Hypertension: Evidence Update March 2013

A summary of selected new evidence relevant to NICE clinical guideline 127 ‘Clinical management of primary hypertension in adults’ (2011)
Evidence Updates provide a summary of selected new evidence published since the literature search was last conducted for the accredited guidance they relate to. They reduce the need for individuals, managers and commissioners to search for new evidence. Evidence Updates highlight key points from the new evidence and provide a commentary describing its strengths and weaknesses. They also indicate whether the new evidence may have a potential impact on current guidance. For contextual information, this Evidence Update should be read in conjunction with the relevant clinical guideline, available from the NHS Evidence topic page for hypertension.

Evidence Updates do not replace current accredited guidance and do not provide formal practice recommendations.

NHS Evidence is a service provided by NICE to improve use of, and access to, evidence-based information about health and social care.
Introduction

This Evidence Update identifies new evidence that is relevant to, and may have a potential impact on, the following reference guidance:


A search was conducted for new evidence from 29 November 2010 to 21 September 2012. A total of 1948 pieces of evidence were initially identified. Following removal of duplicates and a series of automated and manual sifts, 20 items were selected for the Evidence Update (see Appendix A for details of the evidence search and selection process). An Evidence Update Advisory Group, comprising topic experts, reviewed the prioritised evidence and provided a commentary.

Although the process of updating NICE guidance is distinct from the process of an Evidence Update, the relevant NICE guidance development centres have been made aware of the new evidence, which will be considered when guidance is reviewed.

Feedback

If you have any comments you would like to make on this Evidence Update, please email contactus@evidence.nhs.uk

1 NICE-accredited guidance is denoted by the Accreditation Mark ©
**Key points**

The following table summarises what the Evidence Update Advisory Group (EUAG) decided were the key points for this Evidence Update. It also indicates the EUAG’s opinion on whether the new evidence may have a potential impact on the current guidance listed in the introduction. For further details of the evidence behind these key points, please see the full commentaries.

The section headings used in the table below are taken from the guidance.

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<table>
<thead>
<tr>
<th>Key point</th>
<th>Potential impact on guidance</th>
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<tbody>
<tr>
<td><strong>Diagnosing hypertension</strong></td>
<td></td>
</tr>
<tr>
<td>• Automated clinic blood pressure measurement providing a series of readings may result in more accurate blood pressure measurement than manual blood pressure measurement, but may still overestimate blood pressure in some patients when compared with ambulatory blood pressure monitoring.</td>
<td>✓</td>
</tr>
<tr>
<td>• Differences of more than 15 mmHg in blood pressure readings between arms may indicate increased risk of underlying vascular disease and an increased risk of all cause and cardiovascular mortality.</td>
<td>✓</td>
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<tr>
<td><strong>Initiating and monitoring antihypertensive drug treatment including blood pressure targets</strong></td>
<td></td>
</tr>
<tr>
<td>• The longer term benefit of drug treatment of stage 1 hypertension remains uncertain in patients without target organ damage, existing cardiovascular disease or at low risk of cardiovascular disease.</td>
<td>✓</td>
</tr>
<tr>
<td>• Telemonitoring of blood pressure control may result in greater reductions in blood pressure when compared with usual care; however further research is needed.</td>
<td>✓</td>
</tr>
<tr>
<td>• Home blood pressure monitoring may be associated with greater reductions in blood pressure compared with clinic blood pressure monitoring; however, the effect size seems to be small and further research is needed.</td>
<td>✓</td>
</tr>
<tr>
<td>• There is uncertainty about the optimal timing of antihypertensive medication and whether evening dosing versus morning dosing of antihypertensive drugs is associated with any significant impact on blood pressure reduction, cardiovascular outcomes or adverse events – further research is needed.</td>
<td>✓</td>
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</table>
### Choosing antihypertensive drug treatment

<table>
<thead>
<tr>
<th>Key point</th>
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<tr>
<td>• Early treatment of hypertension may prolong life expectancy with regard to cardiovascular mortality.</td>
<td>✓</td>
</tr>
<tr>
<td>• Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-II receptor blockers (ARBs) seem to be associated with lower all-cause and cardiovascular mortality when compared with control (active control, placebo or usual care).</td>
<td>✓</td>
</tr>
<tr>
<td>• Diuretics may be more effective than other classes of antihypertensive drugs in preventing heart failure.</td>
<td>✓</td>
</tr>
<tr>
<td>• Initial therapy with low-dose hydrochlorothiazide does not seem to reduce blood pressure as much as other classes of antihypertensive drugs.</td>
<td>✓</td>
</tr>
<tr>
<td>• Initial antihypertensive therapy with beta-blockers may be less effective than treatment with calcium channel blockers, diuretic therapy and renin-angiotensin system blockers at preventing cardiovascular events and mortality in people with hypertension. Beta blockers may also be associated with greater discontinuations due to adverse events than other classes of antihypertensive drugs.</td>
<td>✓</td>
</tr>
<tr>
<td>• Spironolactone(^2) reduces blood pressure when compared with placebo in people with resistant hypertension despite treatment with at least 3 antihypertensive drugs.</td>
<td>✓</td>
</tr>
<tr>
<td>• Limited evidence suggests that loop diuretics may reduce blood pressure compared with placebo; more research is needed.</td>
<td>✓</td>
</tr>
<tr>
<td>• The maximum blood pressure lowering effect of antihypertensive treatment may be estimated from the response seen in the first 1–2 weeks of treatment with an antihypertensive drug.</td>
<td>✓</td>
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</tbody>
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### Patient education and adherence to treatment

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>• People with hypertension appear to have similar perspectives on hypertension and their treatment, and the reasons for non-adherence to therapy do not seem to vary substantially between geographical and ethnic groups.</td>
<td>✓</td>
</tr>
</tbody>
</table>

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### Areas not currently covered by NICE guidance

<table>
<thead>
<tr>
<th>Key point</th>
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</tr>
</thead>
<tbody>
<tr>
<td>• An implantable device designed to activate baroreceptors to reduce blood pressure does not appear to reduce blood pressure compared with control in people with uncontrolled hypertension. Further studies are needed to determine safety and efficacy.</td>
<td>✓</td>
</tr>
<tr>
<td>• A guided breathing device does not appear to be an effective treatment to reduce blood pressure in people with hypertension.</td>
<td>✓</td>
</tr>
</tbody>
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\(^2\) At the time of publication of this Evidence Update, spironolactone did not have UK marketing authorisation for this indication.
1 Commentary on new evidence

These commentaries analyse the key references identified specifically for the Evidence Update. The commentaries focus on the ‘key references’ (those identified through the search process and prioritised by the EUAG for inclusion in the Evidence Update), which are identified in bold text. Supporting references provide context or additional information to the commentary. Section headings are taken from the guidance.

1.1 Measuring blood pressure

No new key evidence was found for this section.

1.2 Diagnosing hypertension

Automatic versus manual measurement and correlation with ambulatory blood pressure monitoring (ABPM)

**NICE CG127** recommends offering ABPM to confirm the diagnosis of hypertension in people with a clinic blood pressure of 140/90 mmHg or higher.

**Myers et al. (2011)** reported results from the conventional versus automated measurement of blood pressure in the office (CAMBO) randomised controlled trial (RCT), in which 88 Canadian family doctors who used manual sphygmomanometers were randomly assigned by site (67 practices) to use automated clinic blood pressure measurement with the BpTRU automated sphygmomanometer or to continue with manual blood pressure measurement. The primary outcome measure was the difference between awake systolic ABPM and automated clinic blood pressure compared with the difference between awake systolic ABPM and manual clinic blood pressure.

The study included patients with hypertension who were aged older than 45 years with at least 160 mmHg systolic and less than 95 mmHg diastolic for untreated people and at least 140 mmHg systolic and less than 90 mmHg diastolic for people receiving antihypertensive drugs. Exclusion criteria were serious coexisting illness or diabetes, more than twice the normal value of serum creatinine, or a history of non-adherence to therapy. All participants (n=555) had 24 hour ABPM after the clinic measurement. The size of groups differed (n=303 in the automated measurement group and n=252 in the manual measurement group) partly because more of the sites randomly assigned to automated measurement had multiple clinicians working in the practice.

The BpTRU device took an initial measurement to verify the correct positioning of the cuff, then the participant was left alone while a further 5 readings were taken at 2-minute intervals. No additional instructions on proper blood pressure measurement technique were given to doctors in either the manual or automated measurement groups.

The mean difference in blood pressure between automated clinic measurement and awake average ABPM was −2.3 mmHg (95% confidence interval [CI] −0.3 to −4.3, p=0.02) for systolic pressure and −3.3 mmHg (95% CI −2.2 to −4.4, p<0.001) for diastolic pressure. The mean difference in blood pressure between manual clinic blood pressure measurement and ABPM was −6.5 mmHg (95% CI −4.3 to −8.6, p<0.001) for systolic pressure and −4.3 mmHg (95% CI −2.9 to −5.8, p<0.001) for diastolic pressure. For systolic blood pressure, the difference between the automated group and the manual group was significant (p=0.006), but the difference in diastolic blood pressure was not significant.

The authors noted that further research is needed before these results can be applied to hypertensive populations other than that studied in this trial.
This evidence suggests that automated clinic blood pressure measurement based on multiple readings may give a more accurate blood pressure reading when compared with manual clinic blood pressure measurement. However, automatic clinic blood pressure measurement still resulted in a significantly higher reading than the corresponding ABPM awake average blood pressure. These results support the recommendation in NICE CG127 to confirm a clinic diagnosis of hypertension with ABPM.

**Key reference**

**Differences in blood pressure between arms**

NICE CG127 recommends measuring blood pressure in both arms when considering a diagnosis of hypertension. If the difference in readings between arms is more than 20 mmHg then the measurements should be repeated. If the difference in readings between arms remains more than 20 mmHg on the second measurement, subsequent measurements should be conducted in the arm with the higher reading. The full version of NICE CG127 notes that such large differences between arms indicates underlying vascular disease and that consistent inter-arm differences of more than 20/10 mmHg may suggest pathology warranting specialist referral.

Clark et al. (2012) conducted a meta-analysis of 20 cohort or cross-sectional studies of differences in systolic blood pressure between arms in populations of adults of 18 years or older with data for central vascular disease, peripheral vascular disease or death.

From 5 case series (n=135) of people with angiographically proven asymptomatic subclavian stenosis mean systolic blood pressure was estimated to be 36.9 mmHg (95% CI 35.4 to 38.4) lower in the affected arm than in the other. Pooling of a further 2 datasets (n=532) allowed estimation of the risk of subclavian stenosis of more than 50% occlusion at angiography and a difference of 10 mmHg or more between arms (relative risk [RR]=8.8, 95% CI 3.6 to 21.2, p<0.0001).

There was no significant association between a difference of 15 mmHg or more between arms and a history of coronary artery disease when compared with a difference between arms of less than 15 mmHg in 7 cohorts (RR=1.13 95% CI 0.78 to 1.63, n=5033). A between-arm difference of 15 mmHg or more was associated with significantly increased risks of all cause (hazard ratio [HR] =1.55, 95% CI 1.07 to 2.25) and cardiovascular mortality (HR=1.68, 95% CI 1.11 to 2.53). The authors noted that they had insufficient data to establish an effect of small studies or publication bias.

The results of this study suggest a difference in systolic blood pressure of more than 15 mmHg between arms may indicate increased risk of vascular disease (that is, subclavian stenosis), and is associated with an increased risk of all cause and cardiovascular mortality. These results provide some support for the existing NICE CG127 recommendation to: measure blood pressure in both arms and use the arm with the highest blood pressure measurement for all subsequent readings. It is also noted in full version of NICE CG127 that differences in blood pressure between arms of 20 mmHg or more may also indicate underlying pathology that warrants specialist investigation.

**Key reference**
1.3 **Assessing cardiovascular risk and target organ damage**

No new key evidence was found for this section.

1.4 **Lifestyle interventions**

New evidence was not searched for this section (see Appendix A for details of the evidence search and selection process).

1.5 **Initiating and monitoring antihypertensive drug treatment, including blood pressure targets**

**Drug treatment for mild hypertension**

*NICE CG127* recommends antihypertensive drug treatment for people aged under 80 years with stage 1 hypertension (clinic blood pressure 140/90 to 160/100 mmHg and subsequent ABPM daytime average or home blood pressure monitoring [HBPM] average of 135/85 to 150/95 mmHg) and one or more of: target organ damage, established cardiovascular disease, renal disease, diabetes, or 10-year cardiovascular risk of 20% or higher.

In a Cochrane review, Diao et al. (2012), assessed 4 trials (n=8912) of antihypertensive drug treatment in people with mild hypertension (blood pressure of 140–159 mmHg systolic or 90–99 mmHg diastolic) and no evidence of cardiovascular disease at baseline. After 4–5 years of treatment with antihypertensive drugs, no significant differences were seen for total mortality (RR=0.85, 95% CI 0.63 to 1.15) coronary heart disease (n=7080, RR=1.12, 95% CI 0.80 to 1.57), stroke (RR=0.51, 95% CI 0.24 to 1.08), or total cardiovascular events (RR=0.97, 95% CI 0.72 to 1.32) compared with placebo. Data on withdrawals due to adverse effects were only available from all patients in one of the included trials and not from the subgroup of patients with mild hypertension. Withdrawals due to adverse events among participants with mild to moderate hypertension (n=17,354) were more common in people on antihypertensive drug treatment than placebo. (RR=4.80, 95% CI 4.14 to 5.57, absolute risk increase 8.9% over 5 years).

This review is consistent with *NICE CG127*, in that evidence is lacking for benefits of antihypertensive treatment for stage 1 hypertension in people who do not have coexisting conditions that may increase their risk of cardiovascular events.

**Key reference**

Diao D, Wright JM, Cundiff DK et al. (2012) *Pharmacotherapy for mild hypertension*. Cochrane Database of Systematic Reviews issue 8: CD006742

**Telemonitoring**

*NICE CG127* does not include recommendations on telemonitoring; it states that the response to antihypertensive treatment should be monitored by clinic blood pressure measurements; ABPM or HBPM may be considered as an adjunct to clinic measurements for people identified as having a 'white-coat effect'.

Verberk et al. (2011) did a meta-analysis of 9 RCTs (n=2501) evaluating telemonitoring of hypertension that reported change in blood pressure or proportion of participants reaching their target blood pressure. Overall, telemonitoring decreased systolic blood pressure significantly more than usual care (mean difference of change with telemonitoring – change with usual care=5.2 mmHg standard deviation [SD]±1.5, p<0.001). Diastolic blood pressure also reduced significantly more with telemonitoring than with usual care (mean difference=2.1 SD ±0.8 mmHg, p<0.01. Additional
analysis to account for possible publication bias showed slightly smaller differences which were still significant (data not reported).

Although no tests for heterogeneity were reported, the authors noted that the included studies differed in equipment used, participants, blood pressure endpoints and study design. The authors did not comment on the quality of included studies.

The results of the study by Verberk et al. (2011) suggest there may be a small reduction in blood pressure in people with treated hypertension who use telemonitoring of their blood pressure control. However, further research is needed. This evidence is insufficient to affect current recommendations in NICE CG127, that is, to continue to monitor blood pressure control using clinic blood pressure unless the patient has been previously determined to have a ‘white-coat effect’, in which case blood pressure control should be monitored with home blood pressure readings or ABPM.

Key reference

Home versus clinic blood pressure monitoring
NICE CG127 recommends monitoring response to blood pressure lowering treatment by measuring blood pressure in the clinic. However, ABPM or HBPM may be considered as an adjunct to clinic measurements in people with an identified white-coat effect.

A meta-analysis by Agarwal et al. (2011) assessed HBPM compared with clinic blood pressure measurement in 37 RCTs (n=9446) to determine whether HBPM resulted in improvements in blood pressure control or more responsive changes in antihypertensive drug use.

The mean change in systolic blood pressure was −2.63 mmHg (95% CI −4.24 to −1.02, p<0.0001) for those using HBPM when compared with clinic measurement to monitor blood pressure control: the mean change in diastolic blood pressure was −1.68 mmHg (95% CI −2.58 to −0.79, p<0.0001). Subgroup analysis showed that studies that did not use drug titration based on the results of HBPM resulted in lower blood pressure (mean=−2.46, 95% CI −3.44 to −1.49) than studies that did use drug titration (mean=−0.58, 95% CI −1.94 to 0.79, p=0.028). However, significantly greater response rates were seen with drug titration.

The authors reported significant heterogeneity between studies in both systolic and diastolic blood pressure and in response rates for HBPM. They additionally noted the paradox in that mean blood pressure was lowered more, but that response rates increased when no drug titration was used.

In a single-centre RCT, Fuchs et al. (2012) compared HBPM and no changes to drug regimens with usual care in patients with uncontrolled hypertension (n=136). Participants were randomly assigned to 1 of 4 groups: HBPM, pharmacist care, HBPM plus pharmacist care, and usual care. This report pooled the results of the two HBPM groups as the intervention group and pooled the pharmacist only and usual care groups as the control group. Exclusion criteria included blood pressure of 180/110 mmHg or higher and serious coexisting conditions. The primary outcomes were the differences between 24 hour, mean night-time and mean day-time blood pressure measured by ABPM between baseline and the end of the trial.

Baseline blood pressure was the mean of 6 measurements in 3 visits taken with an aneroid sphygmomanometer and the mean of 4 measurements in 2 visits with an automatic oscillometric blood pressure measuring device. Clinic hypertension was defined as 140/90 mmHg or higher. All participants additionally had 24 hour ABPM, for which hypertension was defined as 130/80 mmHg or higher.
People assigned to HBPM used an automatic oscillometric device and a blood pressure diary and were instructed to take 6 measurements every day. At follow up visits at 7, 30, and 60 days the readings from the automatic oscillometric device were correlated with the blood pressure diary. At 7 days, instructions were reinforced; at subsequent follow-up visits patients were given advice on lifestyle modifications to help with lowering blood pressure.

People assigned to usual care had follow-up at 7, 30 and 60 days to receive the same advice as the intervention group. 24 hour ABPM was repeated in all participants at the end of the study and analysis was done only for 121 participants who completed this second round of ABPM. Pharmacist care was not defined.

Adherence to HBPM was 94% at the end of the first week and 85% at the end of the trial. The change in ABPM results between baseline and end of trial in the HBPM group was significantly more than that of the control group for both systolic blood pressure (mean [SD]=8.8±13.1 mmHg vs 3.4±11.6 mmHg respectively, p=0.02) and diastolic blood pressure (mean [SD]=5.6±8.4 mmHg vs 1.0±7.9 mmHg respectively, p=0.002). More people in the HBPM group had blood pressure within target at the end of the study (32.4%) compared with control (16.2%, p=0.03).

The authors noted that their results showed a larger effect than two recent meta-analyses in this area, one of which was the Agarwal et al. (2011) meta-analysis. They postulated that this difference in results probably resulted from differences in the protocol of this study compared with studies included in the meta-analyses. Author-noted limitations included that more than 60% of participants were women, which could affect the applicability of findings to men, and the short follow-up.

This new evidence is not likely to affect NICE CG127 because the RCT reported by Fuchs et al. (2012) was small, and in the meta-analysis by Agarwal et al. (2011) the effect size was small and similar to that found in the evidence review in the full version of NICE CG127. Further research into HBPM is needed.

Key references

Morning versus evening dosing
Recommendations in NICE CG127 do not specify the time of day antihypertensive drug treatment should be taken.

A Cochrane review by Zhao et al. (2011) assessed 21 RCTs (n=1993) lasting at least 3 weeks that compared dosing a single antihypertensive drug (angiotensin-converting enzyme [ACE] inhibitors, alpha blockers, angiotensin-II receptor blockers [ARBs], beta-blockers, calcium channel blockers [CCBs], or diuretics) dosed in the morning (6 am to 12 noon) with evening dosing (6 pm to 12 midnight) of the same drug. Participants had primary hypertension (systolic blood pressure 140 mmHg or higher).

The authors stated that the primary outcomes of interest were death from all causes, cardiovascular mortality and cardiovascular morbidity; however, none of the included trials reported any of these outcomes. All trials reported the change from baseline in 24 hour blood pressure.

The mean differences in systolic (−1.71 mmHg, 95% CI −2.78 to −0.65 mmHg) and diastolic (−1.38 mmHg, 95% CI −2.13 to −0.62 mmHg) blood pressure were significantly lower for the
evening regimen. In 5 trials the rates of overall adverse events (RR=0.78 95% CI 0.37 to 1.65) and withdrawals due to adverse events (RR=0.53, 95% CI 0.26 to 1.07) did not differ significantly between morning and evening regimens.

Most included studies were assessed as at high risk of bias due to lack of allocation concealment or selective reporting and there was significant heterogeneity. The authors noted that the current evidence suggests that taking antihypertensive drugs in the evening may reduce 24 hour blood pressure; however, data were not available to determine which regimen has beneficial effects on cardiovascular outcomes or adverse events. This evidence is not likely to have an impact on the recommendations in NICE CG127 and further research is needed.

Key reference

1.6 Choosing antihypertensive drug treatment

Treating hypertension in older people

NICE CG127 recommends the same drugs for people 80 years and over as people aged 55–80 years. However, the target blood pressure for people aged 80 years and over is 150/90 mmHg for clinic measurements, and 145/85 mmHg when using ABPM and HBPM (for example, in people identified as having a ‘white coat effect’ and people who choose to monitor their blood pressure at home).

Beckett et al. (2012) reported on a 1-year open-label extension trial of the Hypertension in the Very Elderly Trial (HYVET). Eligible participants were those in HYVET who had not had a primary or secondary endpoint event by the end of the double-blind phase (n=1882), and 1712 of them consented to take part. The data from the 1-year extension were considered separately from the results of the randomised trial, and compared outcomes in people who were on active treatment in the double-blind phase (n=924) with those of people on placebo during the double-blind phase (n=788). Participants were at least 80 years of age (mean 85 years). To be eligible for the main trial, participants had to have had systolic blood pressure greater than 160 mmHg over a 2-month run-in period.

The main HYVET study (Beckett et al. 2008) was stopped early, after only a median of 1.8 years of follow-up, because of clear evidence of benefit from active treatment: total mortality was reduced by 21% in relative terms (95% confidence interval 4% to 35%; p=0.019). Additionally, intention-to-treat analyses showed that active treatment was associated with significant reductions in the rates of death from stroke (39%, 95% CI 1% to 62%, p=0.05), and rates of heart failure (64%, 95% CI 42% to 78%, p<0.001). No significant differences were seen for rates of fatal and non-fatal stroke (30% reduction, 95% CI −1% to 51%, p=0.06) or death from cardiovascular causes (23% reduction, 95% CI −1% to 40%, p=0.06).

At the start of the open-label extension (Beckett et al. 2012), mean sitting blood pressure was 145.0/76.6 mmHg in the people previously on active treatment, and 159.3/80.8 mmHg in those previously on placebo (p<0.001). The treatment steps in the main trial were: indapamide modified release 1.5 mg; indapamide plus perindopril 2 mg; and indapamide plus perindopril 4 mg. All participants were started on indapamide at the start of the extension study irrespective of whether they were taking indapamide or indapamide plus perindopril at the end of the main trial. The use of additional antihypertensive drugs was allowed if the target was not reached in the extension study, but only 0.9% of people were taking these at 6 months and only 1.8% at the end of the extension study.
The difference between active and placebo groups at the end of the double blind phase was 14.3/4.2 mmHg (p<0.001); however by 6 months the difference was reduced to 1.3/0.6 mmHg (not statistically significant, p value not reported) and at the end of the extension study the difference was 1.0/0.2 mmHg.

Fatal and non-fatal stroke rates (the primary endpoint) did not differ significantly between the groups previously on active or placebo treatment (5.18 versus 9.89 events per 1000 patient years, HR=1.92, 95%CI 0.59 to 6.22, p=0.28). No significant differences were seen in heart failure (HR=0.28, 95% CI 0.03 to 2.73, p=0.28) or cardiovascular events (HR=0.78, 95% CI 0.36 to 1.72, p=0.55). The rates of total mortality (HR=0.48, 95% CI 0.26 to 0.87, p=0.02) and cardiovascular mortality (HR=0.19, 95% CI 0.04 to 0.87, p=0.03) were significantly lower in those who had active treatment in the double-blind phase. Adjustment for age, sex, baseline sitting systolic blood pressure, and previous cardiovascular disease did not change the results.

The main limitations discussed by the authors were the short duration of follow-up and small numbers of events, and that only people still on double-blind treatment at the end of the original trial were included in the extension study. Any person who had an endpoint event in the main trial had been moved to open label treatment and was not eligible to enter the extension study. This study was an extension to an RCT and a relatively low number of events were recorded, so it is probably underpowered to reach any definitive conclusions.

The results suggest that the benefits on cardiovascular morbidity and mortality in those previously allocated to active antihypertensive treatment in the main trial may have continued into this extension study. The HYVET study was influential in the development of recommendations for the treatment of people aged 80 years and over as covered in the evidence review in the full version of NICE CG127. This extension study provides supplemental evidence in support of these recommendations.

Key reference
Beckett N, Peters R, Tuomilehto J et al. (2012) Immediate and late benefits of treating very elderly people with hypertension: results from active treatment extension to Hypertension in the very elderly randomised controlled trial, BMJ 344: d7541

Supporting reference

Long-term mortality benefits of antihypertensive treatment

NICE CG127 recommends offering antihypertensive drug treatment to people of any age with stage 2 hypertension. Additionally, people with isolated systolic hypertension (systolic blood pressure 160 mmHg or more) should be offered the same treatment as people with both raised systolic and diastolic blood pressure, and a thiazide-like diuretic should be offered if diuretic treatment is to be initiated or changed.

Kostis et al. (2011) reported on 22-year follow up of an RCT (Systolic Hypertension in the Elderly Program, SHEP) of chlortalidone in people older than 60 years. At baseline, participants (n=4736) had a systolic blood pressure of 160–219 mmHg and diastolic blood pressure of less than 90 mmHg (mean 170.3/76.6 mmHg) and their mean age was 71.6 years. They were randomised to active treatment or placebo: active treatment started with chlortalidone 12.5 mg, increasing to 25 mg if necessary, with the option of adding atenolol if blood pressure targets were not reached. The target was a systolic blood pressure of less than 160 mmHg for those with a systolic blood pressure of more than 180 mmHg at entry, and a reduction in systolic blood pressure of at least 20 mmHg in the other participants. All participants were advised to take active treatment at the end of the trial. Long-term follow-
up was done by matching personal identifiers of participants to the US National Death Index until 31 December 2006.

At the end of the RCT (4.5 years), the mean systolic blood pressure was 26 mmHg lower than baseline in the active treatment group and 15 mmHg lower in the placebo group. Mean diastolic blood pressure was 9 mmHg lower than at baseline for the active treatment group and 4–5 mmHg lower in the placebo group. Active treatment led to a statistically significant decrease in the risk of fatal and non-fatal stroke (primary endpoint, RR=0.64, 95% CI 0.50 to 0.82), myocardial infarction (RR=0.67, 95% CI 0.47 to 0.96) and heart failure (RR=0.51, 95% CI 0.37 to 0.71). No statistically significant differences were noted in the risk of death from cardiovascular causes (OR=0.80, 95% CI 0.60 to 1.05) or all-cause mortality (OR=0.87, 95% CI 0.73 to 1.05).

During the 22 year follow up, total mortality did not differ significantly between the people who had been on active treatment in SHEP (59.9%) and those who had been on placebo (60.5%, p=0.38). Similar numbers of people in both groups died from coronary heart disease (12.4% vs 13.6% respectively) and stroke (4.6% vs 5.6% respectively); statistical analysis was not reported. However, people who had been on active treatment in the SHEP RCT had significantly longer life expectancy before cardiovascular death, with a gain of 158 days in 22 years (95% CI 36 to 287 days, p=0.009), increasing to 215 days (95% CI 70 to 346 days, p value not reported) in those whose blood pressure was controlled to SHEP targets by the end of the RCT. Life expectancy for all-cause death was not significantly different (p=0.07).

The authors reported that their study was limited by the fact that treatments beyond the randomised phase were observational and information on treatments for hypertension and other conditions such as diabetes, hyperlipidaemia, and surgical and device interventions was not available. They additionally noted that the confidence intervals for life expectancy gain were very wide.

The results of this study suggest that early antihypertensive treatment may lead to prolongation of life expectancy with regard to cardiovascular mortality. This benefit was observed despite the fact that the original clinical trial comparing active versus placebo treatment lasted only 4.5 years and that during the subsequent follow-up of 22 years, all participants were offered antihypertensive therapy. These data provide evidence to support: the longer term benefits of early antihypertensive therapy; the treatment of isolated systolic hypertension; and treatment with thiazide-like diuretics. Therefore this evidence is broadly consistent with recommendations in NICE CG127.

Key reference

ACE-inhibitors or ARBs

NICE CG127 recommends offering ACE inhibitors or ARBs as preferred first line treatment for people younger than 55 years. If an ACE inhibitor is prescribed and is not tolerated (for example, because of cough), a low-cost ARB should be offered. CCBs are recommended as first-line treatment for people older than 55 years and black people of African or Caribbean origin of any age.

In a meta-analysis, van Vark et al. (2012) included 20 randomised controlled trials of at least 100 patients (n=159,998) comparing ACE inhibitors or ARBs with control (placebo, active control or usual care) with an incidence of death of at least 10 people and follow-up of at least 1 year. Studies in which less than two-thirds of participants met each trial’s definition of hypertension were excluded.
The analyses were based on the mortality incidence rate: that is, the number of participants who died divided by the number of patient-years of follow-up. The overall mean follow-up time was 4.3 years. ACE inhibitors were the active treatment in 7 trials (n=76,615) and 13 trials used ARBs as active treatment (n=82,383). The mean baseline systolic blood pressure was 153 mmHg (range of means 135–182 mmHg) and the mean age was 67 years (range of means 59–84 years).

People in the active treatment groups (ACE inhibitors or ARBs) had an all-cause mortality rate of 20.9 deaths per 1000 patient years compared with 23.3 deaths per 1000 patient years in the control group. The hazard ratio for all-cause mortality was significantly lower for active treatment compared with control (HR=0.95, 95% CI 0.91 to 1.00, p=0.032), with no significant heterogeneity between trials. Cardiovascular death was 8.7 deaths per 1000 patient-years for active treatment versus 10.1 deaths per 1000 patient-years for control (HR=0.93, 95% CI 0.88 to 0.99, p=0.018).

The effect on all-cause mortality was almost completely due to the effect of ACE inhibitors, which were associated with a 10% reduction in all-cause mortality compared with control (HR=0.90, 95% CI 0.84 to 0.97, p=0.004). However, ARBs were not associated with a reduction in overall mortality (HR=0.99, 95% CI 0.94 to 1.04, p=0.683). The difference between ACE inhibitors and ARBs was significant (p=0.036). ACE inhibitors were associated with a reduction in death from cardiovascular causes which was of borderline statistical significance (HR 0.88, 95% CI 0.77 to 1.00, p=0.051). The effect of ARBs on this outcome was not significant (HR 0.96, 95% CI 0.90 to 1.01, p=0.143). Meta-regression analysis showed a significant association between mean baseline systolic blood pressure and reductions in mortality (p=0.035). The mortality reduction was highest in trials with the highest baseline systolic blood pressure. Additionally, the mortality reduction was largest in the trials with larger reductions in mean systolic blood pressure compared with control. No significant relationships with mortality were seen for age, sex, or mean follow-up time.

Author-reported limitations included variations in study populations, for example, in definitions of hypertension, dosages of drugs used, or target blood pressure. The meta-analysis was based on trial-level data rather than individual patient data and was not designed to make a head-to-head comparison between ACE inhibitors and ARBs: the authors stated that the difference in effects on all-cause mortality should be considered a post-hoc observation, and should not affect current clinical practice. The inclusion of trials comparing multiple-drug regimens is a potential confounding factor because the effects on blood pressure cannot be reliably attributed to one drug or class of drugs.

This meta-analysis revealed marginal treatment effects on mortality and interpretation is complex due to the heterogeneity between studies and because these effects may be directly related to the overall blood pressure reduction rather than to an effect of a particular class of drugs. This analysis does not influence the recommendations in NICE CG127 to offer either ACE inhibitors or low-cost ARBs as step 1 antihypertensive treatment when indicated.

**Key reference**

**Antihypertensive drugs in prevention of heart failure**
NICE CG127 recommends offering ACE inhibitors or ARBs as preferred first line treatment for people younger than 55 years. CCBs are recommended for people older than 55 years and black people of African or Caribbean origin of any age. Step 2 treatment recommends an ACE inhibitor or ARB plus a CCB. If a CCB is not tolerated or the person has oedema,
evidence of heart failure, or high risk of heart failure, a thiazide-like diuretic should be considered.

In a Bayesian network meta-analysis of 26 randomised controlled trials (n=223,313), Sciarretta et al. (2011) assessed the efficacy of antihypertensive drugs in preventing heart failure. Included studies were published from 1997 to 2009 because the clinical features of patients in trials in that period would be similar to current clinical practice. Inclusion criteria were: studies of at least 200 people; a population with diagnosed hypertension or at high cardiovascular risk with 65% or more of participants with hypertension; and information on the absolute incidence of heart failure and other major cardiovascular events.

Analysis was done for classes of antihypertensive drugs: ACE inhibitors; alpha-blockers; ARBs; beta-blockers; conventional treatment; CCBs; and diuretics compared with placebo and with each other. Conventional treatment varied by study and was beta-blockers or diuretics in 4 studies and any drug other than ARBs in 2 studies (mostly CCBs).

Heart failure occurred in 8554 people (3.8%) over all studies. Compared with placebo, the most effective drugs for preventing heart failure were diuretics (odds ratio [OR]=0.59, 95% credibility interval [CrI] 0.47 to 0.72), then ACE inhibitors (OR=0.71, 95% CrI 0.58 to 0.84), then ARBs (OR=0.76, 95% CrI 0.62 to 0.90) followed by CCBs (OR=0.83, 95% CrI 0.67 to 0.99). Beta-blockers (OR 0.87, 95% CrI 0.64 to 1.12) and alpha-blockers (OR=1.22, 95% CrI 0.85 to 1.69) did not have a significant effect on development of heart failure. In the network meta-analysis, diuretics were more effective than CCBs (OR=0.71, 95% CrI 0.60 to 0.86) and ACE inhibitors (OR=0.83, 95% CrI 0.69 to 0.99). Beta-blockers (OR=1.47, 95% CrI 1.10 to 1.92) and ARBs (OR=1.28, 95% CrI 1.04 to 1.59) were less effective than diuretics.

The authors noted that variations in the criteria for assessing heart failure and the doses of drugs used varied between trials, which may have affected the heart failure incidence seen in the included studies. Another potential limitation noted by the authors was that analyses were generally of first-line treatment, so multiple-drug regimens could not be considered. The analysis also did not take account of the effect of differences in blood pressure reduction obtained with different therapies compared with placebo. Additionally, the authors discussed that fact that this study only addresses the effect of antihypertensive drugs on heart failure, but that other studies have found benefits of specific classes on other important cardiovascular outcomes such as myocardial infarction or stroke.

The recommendation in NICE CG127 to use CCB as the preferred initial or step 2 therapy for people aged 55 years and over, contained an important caveat, that is, the sensitivity analysis in the full version of NICE CG127 had suggested that thiazide-like diuretics would be the preferred treatment in patients with heart failure or at high risk of developing heart failure. The evidence from this recent analysis showing that diuretics may be the most effective treatment to prevent heart failure lends support to the recommendations in NICE CG127.

Key reference

Step 3 treatment
Diuretics
NICE CG127 recommends adding a thiazide-like diuretic at step 3 of the antihypertensive treatment algorithm. If diuretic treatment is to be initiated or changed, a thiazide-like diuretic should be offered, such as chlortalidone (12.5–25.0 mg once daily) or indapamide (1.5 mg modified-release once daily or 2.5 mg once daily) in preference to a conventional thiazide
diuretic such as bendroflumethiazide or hydrochlorothiazide. For people who are already having treatment with bendroflumethiazide or hydrochlorothiazide and whose blood pressure is stable and well controlled, treatment with bendroflumethiazide or hydrochlorothiazide should be continued.

Messerli et al. (2011) did a meta-analysis of 19 trials (n=1463) of hydrochlorothiazide monotherapy compared with active therapy that evaluated efficacy by ABPM. The included studies assessed 12.5–25 mg (14 trials, n=1234) or 50 mg doses (5 trials, n=229). The primary outcome was reduction in blood pressure from baseline to follow-up assessed by 24-hour ABPM.

After a mean of 17 weeks of treatment, hydrochlorothiazide 12.5–25 mg resulted in a reduction in blood pressure from baseline of $\text{−6.5 mmHg (95% CI −5.3 to −7.7 mm Hg)}$ systolic and $\text{−4.5 mmHg (95% CI −3.1 to −6.0 mmHg)}$ diastolic. The 12.5 mg and 25 mg doses separated did not give significantly different results. Other antihypertensive drugs (ACE inhibitors, ARBs, beta-blockers and CCBs resulted in greater reductions in blood pressure ($p<0.001$). Mean absolute differences were $\text{4.5–6.2/2.9–6.7 mmHg}$.

For the hydrochlorothiazide 50 mg group, the reductions were $\text{−12.0 mmHg (95% CI −8.2 to −15.9 mmHg)}$ systolic and $\text{−5.4 mmHg (95% CI −3.2 to −7.7 mmHg)}$: the systolic reduction was statistically significantly better than the 25 mg dose ($p=0.04$) but the diastolic reduction was not ($p=0.97$). However, the authors noted that adverse events would limit the use of doses higher than 25 mg daily.

Of the 14 trials of hydrochlorothiazide 12.5–25 mg, 4 were assessed as low risk of bias, the rest were at high risk of bias. Heterogeneity was also reported to be an issue.

An open-label, 2-year RCT reported by Trimarco et al. 2012 enrolled 2409 people starting antihypertensive drugs, who were randomly assigned to chlortalidone 12.5–25 mg (n=1205) or to any other class of drugs other than diuretics (control group, n=1204). If blood pressure targets were not met, any other antihypertensive including diuretics could be added. People aged 18–75 years (mean 54 years) with previously untreated or poorly controlled stage 1 or 2 hypertension were included. People with clinically significant coexisting conditions were excluded.

Participants had clinic blood pressure measurements taken monthly by aneroid sphygmomanometer until clinic blood pressure was within target range (140/90 mmHg or 130/80 mmHg for people with diabetes), thereafter it was measured every 2 months. Each participant started treatment with 1 drug, which was titrated to the highest dose before another was added based on the GP’s judgement. The primary outcome was adherence to treatment.

The study was completed by 87% of those in the chlortalidone group and 85% of those in the control group. No significant difference was seen in adherence scores between the chlortalidone and control groups (0.91 vs 0.91). Significantly more people in the chlortalidone group had modified treatment (79%) compared with those not on first-line diuretics (44%, $p<0.0001$). Inadequate control of blood pressure was the most common reason for treatment modification (58% of modifications in the chlortalidone group and 37% in the control group, $p<0.0001$). In addition to the open-label nature of the study, a potential limitation of the study noted by the authors was that no pill count was done to confirm concordance with treatment.

The study by Messerli et al. (2011) demonstrates that low-dose hydrochlorothiazide may not be as effective as other antihypertensive treatments at lowering blood pressure. The findings of this analysis are consistent with NICE CG127, which recommends thiazide-like diuretics (for example, chlortalidone or indapamide) should be preferred to thiazide diuretics (hydrochlorothiazide or bendroflumethiazide) when diuretic treatment is indicated for the treatment of hypertension. The study by Trimarco et al. (2012) provides support for the
recommendations in **NICE CG127**, which noted that diuretics may not be the optimal first-line antihypertensive treatment for many people.

**Key references**


**Beta-blockers for hypertension**

**NICE CG127** does not recommend beta-blockers as initial routine therapy for uncomplicated hypertension. Beta-blockers may be considered as step-1 treatment in younger people who have intolerance or contraindication to ACE inhibitors or ARBs, women of child-bearing potential, or people with evidence of increased sympathetic drive.

**Wiysonge et al. (2012)** conducted a Cochrane review of 13 RCTs (n=91,561) of beta-blockers compared with placebo, no treatment or active controls for the first-line treatment of hypertension. The primary outcome was total mortality.

Total mortality did not differ significantly between beta-blockers and placebo (4 trials, n=23,613, RR=0.99, 95% CI 0.88 to 1.11); beta-blockers and diuretics (5 trials, n=18,241, RR=1.04, 95% 0.91 to 1.19); or beta-blockers and ACE inhibitors or ARBs (3 trials, n=10,828, RR=1.10, 95% CI 0.98 to 1.24). However, it was significantly higher for beta-blockers compared with CCBs (4 trials, n=44,825, RR=1.07, 95% 1.00 to 1.14), which corresponded to an absolute risk increase of 0.5% over 5 years.

There was no evidence that beta blockers reduced the risk of coronary heart disease when compared with placebo; ACE inhibitors or ARBs; CCBs; or diuretics. The risk of fatal or non-fatal stroke was significantly lower for beta-blockers compared with placebo (4 trials, n=23,613, RR=0.80, 95% CI 0.66 to 0.96). However, stroke reduction with beta blockers was less than that seen with CCBs (3 trials with 44,167 participants, RR 1.24, 95% CI 1.11 to 1.40) and ACE-inhibitor or ARBs (2 trials with 9951 participants, RR 1.30, 95% CI 1.11 to 1.53), but no significant difference was seen for diuretics (4 trials with 18,135 participants, RR=1.17, 95% CI 0.65 to 2.09).

Discontinuations due to adverse events did not differ significantly between beta-blockers and placebo, diuretics or CCBs. People on a beta-blocker had significantly higher rate of discontinuation than those on ACE inhibitors or ARBs (2 trials, n=9951, RR=1.41, 95% CI 1.29 to 1.54).

The authors stated that this analysis of 13 RCTs suggests that first-line beta-blockers for elevated blood pressure were not as good at decreasing mortality and morbidity as other classes of drugs: diuretics, calcium channel blockers, and renin-angiotensin system inhibitors.

The authors concluded that initiating treatment of hypertension with beta-blockers may lead to modest reductions in cardiovascular disease without significant effects on mortality. These effects of beta-blockers seem to be inferior to those of other antihypertensive drugs. This conclusion is consistent with current guidance in **NICE CG127** that does not consider beta-blockers to be the most effective initial treatment for hypertension.

**Key reference**
Spironolactone in resistant hypertension

**NICE CG127** recommends considering a low dose of spironolactone (25 mg daily) as an option for adding to the antihypertensive regimen at step 4 of the treatment algorithm if blood potassium level is 4.5 mmol/l or lower. At the time of publication of this Evidence Update, spironolactone did not have UK marketing authorisation for this indication.

**Václavík et al. (2011)** reported results of the addition of spironolactone (25 mg) in patients with resistant arterial hypertension (ASPIRANT) study. This randomised placebo-controlled, double blind trial enrolled 117 adults with resistant hypertension defined as clinic blood pressure greater than 140 mmHg systolic or 90 mmHg diastolic despite treatment with at least 3 antihypertensive drugs including a diuretic. People with diabetes or chronic kidney disease were enrolled if their blood pressure exceeded 130 mmHg systolic or 80 mmHg diastolic. The mean age of participants was about 61 years and body-mass index was about 32 kg/m². The mean number of antihypertensive drugs was 4.6 for people in the spironolactone group and 4.5 in the placebo group. Mean clinic blood pressure was 154/92 mmHg and 24 hour ABPM was 141/80 mmHg. Mean daytime ABPM was 142/82 mmHg.

The following groups were excluded: people with severe hypertension (greater than 180 mmHg systolic or 110 mmHg diastolic) needing immediate adjustment of treatment, renal insufficiency (GFR <40 ml/min); pregnant or lactating women or women of childbearing potential not using effective contraception;; hyperkalaemia greater than 5.4 mmol/l or hyponatraemia less than 130 mmol/l; people with known hypersensitivity to spironolactone; and people already taking an aldosterone antagonist. Participants had clinic visits at 4 and 8 weeks, with an additional visit at 2 weeks scheduled for people older than 75 years, and those with diabetes or chronic kidney disease. At each visit, blood pressure was measured 3 times with a calibrated mercury sphygmomanometer and the mean of the second and third readings was recorded. 24-hour ABPM was conducted at baseline and week 8.

The trial was stopped early at the first interim analysis because of significant reductions in systolic blood pressure. However, diastolic blood pressure did not reduce as much as expected and a revised power calculation estimated that about 5 times more participants would be needed to detect a significant difference in diastolic blood pressure between groups.

Spironolactone was associated with a greater reduction in ABPM daytime systolic blood pressure than placebo (mean difference=−5.4 mmHg, 95% CI −10.0 to −0.8 mmHg, p=0.024). The difference in diastolic blood pressure was not significant (mean difference=−1.0 mmHg, 95% CI −4.0 to 2.0 mmHg, p=0.358). The target clinic systolic blood pressure of less than 140 mmHg at 8 weeks was reached in 30 patients (54.5%) using spironolactone and in 24 patients (42.9%) using placebo (p=0.257). Adverse events were reported to be similar between groups with no significant difference in severe adverse events leading to treatment discontinuation (2 events for spironolactone and 1 event for placebo, p=0.618). Serum potassium increased by a median 0.3 mmol/l in the spironolactone group.

The authors noted that the lack of a significant difference in diastolic blood pressure may be influenced by the relatively low baseline diastolic blood pressure (mean office reading 92 mmHg) and that 38% of participants had isolated systolic hypertension.

The results of this study are consistent with the recommendation in **NICE CG127** to consider adding spironolactone to the antihypertensive regimen at step 4 of the treatment algorithm. Nevertheless, the number of studies of the optimal treatment for resistant hypertension identified in the full version of **NICE CG127** was limited, and further research is needed.

**Key reference**

Loop diuretics
Loop diuretics are not recommended in the antihypertensive treatment algorithm in NICE CG127.

Musini et al. (2012) did a Cochrane review of 9 double-blind placebo-controlled trials (n=460) of loop diuretics with at least 3 weeks of follow-up. Included studies had to recruit participants (mean age 54.4 years) with blood pressure of 140 mmHg or more systolic or 90 mmHg or more diastolic and could not titrate dose according to blood pressure response. This Cochrane review was an update of a previous publication, and the search period for new data was January 2009 to February 2012; no new trials were identified.

The best estimate of blood pressure reduction was $-7.9 \text{ mmHg}$ systolic (95% CI $-10.5$ to $-5.4 \text{ mmHg}$) and $-4.4 \text{ mmHg}$ diastolic (95% CI $-5.6$ to $-2.8 \text{ mmHg}$). There were no significant differences between diuretics and placebo in withdrawals due to adverse events.

Generally, the included studies were noted to be at high risk of bias in terms of selective reporting and at low risk of bias in terms of blinding. The authors noted that the meta-analysis did not provide a good estimate of the incidence of harm associated with loop diuretics because of the short duration of included studies. The authors concluded that more RCTs are needed to determine the effects of loop diuretics.

NICE CG 127 does not recommend the use of loop diuretics for the routine treatment of hypertension because, as indicated by this Cochrane review, the evidence base for blood-pressure lowering with loop diuretics remains limited and the studies have mainly been small and of short duration. This new analysis is not likely to affect the recommendations in NICE CG127.

Key reference
Musini VM, Rezapour P, Wright JM et al. (2012) Blood pressure lowering efficacy of loop diuretics for primary hypertension. Cochrane Database of Systematic Reviews issue 8: CD003825

Timing of stepping up treatment
NICE CG127 does not contain recommendations on what timescales should be used when considering stepping up antihypertensive treatment.

Lasserson et al. (2011) systematically reviewed 18 studies (n=4168) including at least 20 participants in each arm who started antihypertensive treatment after a placebo washout period and reported change from baseline in clinic systolic and diastolic blood pressures at least every 2 weeks after starting treatment. The mean reductions in systolic and diastolic blood pressures were extracted and the data were used to derive parameters for a model of the effect of time on blood pressure response.

All included studies used diastolic blood pressure for inclusion so no participants had isolated systolic hypertension. The half-lives of study drugs were 2–24 hours and effects of dose were assessed either by titration during treatment phases or by random assignment to fixed doses. The instrument used for measuring blood pressure and the number of readings taken differed between studies.

On average and across all drugs and doses, the time taken for people to reach 50% of the maximum predicted response to antihypertensive drugs appeared to be about 1 week, and most of the blood-pressure lowering appeared to occur within 4 weeks. When analysis included the effects of a titration schedule, the time to 50% maximum response was longer (1.2 weeks vs 0.7 weeks for systolic and 1.4 weeks vs 0.7 weeks for diastolic), and the plateau was higher (p values not reported).

The data did not show particular benefits of any class of antihypertensive drugs over another; however, the authors noted that there may not have been sufficient power to detect
differences between classes. They suggested that estimation of maximum response could be
done after 1–2 weeks to help clinicians to determine when a newly started antihypertensive
drug can be judged to be ineffective. Additionally, after 4 weeks little further benefit can be
expected. However, further research is needed to see whether treatment strategies based on
these results would result in better outcomes for patients.

This evidence suggests that healthcare professionals need not wait longer than 4 weeks
between titration of antihypertensive drugs. It is not likely to affect recommendations in NICE
CG127, but may be helpful to health professionals and patients when deciding when to move
to the next treatment step if blood pressure is not controlled.

Key reference
Lasserson DS, Buclin T, Glasziou P (2011) How quickly should we titrate antihypertensive medication?
Systematic review modelling blood pressure response from trial data. Heart 97: 1771–5

1.7 Patient education and adherence to treatment

Lay perspectives of hypertension and treatment adherence

NICE CG127 includes recommendations to enhance patient education and adherence to
treatment, and recognises that people vary in their attitudes to their hypertension and their
experience of treatment. Providing details of patient organisations is highlighted as potentially
being helpful. Interventions to overcome practical problems associated with non-adherence
are recommended if a specific need is identified because evidence supporting interventions to
increase adherence is inconclusive.

Marshall et al. (2012) did a systematic review of 53 qualitative studies based on face-to-face
interviews and focus groups about patients’ perspectives of hypertension and drug treatment
in people with uncomplicated hypertension that were published in peer-reviewed journals
(number of participants not reported). Studies based on telephone interviews or
questionnaires were excluded, as were studies with more than 50% of participants with
cardiovascular disease, diabetes or who were pregnant.

Many studies (20) were from the USA, 8 were from the UK, 7 were from Brazil, and the
remainder were from other countries worldwide; 24 studies included only participants from
minority ethnic groups. Topics covered were: patients’ understanding of causes, effects,
exacerbating factors and consequences of hypertension; attitudes to drug treatments; and the
perceived influences of stress, diet and racism.

Major themes of the research included that people thought that hypertension was related to
stress or worrying about work or family life or experiencing racism. Some people felt that their
hypertension was related to a particular stressful event in their lives. Hypertension was also
thought by some people to be temporary or curable, and to be distinct from high blood
pressure by others.

Most people recognised that hypertension caused serious complications such as stroke or
heart disease. Some people reported that taking drugs reduced anxiety or worries mostly
thought to be a direct effect of the drugs, but a few people thought that reduction in worry was
due to protection from the complications of hypertension. Participants in 2 studies thought that
antihypertensive drugs functioned as sedatives.

Headache and dizziness were commonly reported as possible symptoms of hypertension, but
many people reported no symptoms of hypertension. Some people reported taking drugs
according to the prescription, but many reported deliberate non-adherence, often because
people took the drug according to their perceived symptoms or level of stress, or to avoid
side-effects of the drugs. Unintentional non-adherence was due to forgetfulness, busy lives,
and healthcare costs.
The quality of each study was scored, and the score was used as one indicator of the robustness of the findings. Studies with a low quality score were not excluded because of lack of agreement by qualitative researchers on criteria to use, many possible qualitative methods and the role of subjective judgement in analysis.

Contrary to the conclusions of individual studies suggesting that culture-specific education is needed, perceptions of hypertension were similar across ethnic and geographical populations. People from minority ethnic groups reported experiencing racism in many studies, the stress of which was thought to exacerbate hypertension. Additionally, migrant populations perceived that they were more likely to have low paying jobs and more likely to have economic hardship.

The authors noted that to overcome problems with non-adherence, clinicians and educational interventions need to acknowledge and incorporate patients’ concerns and perspectives. For example, instead of denying the possibility of symptoms, it may be more helpful to say that many people report symptoms but they are not a reliable indication of fluctuations in blood pressure.

Although this study suggests that future educational interventions should incorporate and engage with commonly held beliefs about hypertension and adherence to treatment, it may also be useful for clinicians to discuss these topics with their patients. This evidence is not likely to affect recommendations in NICE CG127.

**Key reference**

**Areas not currently covered by NICE guidance**

**Baroreflex activation therapy**
NICE CG127 does not recommend any device-based methods for the treatment of hypertension.

Bisognano et al. (2011) reported on an RCT of baroreflex activation therapy (BAT) in people with uncontrolled hypertension (clinic blood pressure 160/80 mmHg or higher and systolic APBM 135 mmHg or more). All participants had the Rheos system implanted by a vascular, cardiothoracic or neuro-surgeon. The Rheos system consisted of a pulse generator with two leads, one of which was attached to each carotid sinus. Participants (n=265) were randomly assigned 2:1 to have the device turned on 1 month after the implantation procedure or 6 months later.

The trial had 5 primary endpoints: acute efficacy, sustained efficacy, procedural safety, BAT safety, and device safety. All endpoints needed to be met to demonstrate overall safety and efficacy. Efficacy endpoints were based on a reduction in systolic blood pressure of 10 mmHg or more. At baseline, people were taking an average of 5.2 (SD 1.7) antihypertensive drugs.

At 6 months, response (defined as the proportion of subjects that achieved at least a 10 mmHg reduction in systolic blood pressure compared with baseline, and with a superiority margin of 20%), was not significantly different in the group with devices switched on (54%) compared with those whose devices remained off (46%, \( p=0.97 \)). The group with devices switched on showed a mean reduction in blood pressure of 7 mmHg compared with those with devices switched off (\( p=0.08 \)). 88% of those who responded at 6 months maintained response at 12 months (\( p=0.001 \)).
The event-free surgery rate was 74.8%, which was lower than the prespecified safety level of 82% (p=1.00); BAT safety was 91.7% in those whose device was turned on after 1 month and 89.3% in those whose device was switched on 6 months later (p<0.001). Device safety was reported as an event-free rate of 87.2%, which was higher than the prespecified safety level of 72% (p<0.001).

This paper suggests modest blood pressure lowering with this device; however, the authors noted that they did not meet 2 of the 5 endpoints; that further trials are needed; and that a less invasive implant procedure has been developed, which may increase safety in future surgical procedures. This technology is unlikely to influence recommendations in NICE CG127.

**Key reference**

Bisognano JD, Bakris G Nardim MK et al. (2011) **Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized placebo-controlled Rheos pivotal trial.** Journal of the American College of Cardiology 58: 765–73

**Device-guided breathing**

NICE CG127 does not recommend any device-based methods for the treatment of hypertension.

In a meta-analysis, **Mahtani et al. (2012)** assessed 8 trials (n=494) of a device designed to lower breathing rate (Resperate) with the aim of reducing blood pressure. The device uses a breathing monitor and plays tones via headphones to guide inhalation and exhalation, aiming for less than 10 breaths per minute. Control interventions included meditation exercise, relaxing music, blood pressure monitoring or usual care.

Overall, device-guided breathing resulted in a reduction in systolic (~3.06 mmHg, 95% CI −4.68 to −1.43, p=0.0002) and diastolic blood pressure (~2.35 mmHg, 95% CI −3.47 to −1.22, p=0.0001). However, the risk of bias was assessed as moderate in 6 studies and high in 2 others. The authors noted concern that 5 of the trials were conducted or funded by the manufacturer of the device. Excluding these trials left 3 trials in 100 people, which showed no overall effect on systolic (~1.97, 95% CI −6.50 to 2.56, p=0.39) or diastolic blood pressure (~0.04, 95% CI −3.67 to 3.59).

All trials were short, with a maximum intervention duration of 9 weeks, and the authors noted variable compliance across studies, so current data do not allow any conclusions to be made about long-term efficacy. The authors concluded that the overall positive results of device-guided breathing ‘should be interpreted with caution because of study size, cost of device, variability in study quality and potential conflicts of interest from the trial sponsors and the manufacturers of the Resperate device.’

Further independent trials are needed to assess the blood-pressure lowering efficacy of this device. The available evidence does not seem to support the use of this device for the treatment of hypertension and is not likely to influence the recommendations in NICE CG127.

**Key reference**

2 New evidence uncertainties

During the development of the Evidence Update, the following evidence uncertainties were identified for the NHS Evidence UK Database of Uncertainties about the Effects of Treatments (UK DUETs).

Initiating and monitoring antihypertensive drug treatment, including blood pressure targets

- Evening versus morning dosing regimen drug therapy for hypertension
- Pharmacotherapy for mild hypertension

Choosing antihypertensive drug treatment

- Blood pressure lowering efficacy of loop diuretics for primary hypertension
- Different antihypertensive strategies in patients with diabetes, nephropathy and a history of myocardial infarction for the treatment of hypertension and prevention of heart failure

Further evidence uncertainties for hypertension can be found in the UK DUETs database and in the NICE research recommendations database.

UK DUETs was established to publish uncertainties about the effects of treatments that cannot currently be answered by referring to reliable up-to-date systematic reviews of existing research evidence.
Appendix A: Methodology

Scope

The scope of this Evidence Update is taken from the scope of the reference guidance:


The theme of lifestyle interventions was not covered because this body of literature is unlikely to have changed in recent years; certain non-drug interventions were included; and a new theme of blood pressure thresholds, targets or goals was included.

Searches

The literature was searched to identify studies and reviews relevant to the scope. Searches were conducted of the following databases, covering the dates 29 November 2010 (the end of the search period of NICE clinical guideline 127) to 21 September 2012:

- CDSR (Cochrane Database of Systematic Reviews)
- CINAHL (Cumulative Index to Nursing and Allied Health Literature)
- EMBASE (Excerpta Medica database)
- MEDLINE (Medical Literature Analysis and Retrieval System Online)
- NHS EED (Economic Evaluation Database)

Table 1 provides details of the MEDLINE search strategy used, which was adapted to search the other databases listed above. The search strategy was based on the searches used for NICE CG127 with some changes to reflect the changes in scope, and was used in conjunction with validated Scottish Intercollegiate Guidelines Network search filters for RCTs and systematic reviews.

One other study (Clark et al. 2012) was also identified outside of the literature search. Figure 1 provides details of the evidence selection process. The long list of evidence excluded after review by the Chair of the EUAG, and the full search strategies, are available on request from contactus@evidence.nhs.uk

There is more information about how NICE Evidence Updates are developed on the NHS Evidence website.

Table 1 MEDLINE search strategy (adapted for individual databases)

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<td>3</td>
<td>((elevat$ or high or increas$) adj systolic or diastolic or arterial) adj pressure?).ab./freq=2</td>
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<td>((elevat$ or high or increas$) adj systolic or diastolic or arterial) adj pressure?).ab./freq=2</td>
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<td>4</td>
<td>5</td>
<td>((elevat$ or high or increas$) adj blood pressure?).ab./freq=2</td>
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<td>5</td>
<td>6</td>
<td>(elevat$ or high$ or increas$) adj systolic or diastolic or arterial) adj pressure?).ti.</td>
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<td>6</td>
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<td>or1-7</td>
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<td>7</td>
<td>8</td>
<td>(pre eclampsia or preeclampsia or pregnan$ or malignan$ or portal or renal or ocular or intracranial).ti.</td>
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<td>8</td>
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<td>8 not 9</td>
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<td>9</td>
<td>10</td>
<td>8 not 9</td>
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</tbody>
</table>
Figure 1 Flow chart of the evidence selection process

1948 records identified through search

- 471 duplicates from searching

1477 records after duplicates removed

- 935 records excluded at first sift

542 records included after first sift

- 305 records excluded at second sift

237 records included after second sift

- 210 records excluded at critical appraisal and evidence prioritisation

28 records discussed by EUAG

- 1 additional record identified by EUAG outside original search

- 8 records excluded by EUAG

20 records included by EUAG in published Evidence Update

EUAG – Evidence Update Advisory Group
Appendix B: The Evidence Update Advisory Group and Evidence Update project team

Evidence Update Advisory Group

The Evidence Update Advisory Group is a group of topic experts who review the prioritised evidence obtained from the literature search and provide the commentary for the Evidence Update.

Professor Bryan Williams – Chair
Professor of Medicine, Director; National Institute for Health Research University College London Hospitals Biomedical Research Centre, Institute of Cardiovascular Science, University College London.

Professor Mark Caulfield
Director, William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London

Dr John Crimmins
General Practitioner, Vale of Glamorgan

Dr Terry McCormack
General Practitioner, Spring Vale Medical Centre, North Yorkshire

Professor Richard McManus
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