercise and dietary salt.

Evidence from the Blood Pressure Lowering Treatment Trialists’ Collaboration There is now a vast body of evidence, accompanied by a huge weight of literature, on the merits and relative merits of various classes of BP lowering drugs and of a host of individual drugs drawn from these classes. This literature and evidence is captured in the many comprehensive national and international guidelines that are continuously updated and published.^{1–3,18–20} One convincing distillation of this evidence comes from the meta-analyses of Blood Pressure Lowering Treatment Trialists’ Collaboration.^{21–26}

These analyses and reports clearly demonstrate that when pooling the bulk of the available evidence, for example for the prevention of the broadest outcome, “major cardiovascular events”, which includes fatal and non-fatal heart attack, stroke and heart failure, the efficacy

of the various drug classes is almost identical, even across different age groups (FIGURE 3).^{21–23,25}

Some differences do emerge for cause specific outcomes such as coronary heart disease, stroke and heart failure (FIGURE 3). Thus, the Trialists’ analyses demonstrate a possible small advantage of the order of 7–12% for Calcium Channel Blockers (CCB) in preventing stroke²² and a clear and much greater disadvantage for CCBs of the order of 20–30% for the prevention of heart failure (FIGURE 3).²² The collaboration has also demonstrated that angiotensin converting enzyme inhibitors (ACEI) have BP independent benefits for the prevention of coronary heart disease, a property not shared by Angiotensin Receptor Blockers (ARB) or other classes of drug.²⁴

There has also been much debate about the role of the older classes of drugs, the diuretics and β -blockers, in part driven by their adverse metabolic effects^{1–3} but also in part by suggestions that β -blockers are less effective in preventing cardiovascular disease, particularly in older subjects.^{27,28} Indeed this has led to revision of the British recommendations so that the National Institute for Health and Clinical Excellence (NICE) guidelines no longer list β -blockers among first-line classes for uncomplicated hypertension.¹⁸ The Canadian recommendations retain β -blockers among first line agents for general use, but clearly state they are no longer first line for patients >60 years of age.¹⁹ On the other hand, the recent paper from the Trialists’ Collaboration on the influence of age suggests that there is very little to choose between diuretics and β -blockers, when compared with ACEI or CCB, either jointly or separately.²⁵

Despite any differences that may be present, it is evident that there is much more to be gained by combining drugs to maximize the reduction in BP than there is by arguing about the minor advantages of one class over another.

Evidence from individual trials While meta-analyses have many advantages, particularly the greater precision and power derived from pooling large volumes of data, they also have limitations. These include pooling patients from

different populations with differences in risk profile, in underlying disease, in the study drugs and dosages used in treatment, and in concomitant non-study drugs used in the various trials. On the other hand, individual trials also suffer from limitations, including limited power due to smaller sample size, and difficulties in achieving similar BP reductions with different regimens in head-to-head comparisons. Some of the largest and most significant trials have provided evidence of differences between regimens, but these too suffer from differences in the BP reductions achieved.^{27,29,30}

For example, ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) suggested that diuretics were superior to ACEI in preventing stroke, but this was at least in part attributable to a 2 mmHg greater reduction in SBP obtained with the diuretics in the overall population, with a 4 mmHg greater drop in the black subgroup that made up 30% of the population.²⁹ In contrast, the landmark ASCOT trial (Anglo-Scandinavian Cardiac Outcomes) trial reported a significant disadvantage for a diuretic – β -blocker regimen compared to an ACEI-CCB regimen, but this too was partly attributable to a 3 mmHg greater reduction in SBP achieved with the ACEI-CCB combination.²⁷ Similarly, in the ACCOMPLISH trial (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension), a benefit for the prevention of cardiovascular events seen with an ACEI-CCB regimen compared to an ACEI – diuretics regimen, was in part explained by a greater reduction of close to 1 mmHg in SBP.³⁰ Thus, both meta-analyses and individual trials have their limitations.

Comparison of ACEI and ARB: ONTARGET, TRANSCEND, ProFESS Two of the most keenly awaited trials were those comparing ACEI and ARB in a head to head randomized trial – ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint), and comparing an ARB to placebo in hypertensive patients – TRANSCEND (Telmisartan Randomized Assessment Study in ACE-intolerant Subjects with Cardiovascular Disease).^{31,32} ONTARGET compared the ACEI, ramipril and the ARB, telmisartan, and also compared the combination of the two together against ramipril alone in high risk hypertensive patients. The head to head comparison of ramipril and telmisartan established that there was very little difference, though there was a suggestion of slight advantage to the ACEI for the prevention of myocardial infarction and to the ARB for the prevention of stroke.³¹ On the other hand, comparison of telmisartan with placebo in hypertensive patients who were intolerant of ACEI, could not demonstrate a clear benefit of telmisartan for the primary composite outcome.³² In a parallel trial in patients with cerebrovascular disease ProFESS (Prevention Regimen For Effectively avoiding Second Strokes), there was no clear advantage for telmisartan compared to placebo for the prevention of recurrent stroke.³³ Taken together, these 3 trials suggest that ARB should only be preferred when hypertensive patients are intolerant of ACEI.

The other important finding from ONTARGET was that the combination of telmisartan and ramipril conferred no benefit whatsoever for the prevention of cardiovascular end points compared to ramipril alone but that on the other hand, the combination did cause a significant and substantial increase in renal adverse events.³¹ Thus, it

FIGURE 3 Comparisons of blood pressure lowering regimens based on different drug classes

Data from Blood Pressure Lowering Trialists' Collaboration showing comparison of the effects of different blood pressure lowering regimens on major cardiovascular events, coronary heart disease, stroke and heart failure.²² Diamonds represent estimates of relative risk and 95% CI. Adapted from the Lancet²² with permission from the Elsevier.

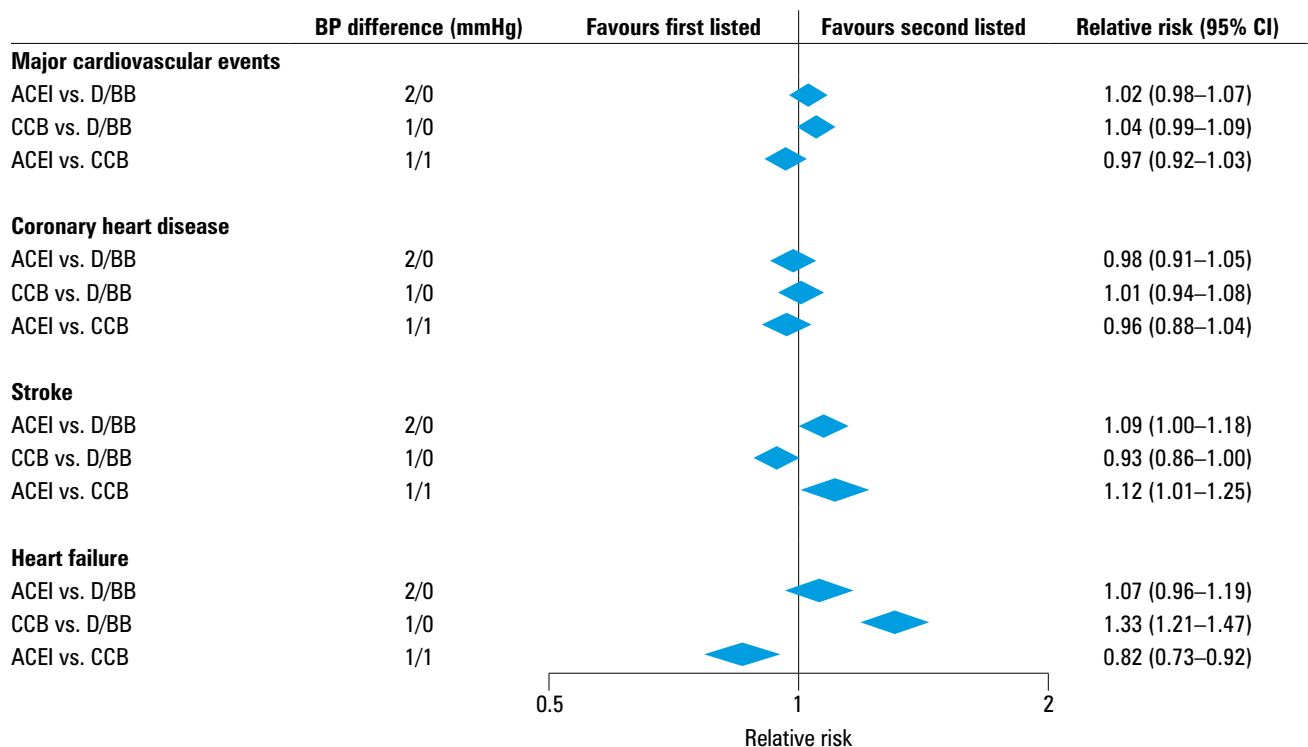


TABLE 1 Recommendations from ESH/ESC guidelines 2007¹

Treat according to total (absolute) cardiovascular risk, not just blood pressure
Emphasis on first choice drug outdated
Due to dominant importance of combination therapy in majority
Tailor the choice to suit the patient
Can initiate therapy with combinations including fixed combinations

is clear that ACEI and ARB do not constitute a first line combination for the management of patients with hypertension and it is our own personal view that this combination is best avoided for patients with uncomplicated hypertension.

Main messages and recommendation The main conclusions that can be drawn from the available evidence today are that:

The key lies in effective reduction of the SBP, accordingly to the absolute or total cardiovascular risk in each patient.

Differences between drug classes are likely to be small, even across different age groups, compared to the benefits of maximizing BP reduction.

Building effective combinations to reduce BP more effectively is more important than continuing to argue about which drug to use for initiating treatment.

Importance of combination therapy These themes are highlighted by the European Society

of Hypertension/European Society of Cardiology guidelines (**TABLE 1**). Indeed these guidelines have a figure (**FIGURE 3** in the original publication) presenting an algorithm for treatment that indicates that for patients with high cardiovascular risk or very high BP, drug treatment should be initiated with a two drug combination at low dose, building up to a higher dose if necessary, or adding a third drug.¹ The other major guidelines all have similar recommendations emphasizing the importance of combination therapy, including the use of fixed-dose or “single pill” combinations that serve to enhance adherence and efficacy.^{1-3,18-20}

Place of major drug classes Our views on the place of the major drug classes are summarized in **TABLE 2**. In essence, we recommend that ACEI, ARB, CCB and diuretics should all be regarded as first line groups. However, our own preference would be to use ARBs when ACEI are not tolerated, since they are clearly not superior,³¹ recent trials against placebo have thrown some doubt on their efficacy^{32,33} and they are more expensive. Caveats include the limitations of ACEI in black subjects, where β -blockers are also less effective, but diuretics and CCB are very effective and should be preferred. Diuretics are very effective in combinations with all the other drug classes, and although there is clear evidence that they have unwanted metabolic effects there is no convincing evidence that they are less effective in the prevention of major cardiovascular events. For these reasons, I would definitely keep diuretics among my first line preferences (**TABLE 2**).^{21-23,25,29}

The place of β -blockers is clearly under a cloud at present^{27,28} though the Blood Pressure Trialists' Collaboration has not found much evidence to confirm the suggestion they are inferior either when used in combination with diuretics^{21-23,25} or when used alone.²⁵ At present my recommendation would be to retain their use in patients who are on them already and whose pressure is well controlled. We would also maintain their use as first line for patients with coronary heart disease and with heart failure. Otherwise, I would recommend keeping β -blockers in reserve for situations where other drugs are not well tolerated. In these situations, they can be used in combination with diuretics or with dihydropyridine CCBs, with which their effects on BP are additive.

Building effective combinations Most of the evidence regarding effective combinations of BP lowering drugs is based on surrogate end points, particularly on the extent to which both elements in a two drug combination contribute to lowering the BP; that is on the extent to which their BP lowering effects are truly additive and independent.³⁴

In this respect, it is clear that drugs that block the renin-angiotensin system (ACEIs and ARBs) combine very well with diuretics where the drugs have complementary actions and each helps

TABLE 2 Personal recommendations: place of drug classes

ACEI	first line (less effective in blacks) good in combinations (but not with β -blockers)
ARB	first line? best when ACEI not tolerated
CCB	first line good in blacks and for isolated systolic hypertension
β -blockers	under a cloud (fully deserved?) first line for coronary heart disease and heart failure
diuretics	still first line excellent foundation for combinations

Abbreviations: ACEI – angiotensin converting enzyme inhibitors, ARB – angiotensin receptor blockers, CCB – calcium channel blockers

TABLE 3 Personal recommendations: combination therapy

Preferred combinations	
ACEI + diuretic	first choice for Caucasian/Asians
ACEI + CCB	very effective
ARB + diuretic	very effective (especially if ACEI not tolerated)
CCB + diuretic	first choice for blacks and isolated systolic hypertension
diuretic + β -blocker	second line but still effective and additive
Combinations to avoid	
ACEI + β -blocker	not additive
ACEI + ARB	excess renal adverse events

Abbreviations: see **TABLE 2**

to limit the side effects of the other.³⁴ Another well tried and effective combination is that of ACEI and CCB.³⁴ The combination of diuretics and β -blockers is also well tried and effective in this respect, though the combination of diuretics and CCBs has been questioned in the past, with suggestions that their blood pressure lowering actions may not be fully additive.³⁵ On the other hand, most guidelines recommend the combination of diuretics and CCBs in black subjects and in subjects with isolated systolic hypertension where they are both known to be effective.¹⁻³

There is much less evidence comparing the efficacy of different combinations in reducing hard cardiovascular endpoints, although this is slowly starting to emerge with ASCOT-blood pressure-lowering arm (BPLA) (comparing ACEI and CCB against diuretics and β -blockers) and ACCOMPLISH (comparing ACEI and diuretics against ACEI and CCB).^{27,30}

Our own personal preferences for combination therapy are summarized in [TABLE 3](#). In my view the best tried combination and my preferred one for Caucasian and Asian populations is that of ACEI and diuretics. It is clear that ARB and diuretics are also effective, though I would prefer to use this combination when ACEI are not well tolerated. The combination of ACEI and CCB is also very effective, as confirmed by ASCOT-BPLA and ACCOMPLISH,^{27,30} but I would await further evidence before preferring this combination to that of ACEI and diuretic. As mentioned earlier, the combination of diuretics and CCB is very effective in black subjects and in isolated systolic hypertension and should be preferred in these situations. Next comes the vexed question of the old and well tried combination of diuretics and β -blockers. Plainly if a patient is well controlled on this combination it should be maintained, but at present I could regard it as second line for the initiation of treatment and keep it in reserve for situations where other combinations are not well tolerated or not very effective ([TABLE 3](#)).

Finally, there are 2 combinations that I would avoid as first line therapy in patients with uncomplicated hypertension and only keep as second line for situations where other combinations are not effective or not well tolerated. These are firstly ACEI and β -blockers, where the actions of the 2 classes in lowering BP are not fully independent nor fully additive,³⁴ and secondly ACEI and ARBs, where the results from ONTARGET clearly indicate this combination has no advantage in preventing hard outcomes, but clear disadvantage in the greater frequency of renal adverse events ([TABLE 3](#)).³¹

CONCLUSIONS Decisions to institute BP lowering therapy should be based on the patients total (absolute) cardiovascular risk, not just on the level of BP. This means that many patients with high risk, who do not fulfill the usual criteria for diagnosis of hypertension, should be treated with BP

lowering drugs. It is also important to manage all cardiovascular risk factors, such as cigarette smoking, raised cholesterol, overweight or hyperglycemia and not just the BP. A multifactorial approach of this nature, as used in the STENO-2 trial³⁶ has produced enviable reductions in cardiovascular morbidity and mortality and provides a very good model for the practicing physician.

The key to good management of BP related disease lies in building good combinations of BP lowering drugs, so as to maximize the effective reduction of SBP. This is much more important than continuing to debate the choice of drug to initiate treatment, since most patients will require combination therapy for effective BP control. Combination therapy, including fixed-dose combinations, should be used to initiate treatment in high risk patients with BP related disease.

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Leczenie nadciśnienia tętniczego

Dane z Blood Pressure Lowering Treatment Trialists' Collaboration i z dużych badań klinicznych

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SŁOWA KLUCZOWE

całkowite ryzyko
sercowo-naczyniowe,
ryzyko całkowite,
obniżanie ciśnienia
krwi, terapia
nadciśnienia, terapia
skojarzona

STRESZCZENIE

Proces podejmowania decyzji o tym, kogo leczyć, powinien być oparty na oszacowaniu całkowitego ryzyka sercowo-naczyniowego, a nie jedynie samej wartości ciśnienia tętniczego krwi, aby pacjenci z rozwiniętą chorobą sercowo-naczyniową lub będący w grupie ryzyka mieli obniżane ciśnienie, nawet jeśli jego wartość może znajdować się w „zakresie normy”.

Leczenie farmakologiczne powinno bazować na pomiarach efektywnego trybu życia. Metaanalizy przeprowadzone w badaniu Blood Pressure Lowering Treatment Trialists' Collaboration wykazały, że różnice pomiędzy klasami leków są niewielkie, nawet pomiędzy różnymi grupami wiekowymi, w porównaniu do korzyści maksymalizacji redukcji ciśnienia tętniczego, a w szczególności ciśnienia skurczowego. Obecnie wytyczne zalecają skupienie się na łączeniu leków, a nie na rozważaniu, którego leku użyć. Popierają one rozpoczęcie leczenia za pomocą kombinacji leków w grupach wysokiego ryzyka. Próby kliniczne wykazały pewne różnice w skuteczności pojedynczych grup leków w zmniejszaniu powikłań takich jak choroba niedokrwienna serca, udar lub niewydolność serca, nadal jednak brak porównania pomiędzy kombinacjami leków.

Preferowana przez nas kombinacja to inhibitory konwertazy angiotensyny (*angiotensin converting enzyme inhibitors* – ACEI) i diuretyki, które są lekami pierwszego wyboru dla rasy białej i Azjatów, oraz antagoniści receptora angiotensyny (*angiotensin receptor blockers* – ARB), które najlepiej stosować z diuretykami w przypadku gdy ACEI nie są tolerowane. ACEI i leki blokujące kanał wapniowy (*calcium channel blockers* – CCB) są także bardzo efektywne, a CCB i diuretyki są bardziej preferowane w przypadku pacjentów czarnoskórych lub tych z izolowanym ciśnieniem skurczowym. U pacjentów z niepowikłanym nadciśnieniem tętniczym należy unikać takich kombinacji jak ACEI i β -blokerzy oraz ACEI i ARB, jako że ich korzystne działania nie sumują się.

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Praca wpłynęła: 21.02.2009.
Przyjęta do druku: 21.02.2009.
Zgłoszono sprzeczność interesów:
jako naukowiec nadzorujący
badania ADVANCE i PROGRESS,
John Chalmers uzyskał grant
na prowadzenie badań od firmy
Servier, zarządzany przez
Uniwersytet w Sydney. Otrzymał
on także honoraria od firm Servier,
Daiichi i Pfizer za wykłady podczas
zjazdów naukowych w ciągu
ostatnich 3 lat.
Pol Arch Med Wewn. 2009;
119 (6): 373-380
Tłumaczyła Agata Kalemba
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Kraków 2009