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Comparative Clinical- and Cost-Effectiveness of Candesartan and Losartan in the Management of Hypertension and Heart Failure

A Systematic Review, Meta- and Cost-Utility Analysis

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ABSTRACT

Background The UK National Health Service (NHS) currently spends in excess of £250 million per annum on angiotensin-II receptor blockers (ARBs) for the treatment of hypertension and heart failure; with candesartan currently dominating the market. With the recent introduction of generic losartan, we set out to directly compare the branded market leader to its now cheaper alternative.

Objectives The primary objectives were to compare the blood pressure (BP) lowering efficacy and cardiovascular outcomes of candesartan and losartan in the treatment of essential hypertension and chronic heart failure respectively. The secondary objective was to model their comparative incremental cost-effectiveness in a UK NHS setting.

Search strategy Cochrane Central Register of Controlled Trials (*Cochrane Library* 2009, issue 2), which contains the Hypertension and Heart Group's specialist register, Medline (1950 to February 2010), and Embase (1980 to February 2010).

Selection criteria Randomised studies of candesartan versus losartan in adults (>18 years).

Main outcome measures Hypertension: mean change from baseline in trough (24 hours post dose) systolic and diastolic BP. Heart Failure: Composite of cardiovascular death and hospital admission for management of heart failure.

Data extraction Two reviewers applied inclusion criteria, assessed trial quality, and extracted data.

Results Nine (three of which met inclusion criteria) and zero trials compared candesartan directly with losartan in the treatment of hypertension and heart failure respectively. A between-treatment difference of -1.96 mmHg (95% confidence interval [CI] -2.40 to -1.51) for trough diastolic BP and -3.00 mmHg (95% CI -3.79 to -2.22) for trough systolic BP in favour of candesartan was observed. Based on this differential, a 10-year Markov model estimates the cost per quality adjusted life-year gained to exceed £40,000 for using candesartan in place of generic losartan.

Conclusion Candesartan reduces BP to a slightly greater extent when compared to losartan, however such difference is unlikely to be cost-effective based on current acquisition costs, perceived NHS affordability thresholds and use of combination regimens. We could find no robust evidence supporting the superiority of candesartan over losartan in the treatment of heart failure. We therefore recommend using generic losartan as the ARB of choice which could save the UK NHS approximately £200 million per annum in drug costs.

What is known about this topic

Several angiotensin-II receptor blockers are licensed for the treatment of hypertension and heart failure; with candesartan currently dominating the market. Until recently, these agents were of comparable price however losartan is now much cheaper than its within-class comparators due to loss of exclusivity.

What this study adds

We could find no case to support the prescribing of candesartan over losartan in the treatment of hypertension or heart failure. Using generic losartan as the angiotensin-II receptor blocker of choice could save the UK NHS approximately £200 million per annum.

INTRODUCTION

Cardiovascular disease (CVD) is the leading cause of morbidity and mortality worldwide,¹ despite advances in diagnosis and management. Hypertension is a major risk factor for CVD, and a risk factor for the development of heart failure. The goal of hypertension therapy is to reduce blood pressure (BP) to less than 140/90 mmHg in elderly patients and to less than 130/85 mmHg in the young or middle-aged and in patients with diabetes mellitus irrespective of age.² Patients with symptomatic chronic heart failure (CHF) have reduced cardiac output, characteristic symptoms of dyspnoea, orthopnoea and decreased exercise capacity and have a high risk of death and hospitalisation.³

Although angiotensin-converting-enzyme (ACE) inhibitors are a well established class of treatment, some patients are unable to tolerate them. In recent years, angiotensin-II receptor blockers (ARBs) have emerged as an alternative option for targeting and inhibiting the renin-angiotensin-aldosterone system (RAAS) by selectively blocking the AT₁ subtype.⁴ ARBs exert a similar antihypertensive effect to ACE inhibitors,^{5,6} however, their specificity avoids major ACE inhibitor-related adverse effects, such as cough and angioedema, which is believed to result from non-specific interference of bradykinin metabolism.⁷ Compared with losartan (Cozaar; MSD), the first ARB to receive a marketing authorisation for the management of hypertension, candesartan (Amias; Takeda), the current market leader, has a slower dissociation rate from the AT₁ receptor,⁸ potentially providing it with a longer-acting antihypertensive effect.

Until recently both agents were comparably priced, however, the patent for losartan has now expired and cheaper generic alternatives are emerging. We therefore undertook a systematic review and meta-analysis of all published studies comparing losartan and candesartan in a head-to-head randomised controlled trial design to obtain estimates on their relative efficacy and cost-effectiveness.

METHODS

Systematic review & meta-analysis

We searched for relevant randomised trials in the Cochrane Central Register of Controlled Trials (Cochrane Library 2009, issue 2), which contains the Hypertension and Heart Group's specialist register, Medline (1950 to February 2010), and Embase (1980 to February 2010). The search terms and limits are provided as supplementary material. In addition to the database search strategy, we hand-searched the reference list of identified manuscripts to identify additional relevant studies. To formulate and ensure optimal reporting of the systematic review and meta-analysis, the established PRISMA [Preferred Reporting Items for Systematic reviews and Meta-analysis] statement was followed.⁹

Inclusion criteria

For hypertension, we included trials if they were of randomised, double-blind, active-controlled design (investigating candesartan and losartan), provided they recruited adult patients (>18 years), were of parallel or cross-over design and the treatment period was of at least four weeks duration. For heart failure, we included trials if they were of randomised, double-blind, active- or placebo-controlled design of adult patients (> 18 years) with a left ventricular ejection fraction (LVEF) not exceeding 40%.

Exclusion criteria

Studies were excluded if they were open-label, observational, or not fully published (e.g. only presented at conference proceedings or solely available in abstract form). Non-English language publications were also excluded.

Endpoints

The primary efficacy endpoints for extraction from the hypertension trials were the mean change from baseline in trough (24 hours post dose) diastolic BP (DBP) and systolic BP (SBP). The primary efficacy endpoint for extraction from the heart failure trials was a composite of cardiovascular death and hospital admission for management of heart failure.

Data from systematic reviews or previous meta-analyses were not used to enable the collection of data from original sources; however any such publications identified served as a comparator to ensure that all relevant studies had been included within this review. Secondary searches were conducted from the reference lists of manuscripts identified. To minimise bias, two investigators (P.N.B. and A.M.G.) reviewed references and abstracts retrieved by the search and selected potentially relevant publications against the pre-specified inclusion and exclusion criteria. Important clinical and methodological study characteristics were extracted onto a standard form, checked, and recorded. Any discrepancies or lack of agreement between the two reviewers were referred to a third independent investigator (A.D.H.) for arbitration. An assessment of risk of bias (using established criteria)¹⁰ was also undertaken. All analyses were based on *intention-to-treat* data. For any trials that reported data using a *per-protocol* analysis, *intention-to-treat* values were extracted.

We used a random-effects model^{11;12} to compare outcomes, reported as the weighted mean difference; therefore estimates meta-analysed over multiple trials are average treatment effects. To assess the presence of heterogeneity across pooled studies, the Cochran Q and Higgins I-squared statistics were calculated.¹³ Analyses were conducted using *StatsDirect*® version 2.7.7 (Altrincham, Cheshire, UK).

Cost-utility analysis

A ten-year cost-utility analysis of adopting losartan or candesartan using a Markov state transition model (see Figure 2) was developed using *Microsoft Excel* (*Microsoft Corporation, 2007*). Structurally, the model assumes that all patients can be in one unique health state in a given cycle (one of: 'Well', 'Coronary Heart Disease (CHD)', 'Stroke' and 'Death') with the entire cohort initially in the 'Well' state. We use a ten-year time horizon and annual cycle length for comparison of the costs and health outcomes for patients with essential hypertension, from the viewpoint of the UK National Health Service (NHS). We consider development of primary disease and subsequent quality-adjusted survival.

Baseline risk parameters (age, gender, SBP), smoking status, presence/absence of diabetes or atrial fibrillation (AF) and high density lipoprotein (HDL) levels and drug treatment effects on SBP were computed. A risk sub-model was then used to calculate the age- and sex-related probabilities of stroke and CHD risk for each year in the model, based on Framingham risk equations.^{14,15} As noted by Wolf PA *et al* (1991), SBP is an accurate predictor of stroke risk.¹⁵ Although, other studies have tried to improve the predictive value of outcomes beyond that which the well established Framingham risk score could predict, a recent review showed that the studies were hampered by methodological flaws.¹⁶ We model male and female cohorts separately into baseline risk by SBP level (mild 140 mmHg, moderate 165mmHg, high 180mmHg) and calculate subsequent mortality due to myocardial infarction (MI) and cerebrovascular events.

To overcome the normal fixed temporal probability limitation of standard Markov models, annual time-dependent transition probabilities were calculated using look-up tables for age and gender-related all-cause mortality from UK life tables and data from the MI/stroke mortality in the Framingham follow-up study.¹⁷ Mortality was limited to 10 years post-disease since the regression equations for stroke progression are valid only for a 10-year period. Half-cycle correction was used when calculating life-years.¹⁸

For a one thousand essential hypertension patient cohort simulation, given varying baseline risks of developing CHD and CVD, we calculated the following secondary economic outcomes: total and average costs per strategy, life-years gained, quality-adjusted life-years (QALYs) gained and report the primary outcome of incremental cost-effectiveness ratios (ICERs) of the two treatments by calculating the ratio of the averaged incremental costs to incremental QALYs. An ICER value of £30,000 per QALY was used as an upper threshold for NHS cost-effectiveness.

Best estimates of disease-state costs and utility values for the base-case model were estimated from the published literature. We considered the direct costs for drug acquisition and those associated with managing initial non-fatal stroke and CHD events as well as the costs for ongoing management, inflated from 2005 to 2009 base year values using the Hospital and Community Pay & Price Index.¹⁹ In line with the National Institute for Health and Clinical Excellence (NICE) Technology Appraisals, annual disease-state quality-of-life was estimated, assuming that MI survivors had higher utility after their initial events and stroke survivors had constant utility thereafter. Cost and health benefits were discounted at a rate of 3.5% in concordance with NICE Technology Appraisal guidance. We assume equal utility loss in both arms due to adverse treatment effects since we are comparing two drugs within the same class without proven evidence of any tolerability differences. The death state is associated with zero cost and utility.

RESULTS

Hypertension

Overall, nine studies fulfilled inclusion criteria for hypertension representing 3090 patients.²⁰⁻²⁷ A summary of the characteristics of the studies included within this review are given in Table 1. Further details of the studies are included as supplementary material. Of the nine studies, two compared low-dose losartan with low-dose candesartan (50mg versus 8mg); two compared low-dose losartan with mid-dose candesartan (50mg versus 16mg); two compared high-dose losartan with mid-dose candesartan (100mg versus 16mg); and three compared high-dose losartan with high-dose candesartan (100mg versus 32mg). The primary efficacy endpoint data were extracted from these studies and pooled to estimate the weighted average reduction in DBP and SBP from baseline in the two treatment groups (see Figure 3a and Figure 3b respectively). These analyses estimate a between-treatment difference of -1.89 mmHg (95% confidence interval (CI) -2.29 to -1.48) for trough DBP and -2.96 mmHg (95% CI -3.60 to -2.32) for trough SBP in favour of candesartan. Overall, the nine studies generated an I-squared statistic of 32.6% for trough DBP and 52.4% for trough SBP indicating that although the results are statistically significant, there is a mild-to-moderate degree of heterogeneity between the individual studies when combined.

For the purpose of the cost utility-analysis we re-performed the meta-analysis using only the three studies which investigated both ARBs at their respective maximal licensed doses to derive a point estimate based on data reporting on comparative doses (see Figure 4a and Figure 4b for reduction in DBP and SBP from baseline, respectively). This produced a between-treatment difference of -1.96 mmHg (95% CI -2.40 to -1.51) for trough DBP and -3.00 mmHg (95% CI -3.79 to -2.22) for trough SBP in favour of candesartan.

Base-case cost-utility model

The base-case Markov model uses a generic losartan retail price of £6.47 (100mg; 28-day pack price) compared to the list price for candesartan 32mg (£16.13; 28-day pack price) at a moderate baseline risk (SBP: 165mmHg) in a cohort of males and females aged 65 years. The difference in mean trough SBP between candesartan and losartan was obtained from the meta-analysis (-3.00 mmHg). The estimated ICERs for males and females with 'moderate' risk are £44,930 and £53,804, respectively, demonstrating the cost-effectiveness of losartan relative to candesartan at current generic acquisition costs over a 10-year horizon.

Sensitivity analyses

We also modelled four alternative scenarios using one-way sensitivity analyses from the base-case model:

Variation in baseline risk

The baseline risk was varied by increasing the cohort pre-treatment SBP in the range 140-180mmHg. The cost-effectiveness of candesartan decreases as the baseline risk lowers, as would be expected as the value of treatment is less when fewer patients develop disease. The range of ICERs is £41,469 – £52,644 for males and £41,591 – £85,244 for females.

Variation in hypertensive effectiveness

We firstly looked at cost-effectiveness variations from the base-case for males and females at the limits of the 95% CI for the trough SBP identified in the random effects meta-analysis (-2.22 to -3.79 mmHg). The ICERs are £71,049 and £87,015 for a 2.22mmHg SBP reduction in males and females, respectively, and £44,930 and £53,804 for a 3.79mmHg SBP reduction in males and females, respectively. Therefore, within the identified pooled range of statistical uncertainty, losartan remains the most cost-effective treatment strategy.

Projected pricing for losartan

Based on previous price falls following patent loss, the acquisition cost of generic losartan may drop to around £0.88 per pack. Based on these figures the base-case ICER would further increase to £74,901 and £91,368 for males and females, respectively. Hence candesartan becomes increasingly unfavourable.

Variation in age

Finally, we looked at variation in the cost-effectiveness with changes in the cohort starting age for males and females. The ICER at 35 years was £151,140 and £369,075 for males and females, respectively, decreasing to the base-case values at age 65. Therefore, throughout the wide range of initial ages, losartan remains the cost-effective strategy.

Heart Failure

Overall, six studies were identified for heart failure; three studies reporting on losartan and three studies reporting on candesartan; although no published head-to-head studies were found (see Table 1).

DISCUSSION

Hypertension

This analysis provides a comprehensive overall estimate of the between-treatment difference in efficacy (reduction in BP) for candesartan as compared to losartan. A between-treatment difference of -1.96 mmHg (95% CI -2.40 to -1.51) for trough DBP and -3.00 mmHg (95% CI -3.79 to -2.22) for trough SBP in favour of candesartan was observed based on comparative studies at their maximal licensed doses.

Based on our calculated BP-differential and using a 10-year Markov model, we estimate that the cost per QALY-gained will exceed £40,000 if candesartan was used in preference to generic losartan. Our base-case model used a cohort of patients at moderate CHD/CVD risk (baseline SBP of 165 mmHg) and the results demonstrate cost-effectiveness of losartan with ICERs [for candesartan] of £44,930 and £53,804, for males and females, respectively. Sensitivity analyses suggests that the case for losartan adoption holds across plausible variation in CHD and CVD risk, relative hypertension reducing effect, gender and patient cohort starting age. This case is strengthened further in a situation where the acquisition cost of the generic drug falls further[#], as predicted, or if the patient is female, younger or mildly hypertensive. **In addition, the population level benefit achieved by reducing BP could be attained by using cheaper low dose combination therapy regimens.**

Heart Failure

In the absence of comparative trials directly comparing the efficacy of candesartan versus losartan in CHF, a qualitative analysis of the key studies was undertaken as an alternative to a quantitative meta-analysis.

Candesartan

The CHARM-Alternative study²⁸ was a placebo-controlled randomised trial of candesartan in 2,028 patients with a LVEF \leq 40% who were intolerant of an ACE inhibitor (72% cough, 13% symptomatic hypotension, 12% renal dysfunction). The primary composite endpoint was significantly reduced with candesartan (334/1013) in comparison with placebo (406/1015) [hazard ratio (HR) 0.77, 95% CI 0.67-0.89; $p=0.0004$]. This corresponds to a relative risk reduction (RRR) of 23% (absolute difference = 7%) and a number needed to treat (NNT) of 14 (i.e. fourteen patients need to be treated for the duration of the study to prevent one patient from dying of a cardiovascular event or being hospitalised for treatment of heart failure). The primary endpoint was powered to a statistically significant level by the reduction in hospital admission for CHF [HR 0.68, 95% CI 0.57 to 0.81; $p<0.0001$] as the reduction in cardiovascular death was non-significant [HR 0.85, 95% CI 0.71 to 1.02; $p=0.072$].

The CHARM-Added study²⁹ (ACE inhibitor + candesartan versus ACE inhibitor + placebo) recruited 2,548 patients with a LVEF \leq 40% who were receiving an optimal tolerated dose of an ACE inhibitor. The primary composite endpoint (cardiovascular death and hospital admission for HF) was significantly reduced [by 15%] with candesartan (483/1276) in comparison with placebo (538/1272) [Hazard ratio (HR) 0.85, 95% CI 0.75-0.96, $p=0.011$]. This corresponds to a RRR of 16% (absolute difference = 4.4%) and a NNT of 23. A statistically significant reduction was observed for both components of the primary endpoint: cardiovascular death [HR 0.84, 95% CI 0.72 to 0.98; $p=0.029$] and hospital admission for CHF [HR 0.83, 95% CI 0.71 to 0.96; $p=0.014$]. The composite secondary endpoint of all-cause mortality or first CHF hospitalisation was also significantly reduced in the candesartan group [HR 0.87, 95% CI 0.78-0.98; $p=0.021$]. Of note, at baseline, 55% of patients randomised to receive dual therapy were taking a beta-blocker, whilst only 17% were also taking spironolactone [aldosterone antagonist]. With regards to safety, of the 74 patients treated with candesartan + ACE inhibitor who were also taking spironolactone, three (4%) developed serum potassium levels >6 mmol/L compared with one of 71 (1%) in the placebo group (number-needed-to-harm = 33).

Losartan

In comparison, the recently published HEAAL study³⁰ (low dose losartan [50mg daily] versus high dose losartan [150mg daily]) recruited 3,846 patients with a LVEF \leq 40% and a documented intolerance to an ACE inhibitor. The proportion of patients who met the primary composite endpoint (death and admission for HF) was 43% (losartan 150mg) versus 46% (losartan 50mg), which was regarded as a modest yet significant benefit (HR 0.90, 95% confidence intervals 0.82 to 0.99; $p=0.027$). In comparison with the CHARM-Added study, at baseline, 72% of patients randomised to both arms were taking a beta-blocker, and 38% were also taking an aldosterone antagonist. Overall, the authors reported superiority of losartan 150mg once daily over 50mg once daily for the treatment of CHF. With regards to safety, losartan 150mg daily compared with 50mg daily was noted to cause a significant reduction in GFR (6.1mL/min versus 1.9mL/min; $p<0.001$, respectively). The incidence of premature discontinuation from therapy as a result of hyperkalaemia, hypotension, renal impairment, and angioedema was non-significantly different between the two arms ($p=0.20$, $p=0.65$, $p=0.22$, and $p=0.12$, respectively). The investigators put forward the hypothesis that up-titrating

1
2 the dose of losartan as monotherapy may provide equally favourable results to a combination of ACE inhibitor and
3 ARB as demonstrated in the CHARM-Added study.
4

5 **UK Licensing**

6 Both losartan and candesartan hold a marketing authorisation for the treatment of essential hypertension and CHF (in
7 patient with a LVEF \leq 40%). Two key differences in their licensing criteria are noted: [1] Essential hypertension:
8 candesartan is indicated for adults only, whereas losartan is also indicated for children and adolescents aged 6-18
9 years; and [2] CHF: candesartan is indicated for use as monotherapy or in combination with an ACE inhibitor (following
10 disease progression, incompatibility, or contraindication), whereas losartan is only indicated as monotherapy in place
11 of an ACE inhibitor.
12

13 **Strengths & Limitations**

14 The use of meta-analyses in estimating comparative-effectiveness has several strengths but some important
15 limitations are apparent. First, all data included within this analysis were extracted from robust trials which met strict
16 inclusion criteria. The requirement of a randomised, double-blinded, controlled trial ensured that the final dataset
17 would be subject to the least possible amount of bias. Second, the efficacy outcome selected (reduction in SBP) is well
18 accepted as an informative outcome measure concerning hypertension and risk factor for the development of CVD.
19 Third, all included study manuscripts were published in full allowing for *intention-to-treat* analyses.
20
21

22 However, the results obtained from our meta-analysis are subject to the limitations that are inherent in any meta-
23 analysis. First, individual prospective studies only provide information over a short period of time (4 to 12 weeks)
24 whilst the implications are extrapolated for life-long therapy. Second, excluding trials that have not been published
25 may exaggerate the treatment effects observed as publications tend to favour those with positive results. Third,
26 pooling of data from trials with differences in trial design, methodology, and patient groups may result in a
27 heterogeneous dataset from which conclusions are drawn. However, such differences in patient groups may serve to
28 strengthen the meta-analysis by allowing generalisability of the results to a broader group. Furthermore, the use of a
29 random-effects model and tests to identify the presence of significant heterogeneity aid to minimise and highlight the
30 impact of such effect. Fourth, this analysis was restricted to data relating to the adult population, therefore it cannot
31 be directly extrapolated to patients under the age of 18 years. Fifth, doses employed within the clinical trials are not
32 always consistent with those used in clinical practice, therefore limiting the external validity of these data. To
33 minimise the extent of this, only data comparing high-dose losartan with high-dose candesartan were used in the
34 subsequent cost-utility analysis. Finally, data within this analysis only relates to the use of losartan and candesartan
35 for the treatment of hypertension in patients with no other co-morbidities and therefore cannot be directly
36 extrapolated to all patients.
37
38

39 We used best evidence and the well validated Framingham risk equations as criteria for the development of disease
40 and subsequent mortality in our cost-utility analysis. Our model is however subject to some caveats. The model
41 calculates only the first episode of MI or stroke events and the subsequent quality-of-life and costs associated with
42 survivors. It does not consider that stroke patients may experience a fatal MI or *vice versa*. Whilst we could have
43 constructed a fully probabilistic model, for ease of understanding and presentation we used deterministic analyses
44 allowing for uncertainty using sensitivity analysis. This showed, that under plausible variation in key parameter values
45 using one-way sensitivity analyses, that losartan remains the more cost-effective of the two studied ARBs.
46
47

48 **Place in therapy for ARBS**

49 Currently there are 11 ACE inhibitors and seven ARBs available in the UK.³¹ The UK National Institute for Health and
50 Clinical Excellence (NICE) offers guidance on the use of these drugs in the following areas: CHF, hypertension, MI
51 (secondary prevention), type II diabetes, and chronic kidney disease. Where either an ACE inhibitor or an ARB is
52 indicated, NICE recommend that an ACE inhibitor is routinely the drug of choice on the basis that there is a more
53 robust evidence-base for their use. A recent review also suggested that ARBs may be less effective than even cheaper
54 ACE inhibitors for MI protection.³² However a meta-analysis has suggested that ARBs are indeed as effective as ACE
55 inhibitors on the risk of MI, cardiovascular mortality and total mortality and also concluded that they may even be
56 slightly more protective than ACE inhibitors on the risk of stroke.³³ As CHD is more common than cerebrovascular
57 disease it seems reasonable that ACE inhibitors remain first-line in all (except perhaps in some high-risk groups).
58

59 For the treatment of hypertension, if either an ACE inhibitor or an ARB is indicated, the NICE recommendation
60 stipulates using a drug that can be taken once daily, is generically prescribed, and minimises cost.³⁴ For heart failure,
combined treatment with both an ACE inhibitor and an ARB currently has a limited role. For patients with heart failure
who remain symptomatic despite the use of a diuretic, beta-blocker, and ACE inhibitor, options include to either add

1
2
3 in and aldosterone antagonist, an ARB or hydralazine combined with a nitrate.³⁵ Routine treatment with an ACE
4 inhibitor in combination with an ARB is not recommended as recent publications have found little evidence to support
5 this.^{36,37} A recently published meta-analysis regarding the use of an ARB in combination with an ACE inhibitor
6 concluded that there was no clear survival benefits associated with the combination treatment strategy.³⁸
7

8 **ARB prescribing recommendations**

9 We recommend that generic losartan be initiated in all patients indicated for an ARB in both hypertension and heart
10 failure. ARBs should not routinely be combined with ACE-inhibitors and primarily be used in patients who are ACE-
11 inhibitor intolerant. For example, for existing patients on candesartan for hypertension we recommend changing to
12 losartan except in the rare scenario of prior intolerance to losartan. For existing patients on candesartan for heart
13 failure where not already on maximal target dose, ARB dose escalation is encouraged. If a patient on candesartan is
14 due for dose escalation, we recommend changing to losartan at this point unless intolerant. Where a patient is on
15 maximal dose candesartan for heart failure, we recommend that the decision to switch be considered on a case-by-
16 case basis by the responsible physician.
17

18 **Dosing**

19 The losartan dose used in hypertension should be 50mg or 100mg daily depending on whether the existing ARB dose
20 is at the lower or upper end of its dosing schedule. 150mg daily is now the target dose for heart failure [unlicensed].
21

22 **CONCLUSION**

23
24 Although candesartan, the most widely prescribed ARB, appears to reduce BP to a slightly greater extent when
25 compared to losartan, such difference is of questionable clinical significance in the context of combination drug
26 regimens and does not appear to be cost-effective based on current and future acquisition costs of losartan and
27 perceived NHS affordability thresholds. We could find no robust evidence supporting the superiority of candesartan
28 over losartan in the treatment of heart failure. We therefore recommend adopting generic losartan as the ARB of
29 choice which could, based on 2009 prescribing figures in primary care alone, save the UK NHS approximately £200
30 million per annum in drug costs.
31

32
33 **#At the time of publication, the price of generic losartan had fallen to £3 per pack.**
34

35 *Competing interests: We declare no support from any organisation for the submitted work; no financial relationships*
36 *with any organisations that might have an interest in the submitted work in the previous three years and no other*
37 *relationships or activities that could appear to have influenced the submitted work.*
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FIGURES

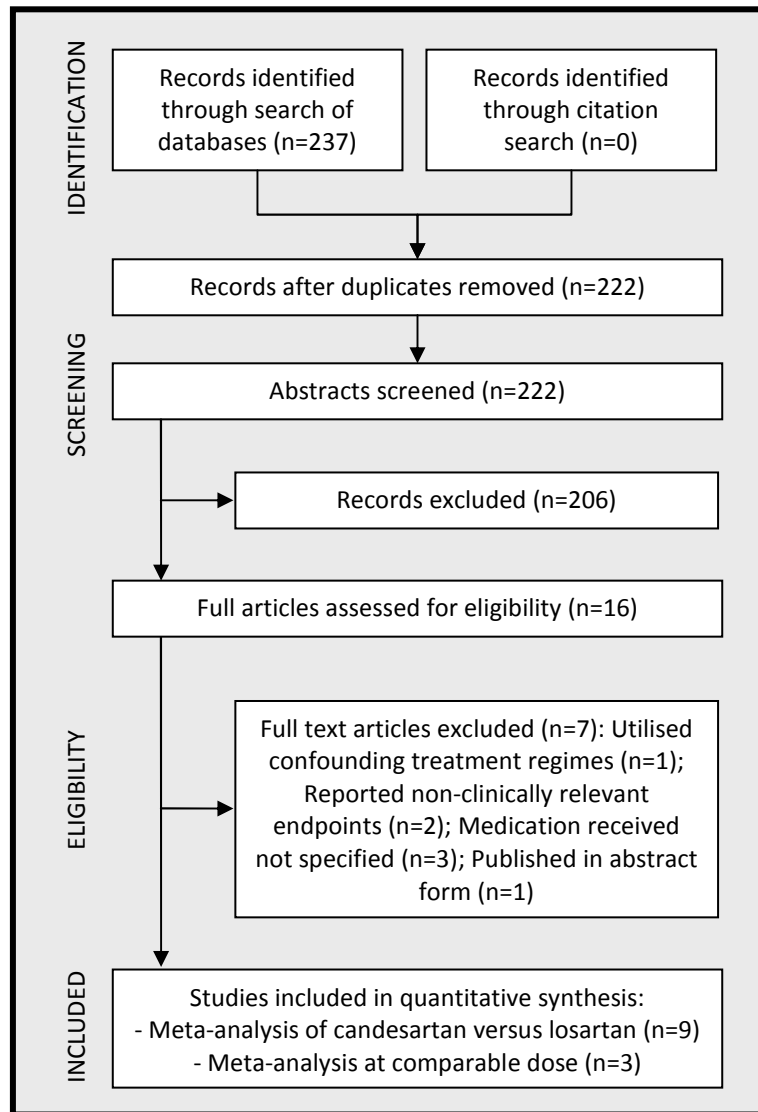


Figure 1a: Flow of studies identified from the systematic review for hypertension

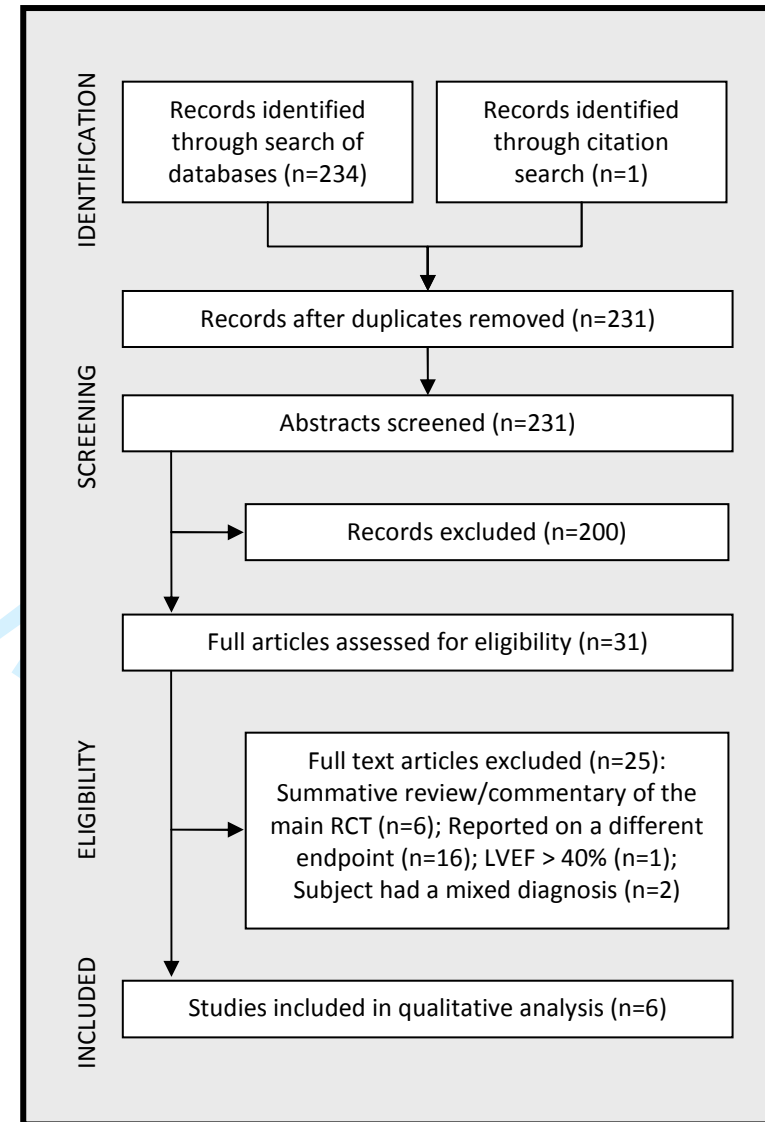


Figure 1b: Flow of studies identified from the systematic review for heart failure

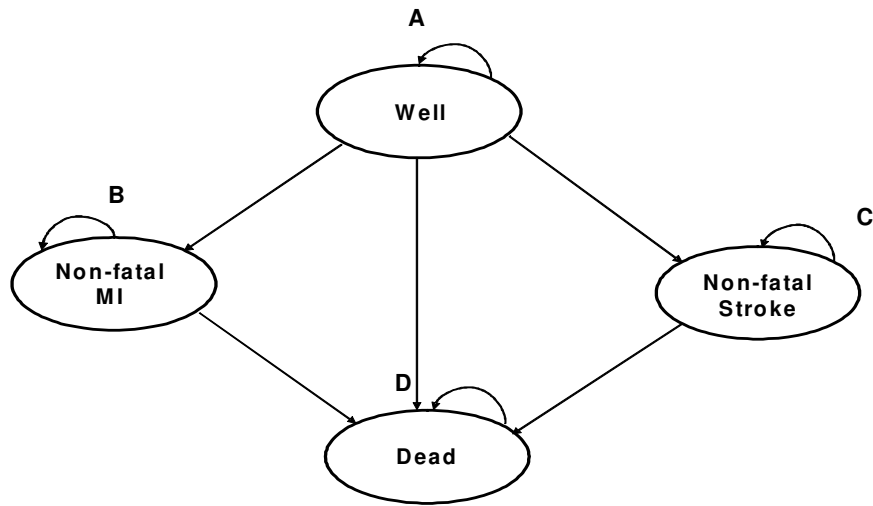


Figure 2: Markov State Transition diagram used for the cost utility-analysis. The patient cohort all start in State A ('Well') and can transition annually to the CHD and cerebrovascular disease states (B and C) denoted by the arrows, or they can survive or die from either myocardial infarction (MI) or stroke events from states B and C, respectively or die from other causes. The time horizon of the model is 10 years.

Review Only

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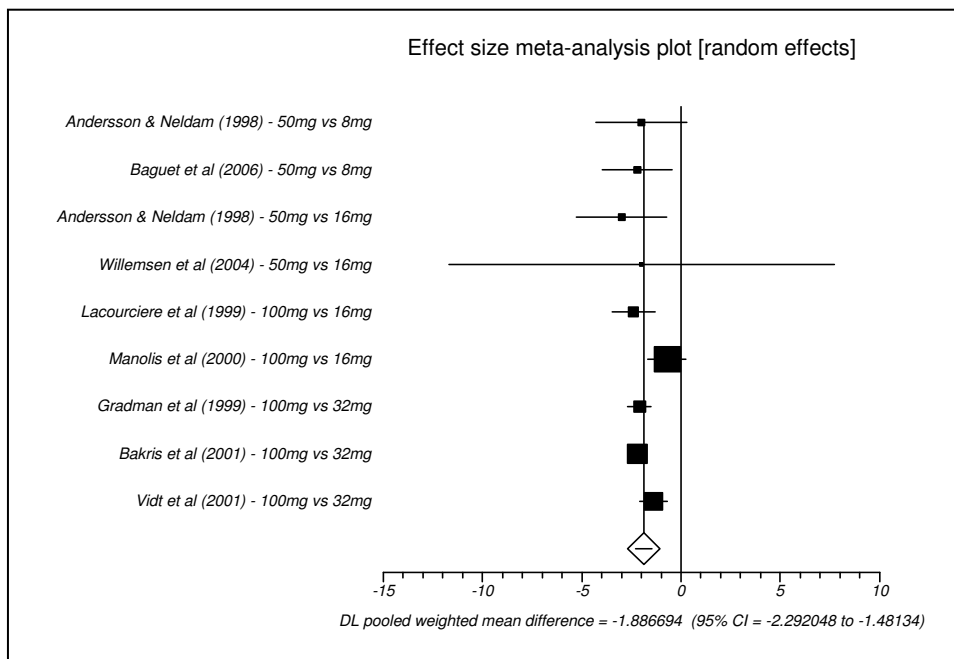


Figure 3a: Forest plot of the weighted mean difference (WMD) for absolute difference in trough diastolic blood pressure from baseline to end of study period (4 to 12 weeks) of randomised controlled trials comparing losartan with candesartan as monotherapy for the treatment of mild-to-moderate hypertension. The black squares represent the WMD for individual studies and the horizontal line represents the associated 95% confidence interval. The diamond and horizontal line within it represents the random-effects pooled WMD and its corresponding 95% confidence interval. Estimates to the left of the vertical line (i.e. WMD < 0) are indicative of a significant difference in trough diastolic blood pressure in favour of candesartan. Statistical significance is inferred where the confidence interval does not cross the vertical line of unity.

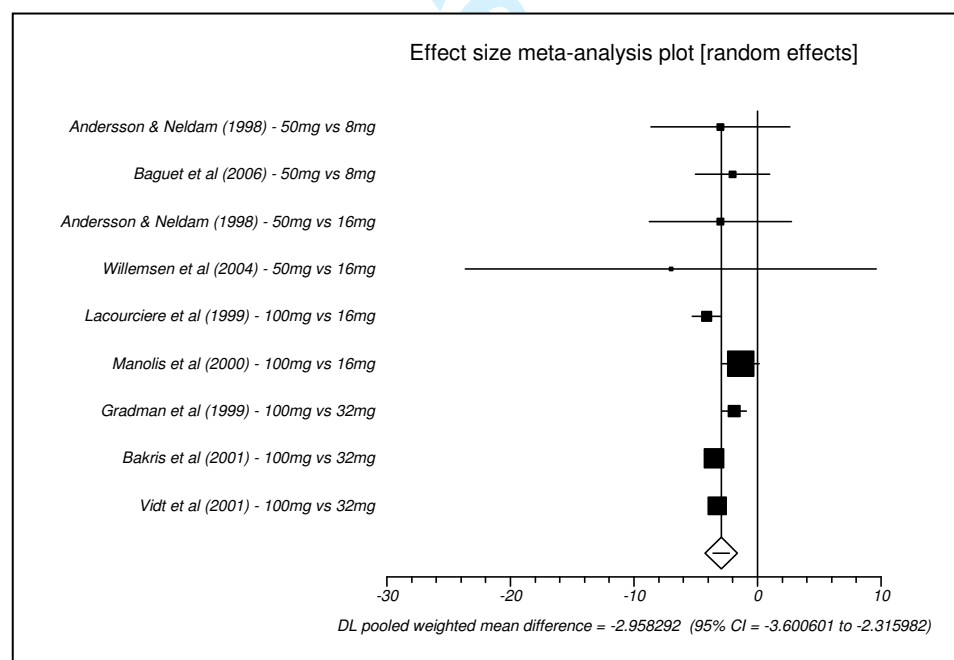


Figure 3b: Forest plot of the weighted mean difference (WMD) for absolute difference in trough systolic blood pressure from baseline to end of study period (4 to 12 weeks) of randomised controlled trials comparing losartan with candesartan as monotherapy for the treatment of mild-to-moderate hypertension. The black squares represent the WMD for individual studies and the horizontal line represents the 95% confidence interval of the WMD. The diamond and horizontal line within it represents the random-effects pooled WMD and its corresponding 95% confidence interval. Estimates to the left of the vertical line (i.e. WMD < 0) are indicative of a significant difference in trough systolic blood pressure in favour of candesartan. Statistical significance is inferred where the confidence interval does not cross the vertical line of unity.

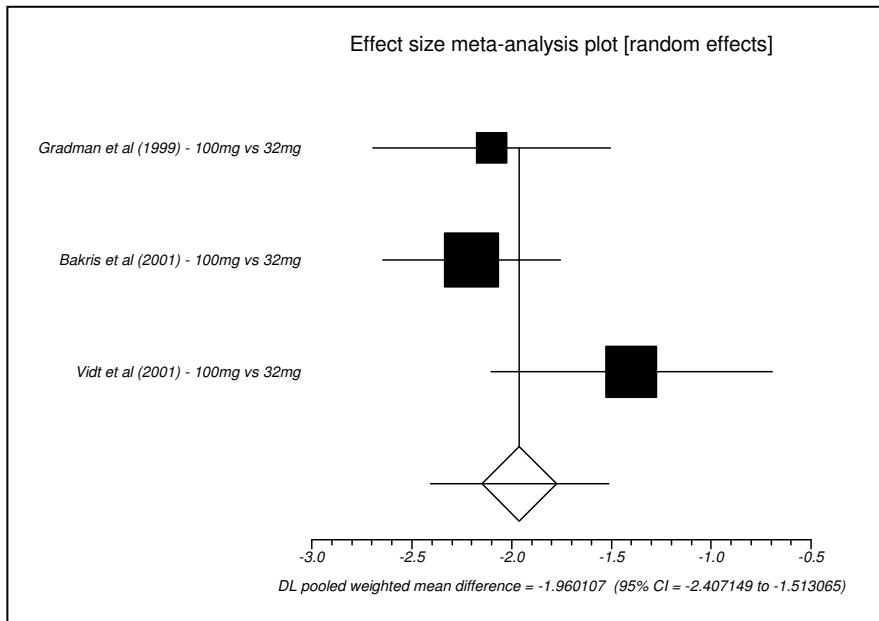


Figure 4a: Forest plot of the weighted mean difference (WMD) for absolute difference in trough diastolic blood pressure from baseline to end of study period (4 to 12 weeks) of randomised controlled trials comparing losartan with candesartan at their maximum licensed doses as monotherapy for the treatment of mild-to-moderate hypertension. The black squares represent the WMD for individual studies and the horizontal line represents the 95% confidence interval of the WMD. The diamond and horizontal line within it represents the random-effects pooled WMD and its corresponding 95% confidence interval. A WMD < 0 is indicative of a significant difference in trough diastolic blood pressure in favour of candesartan.

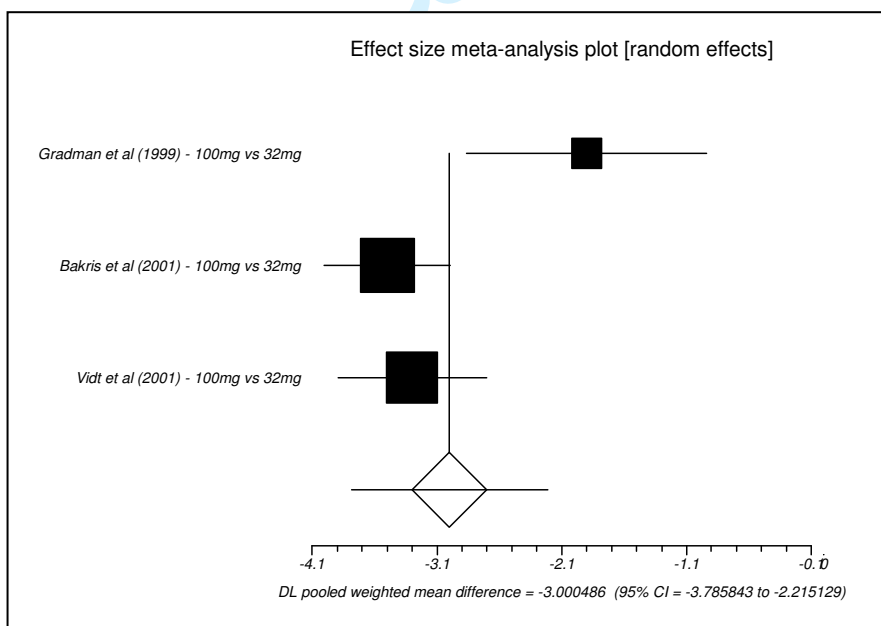


Figure 4b: Forest plot of the weighted mean difference (WMD) for absolute difference in trough systolic blood pressure from baseline to end of study period (4 to 12 weeks) of randomised controlled trials comparing losartan with candesartan at their maximum licensed doses as monotherapy for the treatment of mild-to-moderate hypertension. The black squares represent the WMD for individual studies and the horizontal line represents the 95% confidence interval of the WMD. The diamond and horizontal line within its represents the random-effects pooled WMD and its corresponding 95% confidence interval. A WMD < 0 is indicative of a significant difference in trough systolic blood pressure in favour of candesartan.

TABLES

Table 1: Characteristics of studies included within the systematic review of candesartan and losartan in the treatment of hypertension and heart failure.

Study	Study design (weeks of treatment)	Daily treatment dose (number of subjects)	Subjects			
			Diagnosis	Male:Female	Mean age (range)	Non-black:Black
Hypertension studies						
Andersson OK and Neldam S (1998) ²⁰	Parallel, non-forced titration (8)	Losartan 50mg (83), Candesartan 8mg (82), Candesartan 16mg (84), placebo (85)	Mild-moderate	188:146	60 (20-80)	334:0
Lacourcière Y et al (1999) ²⁵	Parallel, Forced titration (8)	Losartan 100mg (115), Candesartan 16mg (116), placebo (37)	Mild-moderate	165:102	55 (20-80)	261:6
Gradman AH et al (1999) ²³	Parallel, non-forced titration (8)	Losartan 50/100mg (170), Candesartan 16/32mg (162)	Moderate	191:141	54 (18-80)	291:41
Manolis AJ et al (2000) ²⁶	Parallel, non-forced titration (12)	Losartan 50/100mg (461), Candesartan 8/16mg (458), Losartan+hydrochlorothiazide 50+12.5mg (232)	Mild-moderate	608:553	51 (20-80)	635:526
Bakris G et al (2001) ²²	Parallel, Forced titration (8)	Losartan 100mg (332), Candesartan 32mg (322)	Moderate	380:274	54 (18-80)	541:113
Vidt DG et al (2001) ²⁴	Parallel, Forced titration (8)	Losartan 100mg (304), Candesartan 32mg (307)	Moderate	358:253	55 (18-80)	490:121
Willemsen JM et al (2004) ²⁷	Cross-over, non-forced (4)	Losartan 50mg, Candesartan 16mg, placebo (total n=13)	Mild-moderate	8:5	52 (39-58)	Not stated
Baguet JP et al (2006) ²¹	Parallel, non-forced titration (6)	Losartan 50mg (89), Candesartan 8mg (87), placebo (80)	Mild-moderate	153:103	54 (18-75)	Not stated
Heart Failure studies						
Candesartan						
Granger CB et al (2003) ²⁸	Parallel (146)	Candesartan 32mg (1013), placebo (1015)	LVEF ≤ 40%; NYHA II-IV	1382:646	67 (not stated)	1955:73
McMurray JJV et al (2003) ³⁹	Parallel (178)	Candesartan 32mg (1276), placebo (1272)	LVEF ≤ 40%; NYHA II-IV	2006:542	64 (not stated)	2421:127
Granger CB et al (2000) ⁴⁰	Parallel (12)	Candesartan 16mg (179), placebo (91)	LVEF ≤ 40%; NYHA II-IV	186:84	65 (58-74)	Not stated
Losartan						
Konstam MA et al (2009) ³⁰	Parallel (4.7 years)	Losartan 50mg (1927), Losartan 150mg (1913)	LVEF ≤ 40%; NYHA II-IV	2691:1149	66 (56-73)	35:3805
Pitt B et al (2000) ⁴¹	Parallel (79)	Losartan 50mg (1578), Captopril 150mg (1574)	LVEF ≤ 40%; NYHA II-IV	2185:966	72 (not stated)	67:3085
Pitt B et al (1997) ⁴²	Parallel (48)	Losartan 50mg (352), Captopril 150mg (370)	LVEF ≤ 40%; NYHA II-IV	482:240	74 (not stated)	688:34

*Weeks of treatment refers to the double-blind period consisting of both the titration-to-target and target-stabilisation phases (where applicable).

Table 2: Cost and utility parameters used in the base-case cost-utility model comparing candesartan and losartan for the treatment of hypertension. *Cost inflated to 2009 base year.

Parameter	Base-case value	Source
Annual drug cost of candesartan (32mg)	£193.56	BNF (2009) ³¹
Annual drug cost of generic losartan (100mg)	£77.64	TEVA pharmaceuticals ⁴³
Projected annual drug cost of generic losartan (100mg)	£10.56	Expert opinion
Annual cost of stroke survivor [cost in first year]	£2163 [£8046*]	NICE Guideline CG034 ³⁴
Annual cost of MI survivor [cost in first year]	£500 [£4448*]	NICE Guideline CG034 ³⁴
Utility weight of stroke survivor	0.63	NICE Guideline CG034 ³⁴
Utility weight of MI survivor [first year]	0.88 [0.76]	NICE Guideline CG034 ³⁴
Treatment effect difference (incremental reduction in SBP)	-3.00mmHg	Meta-analysis

Table 3: Variation of ICER with baseline risk when comparing candesartan and losartan for the treatment of hypertension .

Baseline Risk / SBP	ICER (£ / QALY)	
Males	Generic losartan (£77.64 p.a.)	Projected generic price (£10.56 p.a.)
Mild (140mmHg)	£52,644	£87,946
Moderate (165mmHg)	£44,930	£74,901
High (180mmHg)	£41,469	£69,076
Females		
Mild (140mmHg)	£85,244	£142,449
Moderate (165mmHg)	£53,804	£91,368
High (180mmHg)	£41,591	£71,430

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SUPPLEMENTARY MATERIAL

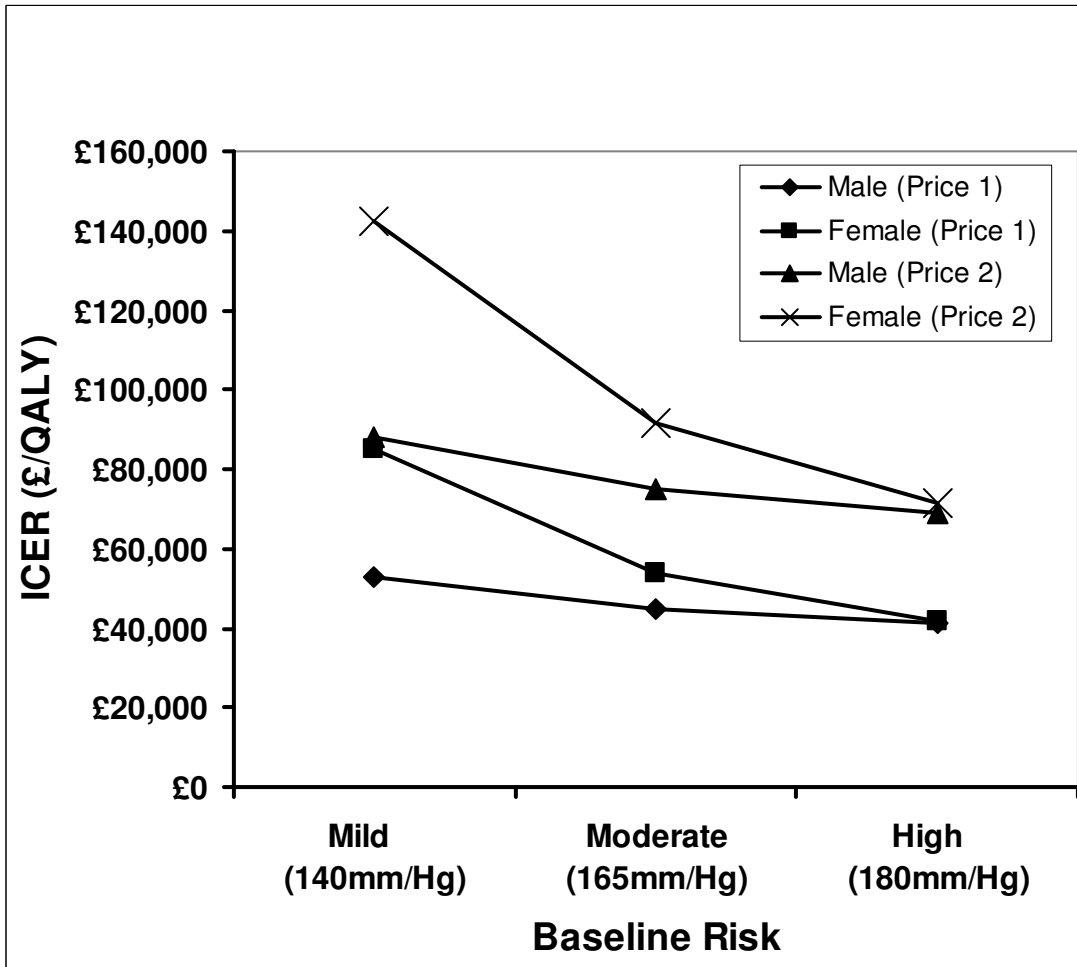


Figure 1: Incremental cost-effectiveness ratios (ICERs) of candesartan and losartan versus baseline hypertension risk. Results are displayed for males and females at two generic losartan prices: Price 1 (£77.64 p.a.) and Price 2 (£10.56 p.a.).

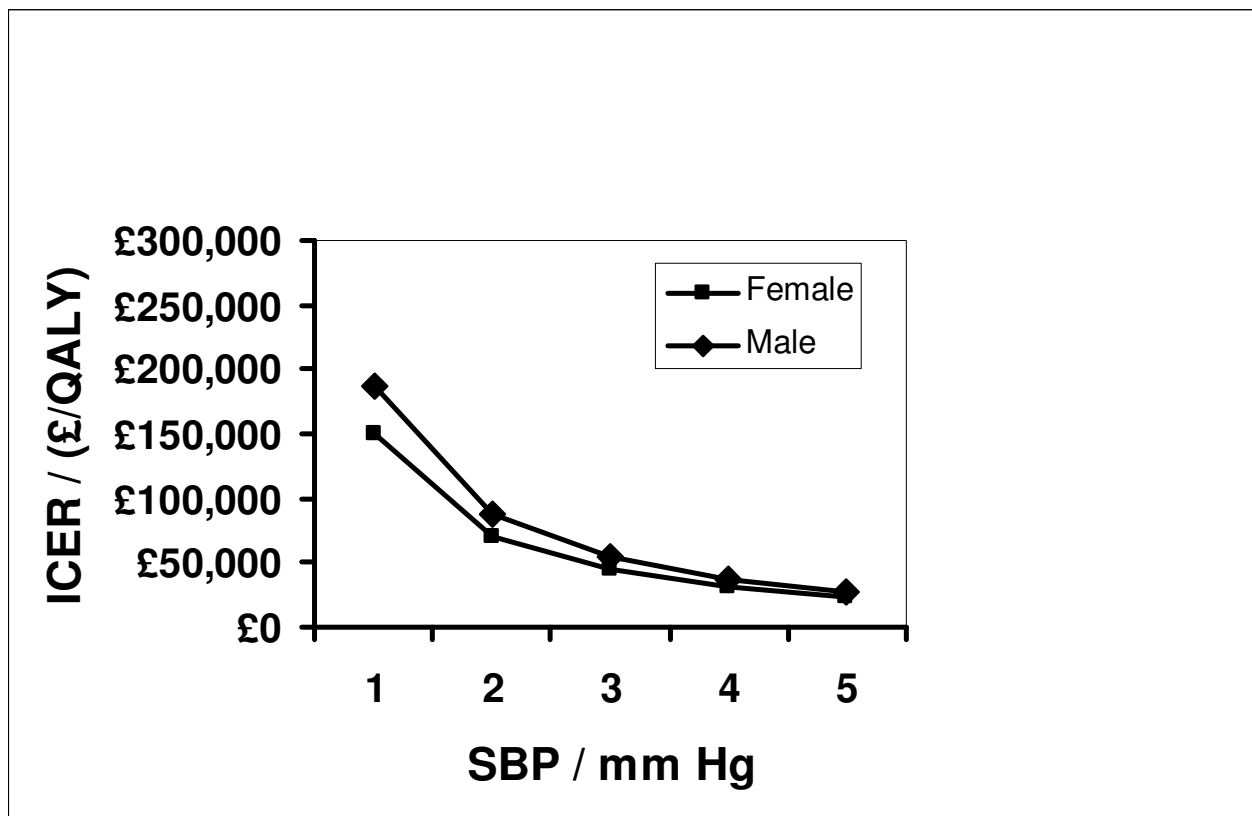


Figure 2: One-way sensitivity analysis on the Incremental cost-effectiveness ratio (ICER) of candesartan relative to losartan versus difference in relative anti-hypertensive effect on systolic blood pressure (SBP) of candesartan relative to losartan.

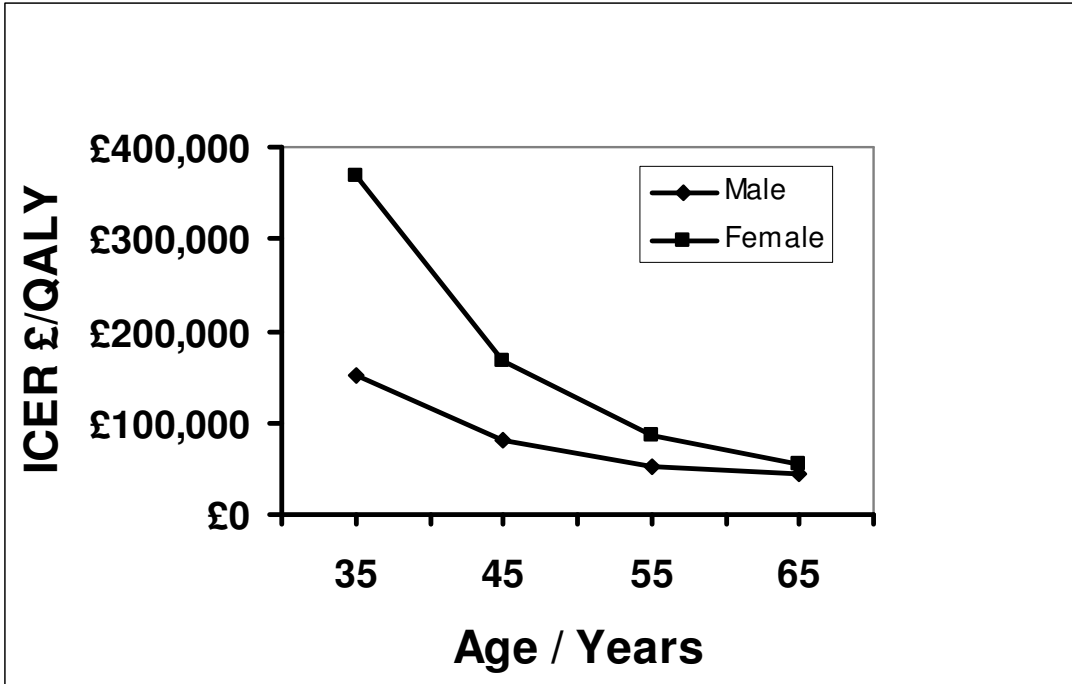


Figure 3: One-way sensitivity analysis on the Incremental cost-effectiveness ratio (ICER) of candesartan relative to losartan versus cohort starting age in the age range (35 – 65 years) for males and females.

Table 1: Search strategy

Search no.	Search term
#1	Losartan [MeSH]
#2	Candesartan
#3	Candesartan cilexetil
#4	Hypertension [MeSH]
#5	Heart failure [MeSH]
#6	#1 AND (#2 OR #3) AND #4
#6	#1 AND (#2 OR #3) AND #5

Table 2: Limits applied within each database searched

Database	Limits applied
PubMed	Humans; Randomised controlled trial; English; all adult: 19+ years
Cochrane	Nil
Embase	Full text; Human; English language ; Article OR Erratum; Adult <18 to 64 years> OR aged <65 years+

Primary inclusion criteria

- Adults
- Randomised controlled trial
- Double-blind
- Placebo- or active-controlled
- Duration greater or equal to 4 weeks
- Hypertension (primary)
- Heart failure
- English language

Primary exclusion criteria

- Systematic reviews
- Non-randomised trials
- Trials which were of less than 4 weeks duration
- Trials which permitted the use of other therapies which may have confounded the clarity of the outcome of the drug being assessed, e.g. calcium channel blockers
- Trials which used a response conditional design where patients were allocated treatment only if they showed a predetermined response to treatment during a baseline period before randomisation
- Trials which recruited patients into the randomised, double-blind phase following an open-label period (single-blind permitted)

Table 3: Raw data extracted from clinical trials included within meta-analyses

Drug	Losartan				Candesartan			
Study	Mean (max) dose	Baseline	SBP [95% CI]	DBP [95% CI]	Mean (max) dose	Baseline	SBP [95% CI]	DBP [95% CI]
Lacourcière Y et al (1999) – Forced titration – week 8	100mg (from 50mg at week 4) [n=115]	153.0/100.2 mmHg	Peak -10.3mmHg [-12.6 to -8.0] Trough -8.2mmHg [-10.7 to -5.7]	Peak -7.7mmHg [-9.3 to -6.2] Trough -5.8mmHg [-7.5 to -4.1]	16mg (from 8mg at week 4) [n=116]	155.1/101.8 mmHg	Peak -14.5mmHg [-16.8 to -12.3] Trough -12.4mmHg [-14.8 to -10.0]	Peak -9.4mmHg [-10.9 to -7.9] Trough -8.2mmHg [-9.9 to -6.5]
Gradman AH et al (1999) – Not forced titration – week 8	100mg (from 50mg at week 4) [n=170; 56% not forced]	154.1/100.5 mmHg	Peak -14.4mmHg [-16.8 to -12.1] Trough -10.0mmHg [-12.2 to -7.8]	Peak -9.6mmHg [-11.1 to -8.2] Trough -8.9mmHg [-10.1 to -7.6]	32mg (from 16mg at week 4) [n=162; 52% not forced]	152.9/100.3 mmHg	Peak -16.5mmHg [-18.8 to -14.1] Trough -11.9mmHg [-14.1 to -9.6]	Peak -12.6mmHg [-14.0 to -11.1] Trough -11.0mmHg [-12.3 to -9.8]
Bakris G et al (2001) – CLAIM study – Forced titration – week 8	100mg (from 50mg at week 2) [n=332]	152.0/99.9 mmHg	Peak -12.6mmHg [not reported] Trough -9.8mmHg [not reported]	Peak -10.1mmHg [not reported] Trough -8.7mmHg [not reported]	32mg (from 16mg at week 2) [n=322]	152.6/100.1 mmHg	Peak -15.2mmHg [not reported] Trough -13.3mmHg [not reported]	Peak -11.6mmHg [no CI] Trough -10.9mmHg [no CI]
Vidt DG et al (2001) – CLAIM II study – Forced titration – week 8	100mg (from 50mg at week 2) [n=304]	152.2/100.2 mmHg	Peak -12.0mmHg [not reported] Trough -10.1mmHg [not reported]	Peak -9.5mmHg [not reported] Trough -9.1mmHg [not reported]	32mg (from 16mg at week 2) [n=307]	153.6/100.4 mmHg	Peak -15.5mmHg [not reported] Trough -13.4mmHg [not reported]	Peak -12.9mmHg [no CI] Trough -10.5mmHg [no CI]
Andersson OK and Neldam S (1998) – No titration – week 8 (low dose)	50mg [n=83]	168/104 mmHg	Peak -19mmHg [not reported] Trough -11.0mmHg [not reported]	-12mmHg [not reported] Trough -7.0mmHg [not reported]	8mg [n=82]	169/102 mmHg	Peak -16mmHg [not reported] Trough -14.0mmHg [not reported]	Peak -10mmHg [no CI] Trough -9.0mmHg [no CI]
Andersson OK and Neldam S (1998) – No titration – week 8 (high dose)	50mg [n=83]	168/104 mmHg	Peak -19mmHg [no CI] Trough -11.0mmHg [no CI]	Peak -12mmHg [no CI] Trough -7.0mmHg [no CI]	16mg [n=84]	168/103 mmHg	Peak -20mmHg [no CI] Trough -14.0mmHg [no CI]	Peak -12mmHg [no CI] Trough -10.0mmHg [no CI]

Drug	Losartan				Candesartan			
Study	Mean (max) dose	Baseline	SBP [95% CI]	DBP [95% CI]	Mean (max) dose	Baseline	SBP [95% CI]	DBP [95% CI]
Baguet et al (2006) – No titration – week 6	50mg [n=89]	161/101 mmHg	Trough -8.8mmHg [no CI]	Trough -5.1mmHg [no CI]	8mg [n=87]	160/101 mmHg	Trough -10.8mmHg [no CI]	Trough -7.3mmHg [no CI]
Willemsen et al (2004) – No titration – week 4	50mg [n=4]	168/105 mmHg	Trough -23mmHg [no CI]	Trough -16mmHg [no CI]	16mg [n=4]	168/105 mmHg	Trough -30mmHg [no CI]	Trough -18mmHg [no CI]
Manolis AJ et al (2000) – Not forced titration – week 12	100mg (from 50mg at week 6) [n=449; 47% had dose increased]	153.0/101.6 mmHg	Trough -14.4mmHg SD=11.7 [-15.5 to -13.3]	Trough -12.4mmHg SD=7.2 [-13.0 to -11.7]	16mg (from 8mg at week 6) [n=462; 45% had dose increased]	152.7/101.6 mmHg	Trough -15.8mmHg SD=12.2 [-16.9 to -14.7]	Trough -13.1mmHg SD=7.6 [-13.8 to -12.4]