Recommendation 5

**Should any of the drug groups (thiazide diuretics, ACE inhibitors, CCB, ARB or beta-blockers) be recommended to adult patients with confirmed hypertension as a preferred initial therapy?**

<u>Critical outcomes</u> – as per outcomes table of the scope (mortality, morbidity, cost, BP control, safety etc.)

There is moderate quality evidence available about the effects of all major antihypertensive drug groups on clinical outcomes in comparison with placebo and moderate to good quality evidence is available on selected head to head comparisons.

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<u>Active treatment versus placebo</u>
A meta-analysis of 24 placebo-controlled RCT-s in first-line treatment of hypertension including 58,040 patients identified the following effects:
- Thiazides (19 RCTs) reduced mortality (RR 0.89, 95% CI 0.83, 0.96), stroke (RR 0.63, 95% CI 0.57, 0.71), CHD (RR 0.84, 95% CI 0.75, 0.95) and CVS (RR 0.70, 95% CI 0.66, 0.76). Low-dose thiazides (8 RCTs) reduced CHD (RR 0.72, 95% CI 0.61, 0.84), but high-dose thiazides (11 RCTs) did not (RR 1.01, 95% CI 0.85, 1.20).
- Beta-blockers (5 RCTs) reduced stroke (RR 0.83, 95% CI 0.72, 0.97) and CVS (RR 0.89, 95% CI 0.81, 0.98) but not CHD (RR 0.90, 95% CI 0.78, 1.03) or mortality (RR 0.96, 95% CI 0.86, 1.07).
- ACE inhibitors (3 RCTs) reduced mortality (RR 0.83, 95% CI 0.72-0.95), stroke (RR 0.65, 95% CI 0.52-0.82), CHD (RR 0.81, 95% CI 0.70-0.94) and CVS (RR 0.76, 95% CI 0.67-0.85).
- Calcium-channel blocker (1 RCT) reduced stroke (RR 0.58, 95% CI 0.41, 0.84) and CVS (RR 0.71, 95% CI 0.57, 0.87) but not CHD (RR 0.77 95% CI 0.55, 1.09) or mortality (RR 0.86 95% CI 0.68, 1.09). No RCTs were found for ARBs or alpha-blockers.

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<u>ACE inhibitors versus calcium-channel blockers</u>
A meta-analysis of three studies comparing ACE inhibitors with calcium-channel blockers (CCBs) showed that ACE inhibitors were associated with a higher incidence of stroke (RR 1.14, 95% CI 1.02 to 1.28) but a lower incidence of new-onset diabetes (RR 0.85, 95% CI 0.75 to 0.98) and heart failure (RR 0.85, 95% CI 0.78 to 0.93). No significant difference was found for mortality.
For MI there was substantial heterogeneity among the studies. Two studies found no significant difference between study drugs in terms of MI incidence, while a third study found that ACE inhibitors were associated with a reduced incidence of MI (RR 0.77, 95% CI 0.62 to 0.96).
Of the two studies reporting the outcomes of unstable angina and revascularisation procedures, neither found any significant difference.
The two studies that reported the frequency of study drug withdrawals each found ACE inhibitors to be associated with more withdrawals than CCBs (respectively: RR 1.17, 95% CI 1.12 to 1.23; RR 1.14, 95% CI 1.06 to 1.24).

<u>ARBs versus calcium-channel blockers</u>
One study was found comparing ARBs with CCBs when used as first-line antihypertensive therapy. ARBs were associated with a higher incidence of MI compared to CCBs (RR 1.17, 95% CI 1.01 to 1.36). There was no significant difference in stroke reduction, mortality or incidence of heart failure.
The study also reported frequencies of adverse events for each drug class and showed several differences, but overall these did not particularly favour either drug. Pre-specified adverse events for ARBs versus CCBs included peripheral oedema (14.9% versus 32.9%, p<0.0001), dizziness (16.5% versus 14.3%, p<0.0001) and headache (14.7% versus 12.5%, p<0.0001). Additional adverse events identified included diarrhoea (8.8% versus 6.8%, p<0.0001), serious cases of angina (4.4% versus 3.1%, p<0.0001) and syncope (1.7% versus 1.0 %, p<0.0001).

<u>ACE inhibitors versus thiazide-type diuretics</u>
A meta-analysis of three studies comparing ACE inhibitors with thiazide-type diuretics showed that ACE inhibitors are associated with a higher incidence of stroke than thiazide-type diuretics (RR 1.13, 95% CI 1.02 to 1.25).  No difference was found for mortality.
For MI, the studies are heterogeneous. One study based in a relatively elderly and predominantly white population reported a lower incidence of MI for ACE inhibitors (RR 0.71, 95% CI 0.51 to 0.98), but the remaining studies found no significant difference.
For heart failure, a meta-analysis of two studies also demonstrated heterogeneity. ALLHAT

reported a higher incidence with ACE inhibitors than thiazide-type diuretics (RR 1.19, 95% CI 1.08 to 1.31), but in ANBP2 there was no significant difference.

One study reported no significant difference in unstable angina but a higher incidence of revascularisation procedures (RR 1.10, 95% CI 1.00 to 1.21) with ACE inhibitors.

Both studies found ACE inhibitors to be associated with a higher incidence of withdrawal compared to thiazide-type diuretics (RR 1.12, 95% CI 1.08 to 1.17; RR 1.10, 95% CI 1.04 to 1.17). One study reported new-onset diabetes as an outcome, and found that the incidence of diabetes after four years of follow-up was significantly higher for thiazide-type diuretics compared to ACE inhibitors (p<0.001).

Calcium-channel blockers versus thiazide-type diuretics
A meta-analysis of five studies comparing calcium-channel blockers with thiazide-type diuretics found no significant differences for mortality, MI or stroke. There was a statistically significantly higher incidence of heart failure with CCBs (RR 1.38, 95% CI 1.25 to 1.53).

Conversely, based on the results of three studies, CCBs are associated with a reduced incidence of new-onset diabetes (RR 0.78, 95% CI 0.64 to 0.96).

Only the ALLHAT study reported unstable angina as an outcome and found no significant difference between the drug classes. For revascularisation procedures, neither ALLHAT nor MIDAS found a significant difference.

In terms of study drug withdrawal, one study (INSIGHT) found thiazide-type diuretics to be associated with more withdrawals than CCBs (RR 1.20, 95% CI 1.13 to 1.28), although the other studies did not find a significant difference between the two drug classes.

Beta-blockers versus thiazide-type diuretics
Three studies were found comparing the efficacy of beta-blockers and thiazide-type diuretics. One study included only male patients. A meta-analysis of these three studies showed no significant difference between the two drug classes in terms of mortality.

Heterogeneity in the study results suggested that a meta-analysis would be inappropriate for the outcomes of myocardial infarction and stroke. One study (MRC-0)15 found beta-blockers to be associated with a higher incidence of myocardial infarction compared to thiazide-type diuretics (RR 1.63, 95% CI 1.15 to 2.32). No association was found in the other two studies which considered younger patients.

One study in a relatively young population (average age 52 years) found beta-blockers to be associated with a higher incidence of stroke compared to thiazide-type diuretics (RR 2.31, 95% CI 1.33 to 4.00). No association was found in the other two studies.

In terms of the frequency of withdrawal of the study drug, two studies found beta-blockers to be associated with more withdrawals (RR 1.06, 95% CI 1.01 to 1.11; RR 1.29, 95% CI 1.22 to 1.37) while the remaining study reported a non-significant result.

Angiotensin-II receptor antagonists versus beta-blockers
One study (LIFE) was found comparing the angiotensin-II receptor antagonist (ARB) losartan with the beta-blocker atenolol as first-line antihypertensive therapy.

The study found no significant difference between the two treatments in terms of myocardial infarction, revascularisation procedures, heart failure or angina. However, the study did find ARBs to be associated with a reduced incidence of stroke (RR 0.75, 95% CI 0.63 to 0.88), new-onset diabetes (RR 0.75, 95% CI 0.64 to 0.88) and fewer study drug withdrawals (RR 0.86, 95% CI 0.82 to 0.91).

Although mortality was lower in the ARB treatment group, this result was not statistically significant.

Calcium-channel blockers versus beta-blockers
A meta-analysis of three studies compared calcium-channel blockers (CCBs) with beta-blockers. There was no statistically significant difference in mortality or myocardial infarction. Based on the results of the two studies reporting stroke as an outcome, CCBs were associated with a reduced incidence of stroke (RR 0.77, 95% CI 0.67 to 0.88). For heart failure, a meta-analysis of two studies showed substantial heterogeneity, but neither study alone found a statistically significant difference between CCBs and beta-blockers.

Based on the results of one study, CCBs are associated with a reduced incidence of new-onset diabetes (RR 0.71, 95% CI 0.64 to 0.78) and also to be associated with a lower incidence of unstable angina (HR 0.68, 95% CI 0.51 to 0.92) and fewer revascularisation procedures (HR 0.86, 95% CI 0.77 to 0.96) than BBs, but the INVEST study found the association between both classes of drugs to be non-significant for these outcomes.

Study withdrawal was reported in two studies. In ASCOT there were fewer withdrawals associated

with CCBs (RR 0.64, 95% CI 0.52 to 0.77), but in INVEST there was no significant difference.

Angiotensin-II receptor antagonists versus ACE inhibitors
Three RCTs were found. ARB was significantly better than ACEI for less study drug withdrawals [moderate quality evidence] (HR 0,87 (0,81 to 0,92), 23 cases per 1000 pts fewer (14 to 34)), there was non-signifacant difference between ACEI and ARB for mortality (all cause) [high quality evidence], MI (fatal and non-fatal) [moderate quality evidence], stroke (fatal and non-fatal) [moderate quality evidence], angina requiring hospitalisation [moderate quality evidence], coronary revascularisation [high quality evidence], new onset diabetes [moderate quality evidence] and heart failure [moderate quality evidence].

**Summary of effect sizes from the meta-analysis**

| Comparison | Studies | Total n | Effect size RR [95% CI] |
|---|---|---|---|
| **Beta-blockers versus thiazides** | | | |
| 01 Mortality | 3 | 15,765 | 1.04 [0.91, 1.20] |
| 02 Myocardial infarction | 3 | 15,765 | 1.15 [0.82, 1.60] |
| 03 Stroke | 3 | 15,765 | 1.27 [0.73, 2.23] |
| **ARBs versus beta-blockers** | | | |
| 01 Mortality | 1 | 9,103 | 0.89 [0.78, 1.01] |
| 02 Myocardial infarction | 1 | 9,103 | 1.05 [0.86, 1.28] |
| 03 Stroke | 1 | 9,103 | 0.75 [0.63, 0.88] |
| 04 Heart failure | 1 | 9,103 | 0.95 [0.76, 1.18] |
| 05 Diabetes | 1 | 7,998 | 0.75 [0.64, 0.88] |
| **Calcium-channel blockers versus beta-blockers** | | | |
| 01 Mortality | 3 | 44,075 | 0.94 [0.88, 1.00] |
| 02 Myocardial infarction (inc. silent MI) | 3 | 44,075 | 0.93 [0.83, 1.03] |
| 03 Myocardial infarction (exc. silent MI) | 3 | 44,075 | 0.91 [0.81, 1.02] |
| 04 Stroke | 2 | 21,499 | 0.77 [0.67, 0.88] |
| 05 Heart failure | 2 | 41,833 | 0.96 [0.74, 1.26] |
| 06 Diabetes | 1 | 14,112 | 0.71 [0.64, 0.78] |
| **ACE inhibitors versus calcium-channel blockers** | | | |
| 01 Mortality | 3 | 23,625 | 1.04 [0.98, 1.11] |
| 02 Myocardial infarction | 3 | 23,619 | 0.94 [0.74, 1.19] |
| 03 Stroke | 3 | 23,619 | 1.15 [1.03, 1.27] |
| 04 Heart failure | 3 | 23,619 | 0.85 [0.78, 0.93] |
| 05 Diabetes | 2 | 15,501 | 0.85 [0.76, 0.94] |
| **ARBs versus calcium-channel blockers** | | | |
| 01 Mortality | 1 | 15,313 | 1.02 [0.93, 1.12] |
| 02 Myocardial infarction | 1 | 15,313 | 1.17 [1.01, 1.36] |
| 02 Stroke | 1 | 15,313 | 1.14 [0.97, 1.33] |
| 03 Heart failure | 1 | 15,313 | 0.88 [0.76, 1.01] |
| **ACE inhibitors versus thiazides** | | | |
| 01 Mortality | 2 | 29,697 | 1.00 [0.94, 1.06] |
| 02 Myocardial infarction | 3 | 30,204 | 0.87 [0.60, 1.24] |
| 03 Stroke | 3 | 30,204 | 1.13 [1.02, 1.25] |

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| 04 Heart failure | 2 | 29,697 | 1.07 [0.81, 1.41] |
| **Calcium-channel blockers versus thiazides** | | | |
| 01 Mortality | 5 | 32,195 | 0.97 [0.93, 1.02] |
| 02 Myocardial infarction | 5 | 32,195 | 1.02 [0.96, 1.08] |
| 03 Stroke | 5 | 32,195 | 0.93 [0.84, 1.04] |
| 04 Heart failure | 5 | 32,195 | 1.38 [1.25, 1.53] |
| 05 Diabetes | 3 | 20,885 | 0.82 [0.75, 0.90] |

## Guidelines

Several of the reviewed guidelines make recommendations on the choice of the initial therapy.
ESC allows any of the major groups as an initial choice, based on comorbidities.
NICE current guidance (2006) recommends, for people aged 55 or over, a CCB or TZD, and for younger an ACEI, the draft of 2011 recommends for people aged 55 and over a CCB, in case of intolerance or HF risk, a TZD, and for younger, an ACEI or less costly ARB.
Canadian guideline (2009) allows choice between all 5 groups as initial therapy.
Australian (2008) guidance recommends any of the 4 groups, excluding BBL.
Finnish (2009) guidance allows choice between all 5 groups, with some caution about the limited stroke reduction with BBL.

## References

| | Hypertension. The clinical management of primary hypertension in adults. Clinical Guideline. Methods, evidence and recommendations. National Clinical Guideline Centre, London 2011 |
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| Background<br>Sustained elevated blood pressure, unresponsive to lifestyle measures, leads to a critically important clinical question: What class of drug to use first-line? This review answers that question.<br>Objectives<br>Primary objective: To quantify the benefits and harms of the major first-line anti-hypertensive drug classes: thiazides, beta-blockers, calcium channel blockers, angiotensin converting enzyme (ACE) inhibitors, alpha-blockers, and angiotensin II receptor blockers (ARB).<br>Search strategy<br>Electronic search of MEDLINE (Jan. 1966-June 2008), EMBASE, CINAHL, the Cochrane clinical trial register, using standard search strategy of the hypertension review group with additional terms.<br>Selection criteria<br>Randomized trials of at least one year duration comparing one of 6 major drug classes with a placebo or no treatment. More than 70% of people must have BP >140/90 mmHg at baseline.<br>Data collection and analysis<br>The outcomes assessed were mortality, stroke, coronary heart disease (CHD), cardiovascular events (CVS), decrease in systolic and diastolic blood pressure, and withdrawals due to adverse drug effects. Risk ratio (RR) and a fixed effects model were used to combine outcomes across trials.<br>Main results<br>Of 57 trials identified, 24 trials with 28 arms, including 58,040 patients | Wright JM, Musini VM. First-line drugs for hypertension. *Cochrane Database of Systematic Reviews* 2009, Issue 3. Art. No.: CD001841. DOI: 10.1002/14651858.CD001841.pub2. |

met the inclusion criteria.

Thiazides (19 RCTs) reduced mortality (RR 0.89, 95% CI 0.83, 0.96), stroke (RR 0.63, 95% CI 0.57, 0.71), CHD (RR 0.84, 95% CI 0.75, 0.95) and CVS (RR 0.70, 95% CI 0.66, 0.76). Low-dose thiazides (8 RCTs) reduced CHD (RR 0.72, 95% CI 0.61, 0.84), but high-dose thiazides (11 RCTs) did not (RR 1.01, 95% CI 0.85, 1.20).

Beta-blockers (5 RCTs) reduced stroke (RR 0.83, 95% CI 0.72, 0.97) and CVS (RR 0.89, 95% CI 0.81, 0.98) but not CHD (RR 0.90, 95% CI 0.78, 1.03) or mortality (RR 0.96, 95% CI 0.86, 1.07).

ACE inhibitors (3 RCTs) reduced mortality (RR 0.83, 95% CI 0.72-0.95), stroke (RR 0.65, 95% CI 0.52-0.82), CHD (RR 0.81, 95% CI 0.70-0.94) and CVS (RR 0.76, 95% CI 0.67-0.85).

Calcium-channel blocker (1 RCT) reduced stroke (RR 0.58, 95% CI 0.41, 0.84) and CVS (RR 0.71, 95% CI 0.57, 0.87) but not CHD (RR 0.77 95% CI 0.55, 1.09) or mortality (RR 0.86 95% CI 0.68, 1.09). No RCTs were found for ARBs or alpha-blockers.

Authors' conclusions

First-line low-dose thiazides reduce all morbidity and mortality outcomes. First-line ACE inhibitors and calcium channel blockers may be similarly effective but the evidence is less robust. First-line high-dose thiazides and first-line beta-blockers are inferior to first-line low-dose thiazides.

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AB Background This review re-assesses the role of beta-blockade as first-line therapy for hypertension relative to each of the other major classes of antihypertensive drugs. Objectives To quantify the effectiveness and safety of beta-blockers on morbidity and mortality endpoints in adults with hypertension. Search strategy We searched eligible studies up to June 2006 in the Cochrane Controlled Trials Register, Medline, Embase, and reference lists of previous reviews, and by contacting hypertension experts. Selection criteria Randomised controlled trials assessing the effectiveness of beta-blockers compared to placebo, no therapy or other drug classes, as monotherapy or first-line therapy for hypertension, on mortality and morbidity endpoints in men and non-pregnant women aged 18 years or older. Data collection and analysis At least two authors independently applied study selection criteria, assessed study quality, and extracted data; with differences resolved by consensus. We expressed study results as relative risks (RR) with 95% confidence intervals (CI) and conducted quantitative analyses with trial participants in groups to which they were randomly allocated, regardless of which or how much treatment they actually received. In the absence of significant heterogeneity between studies (p>0.1), we performed meta-analysis using a fixed effects method. Otherwise, we used the random effects method and investigated the cause of heterogeneity by stratified analysis. In addition, we used the Higgins statistic to quantify the amount of between-study variability in effect attributable to true heterogeneity rather than chance. Main results Thirteen randomised controlled trials (N=91,561 participants), which met our inclusion criteria, compared beta-blockers to placebo or no treatment (4 trials with 23,613 participants), diuretics (5 trials with 18,241 participants), calcium-channel blockers (CCBs: 4 trials with 44,825 participants), and renin-angiotensin system (RAS) inhibitors (3 trials with 10,828 participants). The risk of all-cause mortality was not different between first-line beta-blockers and placebo (RR 0.99, 95%CI 0.88 to 1.11), diuretics or RAS inhibitors, but was higher for beta-blockers compared to CCBs (RR 1.07, 95%CI 1.00 to 1.14, I(superscript 2)=2.2%; ARI=0.5%, NNH=200). The risk of total cardiovascular disease (CVD) was lower for first-line beta-blockers compared to placebo (RR 0.88, 95%CI 0.79 to 0.97, ARR=0.7%, NNT=140). This is primarily a reflection of the significant decrease in stroke (RR 0.80, 95%CI 0.66 to 0.96; ARR=0.5%, NNT=200); coronary heart disease (CHD) risk was not significantly different between beta-blockers and placebo. The effect of beta-blockers on CVD was significantly worse than that of CCBs (RR 1.18, 95%CI 1.08 to 1.29, ARI=1.3%, NNH=80), but was not significantly different from that of diuretics or RAS inhibitors. Increased total CVD was due to an increase in stroke compared to CCBs (RR 1.24, 95%CI 1.11 to 1.40ARI=0.6%,

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| NNH=180). There was also an increase in stroke with beta-blockers as compared to RAS inhibitors (RR 1.30, 95%CI 1.11 to 1.53, ARI=1.5%, NNH=65). CHD was not significantly different between beta-blockers and diuretics or CCBs or RAS inhibitors. In addition, patients on beta-blockers were more likely to discontinue treatment due to side effects than those on diuretics (RR 1.86, 95%CI 1.39 to 2.50, I(superscript 2)=78.2%, ARI=6.4% NNH=16) and RAS inhibitors (RR 1.41, 95%CI 1.29 to 1.54, I(superscript 2)=12.1%; ARI=5.5%, NNH=18), but there was no significant difference with CCBs. Authors' conclusions The available evidence does not support the use of beta-blockers as first-line drugs in the treatment of hypertension. This conclusion is based on the relatively weak effect of beta-blockers to reduce stroke and the absence of an effect on coronary heart disease when compared to placebo or no treatment. More importantly, it is based on the trend towards worse outcomes in comparison with calcium-channel blockers, renin-angiotensin system inhibitors, and thiazide diuretics. Most of the evidence for these conclusions comes from trials where atenolol was the beta-blocker used (75% of beta-blocker participants in this review). However, it is not known at present whether beta-blockers have differential effects on younger and elderly patients or whether there are differences between the different sub-types of beta-blockers. | |
| AB Background Calcium channel blockers (CCBs) are a relatively new antihypertensive class. The effect of first-line CCBs on the prevention of cardiovascular events, as compared with other antihypertensive drug classes, is unknown. Objectives To determine whether CCBs used as first-line therapy for hypertension are different from other first-line drug classes in reducing the incidence of major adverse cardiovascular events. Search strategy Electronic searches of the Cochrane Central Register of Controlled Trials, MEDLINE, EMBASE and the WHO-ISH Collaboration Register (up to May 2009) were performed. We also checked the references of published studies to identify additional trials. Selection criteria Randomized controlled trial (RCT) comparing first-line CCBs with other antihypertensive classes, with at least 100 randomized hypertensive participants and with a follow-up of at least two years. Data collection and analysis Two authors independently selected the included trials, evaluated the risk of bias and entered the data for analysis. Main results Eighteen RCTs (14 dihydropyridines, 4 non-dihydropyridines) with a total of 141,807 participants were included. All-cause mortality was not different between first-line CCBs and any other first-line antihypertensive classes. CCBs reduced the following outcomes as compared to [beta]-blockers: total cardiovascular events (RR 0.84, 95% CI [0.77, 0.92]), stroke (RR 0.77, 95% CI [0.67, 0.88]) and cardiovascular mortality (RR 0.90, 95% CI [0.81, 0.99]). CCBs increased total cardiovascular events (RR 1.05, 95% CI [1.00, 1.09], p = 0.03) and congestive heart failure events (RR 1.37, 95% CI [1.25, 1.51]) as compared to diuretics. CCBs reduced stroke (RR 0.89, 95% CI [0.80, 0.98]) as compared to ACE inhibitors and reduced stroke (RR 0.85, 95% CI [0.73, 0.99]) and MI (RR 0.83, 95% CI [0.72, 0.96]) as compared to ARBs. CCBs also increased congestive heart failure events as compared to ACE inhibitors (RR 1.16, 95% CI [1.06, 1.27]) and ARBs (RR 1.20, 95% CI [1.06, 1.36]). The other evaluated outcomes were not significantly different. Authors' conclusions Diuretics are preferred first-line over CCBs to optimize reduction of cardiovascular events. The review does not distinguish between CCBs, ACE inhibitors or ARBs, but does provide evidence supporting the use of CCBs over [beta]-blockers. Many of the differences found in the current review are not robust and further trials might change the conclusions. More well-designed RCTs studying the mortality and morbidity of patients taking CCBs as compared with other antihypertensive drug classes are needed for patients with different stages of hypertension, different ages, and with different co-morbidities such as diabetes. | Chen N, Zhou M, Yang M, Guo J, Zhu C, Yang J, Wang Y, Yang X, He L. Calcium channel blockers versus other classes of drugs for hypertension. *Cochrane Database of Systematic Reviews* 2010, Issue 8. Art. No.: CD003654. DOI: 10.1002/14651858.CD003654.pub4. |