London New Drugs Group

APC / DTC Briefing Document

January 2008

ACE Inhibitors and Angiotensin II Receptor-Antagonists for hypertension

Contents:

Summary

- NICE/British Hypertension Society Guidelines[1] state that the first choice of agent in hypertensive patients younger than 55 years (with the exception of black patients) is an angiotensin-converting enzyme inhibitor (ACE inhibitor, ACEI).
- An angiotensin-II receptor antagonist (AIIA) should only be used if an ACE inhibitor is not tolerated.
- In hypertensive patients aged 55 years or older, or in black patients of any age (African or Caribbean descent), the first choice should be either a calcium channel blocker or a thiazide-type diuretic.
- In formulating its recommendations the Guideline Development Group (GDP) felt that the benefits of ACE Inhibitors and AIIAs were closely correlated and that they should be treated as equal in terms of efficacy. The GDG state that ACE Inhibitors should be initiated first because of cost differences. In the absence of clinical outcome data in younger patients, the GDG considered blood pressure lowering as the most suitable surrogate for clinical outcome.
- All currently UK-available ACE Inhibitors and AIIAs are licensed for hypertension. Many have additional licenses (see table 2).
- Suggested choice of therapy, based on both the product licence and the cost of the WHO Defined Daily Dose (DDD), are:
    - Lisinopril and ramipril, which have the widest product licences of the ACE Inhibitors and are the most cost effective. Perindopril also has a wide product licence, but is a more expensive option.
    - The choice of an AIIA for the treatment of hypertension is less straightforward. Candesartan would be the drug of choice at the WHO DDD of 8mg/day in terms of expenditure, but a higher dose is often required.
- No information on dosing equivalents of ACE Inhibitors and AIIAs is available. If changing a patient from an AIIA to an ACE Inhibitor, where the dose falls within the dosing range should be taken into account (i.e. low, maintenance low or maintenance high, or maximum dose) and the equivalent for the new drug chosen. Blood pressure must be closely monitored.

Background

Hypertension is a major but modifiable contributory factor in cardiovascular diseases, such as stroke and coronary heart disease. It has been defined as persistently raised blood pressure above 140/90 mmHg.[1] NICE/British Hypertension Society Guidelines[1] state that drug therapy reduces the risk of cardiovascular disease and death, and should be offered to patients with persistently high blood pressure (160/100 mmHg or more) and those at raised cardiovascular risk with persistent blood pressure of >140/90 mmHg; target blood pressure is ≤140/90 mmHg for non-diabetic patients with hypertension.

The first choice of agent in hypertensive patients younger than 55 years (with the exception of black patients) is an angiotensin-converting enzyme inhibitor (ACE inhibitor, ACEI), or an angiotensin-II receptor antagonist (AIIA) if an ACE Inhibitor is not tolerated because of side effects, such as cough.[1] The incidence of ACE Inhibitor-induced cough has been reported to be in the range of 5-35% among ACE Inhibitor -treated patients, and can occur within hours of the first dose or be delayed for weeks to months after initiation of therapy.[2] (AIIAs do not inhibit the breakdown of bradykinin and other kinins and therefore are unlikely to cause the persistent dry cough that can complicate ACE inhibitor therapy.[3]) In hypertensive patients aged 55 years or older, or in black patients of any age (African or Caribbean descent), the first choice should be either a calcium channel blocker or a thiazide-type diuretic.[1]

In formulating its recommendations, the Guideline Development Group (GDP), assumed a 'drug class effect' when assessing the results of studies using any particular pharmacological agent, unless there was clear evidence to the contrary. In the absence of clinical outcome data in younger patients, the GDG considered that for pragmatic reasons it was essential to make a recommendation and considered blood pressure lowering as the most suitable surrogate for clinical outcome. The GDG also felt that the benefits of ACE Inhibitors and AIIAs were closely correlated and that they should be treated as equal in terms of efficacy. The GDP state that ACE Inhibitors should be initiated first because of cost differences.[1]

ACE inhibitors and AIIAs

The renin-angiotensin-aldosterone system (RAAS) is an important mechanism in the cause of hypertension. Angiotensin II is the principal mediator of the RAAS and is a powerful vasoconstrictor that sustains increased blood pressure in patients with hypertension.[4] ACE Inhibitors act on the enzyme that generates angiotensin-II (angiotensin converting enzyme, ACE), whereas the AIIAs act directly on the major angiotensin-II receptor subtype-1 that responds to angiotensin-II stimulation.[5] Angiotensin II has a number of potential pathogenic properties:[5]

- Heart: myocardial hypertrophy; interstitial fibrosis
- Coronary arteries: endothelial dysfunction with decreased release of nitric oxide; coronary vasoconstriction via release of noradrenaline; increased oxidative stress; promotion of inflammatory response and atheroma; promotion of LDL-cholesterol uptake.
- Kidneys: increased intraglomerular pressure; increased protein leak; glomerular growth and fibrosis; increased sodium reabsorption.
- Adrenals: increased formation of aldosterone.
- Coagulation system: increased fibrinogen, increased PAI-1 (plasminogen activator inhibitor) relative to tissue plasminogen factor.

ACE activity is found mainly in the vascular endothelium of the lungs. It also occurs in all vascular beds, including the coronary arteries. ACE converts angiotensin I to II, and also inactivates the breakdown of bradykinin. Therefore ACE Inhibitors exert their antihypertensive (and anti-heart failure) effects by inhibiting the conversion of angiotensin I to II. This results in the inhibition of vasoconstriction and inactivation of the breakdown of bradykinin and consequential formation of the vasodilatory prostacyclin and nitric oxide.[5]

There are two angiotensin-II receptor subtypes: AT_1 and AT_2 receptors, which both respond to angiotensin-II but link to separate internal signalling pathways.[5] AIIAs are considered AT_1-blockers, whereas ACE Inhibitors block the activity of both receptors by inhibiting the formation of angiotensin-II. The effects of angiotensin-II on the AT_1 receptors include stimulation of contraction, vasoconstriction, myocyte hypertrophy and antinatriuresis. In foetal development the AT_1 receptors act as growth stimulators.

The purpose of this review is to look for the evidence on how to switch from an AIIA to an ACE Inhibitor, for the treatment of hypertension. There are currently 11 ACE Inhibitors and 7 AIIAs licensed in the UK. All are licensed for the treatment of hypertension.[3] The following tables detail their doses, time to peak plasma concentration and half life, as well as licensed indications.

Table 1: Dosing (for hypertension) and pharmacokinetic data for ACE inhibitors and AIIAs.

ACE Inhibitors (trade name)	Initial dose[3]*	Maintenance low dose[3]*	Maintenance high dose[3]*	Maximum dose[3]*	Time to peak plasma concentration[6]	Half life[6]
Captopril (Capoten)	12.5mg bd	25mg bd	50mg bd	50mg tds	Within 60-90 mins	~ 2 hrs
Cilazapril (Vascace)	1mg od	2.5mg od	5mg od	5mg od	Within 2 hrs	9 hrs†
Enalapril (Innovac)	5mg od	10mg od	20mg od	40mg od	~ 4 hrs†	~ 11 hrs†
Fosinopril (Staril)	10mg od	20mg od	40mg od	40mg od	~3 hrs	~11-13 hrs†
Imidapril (Tanatril)	5mg od	10mg od	20mg od	20mg od	3-10 hrs†[7]	10-19 hrs†[7]
Lisinopril (Zestril)	10mg od	20mg od	40mg od	80mg od	7 hrs	12.6 hrs
Moexipril (Perdix)	7.5mg od	15mg od	30mg od	30mg od	1.5 hrs[8]	2-10 hrs†[8]
Perindopril (Coversyl)	4mg od	4mg od	8mg od	8mg od	3-4 hrs†	25 hrs†
Quinapril (Accupro)	10mg od	20mg od	40mg od	80mg od	2 hrs†	3 hrs†
Ramipril (Tritace)	1.25mg od	2.5mg od	5mg od	10mg od	2-4 hrs†	13-17 hrs†
Trandolapril (Gopten)	0.5mg od	1mg od	2mg od	4mg od	4-6 hrs†	16-24 hrs†
Angiotensin II receptor antagonists	**Initial dose[3]***	**Maintenance low dose[3]***	**Maintenance high dose[3]***	**Maximum dose[3]***	**Time to peak plasma concentration[6]**	**Half life[6]**
Candesartan (Amias)	8mg od	8mg od	16mg od	32mg od	3-4 hrs	~9 hrs
Eprosartan (Teveten)	600mg od	600mg od	800mg od	800mg od	1-2 hrs	5-9 hrs
Irbesartan (Aprovel)	150mg od	150mg od	300mg od	300mg od	1.5 – 2 hrs	11-15 hrs
Losartan (Cozaar)	50mg od	50mg od	100mg od	100mg od	3-4 hrs†	6-9 hrs†
Olmesartan (Olmetec)	10mg od	10mg od	20mg od	40mg od	2 hrs	10-15 hrs
Telmisartan (Micardis)	40mg od	20-40mg	40mg	80mg od	3 hrs	24 hrs[9]
Valsartan (Diovan)	80mg od	80mg od	160mg od	160mg od	2-4 hrs[10]	6-9 hrs[10]

* – the Summary of Product Characteristics must be consulted for full prescribing details. These doses are for Adults with hypertension without congestive heart failure, renal/hepatic failure or on other antihypertensive agents. Doses are usually increased after 4 wks of initial therapy.
† - time to peak plasma concentration for active metabolite

Table 2: Licensed indications[3] and WHO Defined Daily Doses for Hypertension[11]

ACE Inhibitors (trade name)	Hypertension	Heart failure	Post MI prophylaxis	Post MI prophylaxis with LV failure	Diabetic nephropathy (type 1)	Diabetic nephropathy (type 2)	Cardiovascular risk reduction	WHO Defined Daily Dose	Cost / 52 weeks[12]
Captopril (Capoten)	✓	✓		✓	✓			50mg	£17.16
Cilazapril (Vascace)	✓	✓						2.5mg	£99.32
Enalapril (Innovace)	✓	✓						10mg	£7.67
Fosinopril (Staril)	✓	✓						15mg	£60.06
Imidapril (Tanatril)	✓							10mg	£99.58
Lisinopril (Zestril)	✓	✓	✓		✓	✓ (early stage)		10mg	£10.14
Moexipril (Perdix)	✓							15mg	£113.10
Perindopril (Coversyl)	✓	✓		✓			✓	4mg	£147.68
Quinapril (Accupro)	✓	✓						15mg	£35.30-42.90
Ramipril (Tritace)	✓	✓		✓			✓	2.5mg	£11.18 – 25.74
Trandolapril (Gopten)	✓	✓						2mg	£89.18
Angiotensin II receptor antagonists	**Hypertension**	**Heart failure**	**Post MI prophylaxis**	**Post MI prophylaxis with LV failure**	**Diabetic nephropathy (type 1)**	**Diabetic nephropathy (type 2)**	**Cardiovascular risk reduction**	**WHO Defined Daily Dose**	**Cost / 52 weeks[22]**
Candesartan (Amias)	✓	✓						8mg	£128.57
Eprosartan (Teveten)	✓							600mg	£186.03
Irbesartan (Aprovel)	✓					✓ (early & late)		150mg	£163.41
Losartan (Cozaar)	✓					✓ (late stage)		50mg	£166.40
Olmesartan (Olmetec)	✓							20mg	£168.35
Telmisartan (Micardis)	✓							40mg	£147.42
Valsartan (Diovan)	✓			✓				80mg	£213.72

Drug selection

There are many comparable parameters which influence the rational choice of drugs from the same class.[13] These include efficacy, potency, route of administration, frequency of dosing, drug interactions, safety, side effects and cost. Drugs in the same class are not often compared with each other and therefore evidence showing whether the benefits of one drug extend to the others may be lacking. Cost is often the primary parameter for choice, especially when there are generic versions of the drugs available. This is overlooked when there is the possible benefit for a specific indication, based on non-surrogate efficacy and safety data. Secondary reasons for choice can be surrogate endpoints, such as blood pressure, pharmacokinetics of the drug such as longer dosing intervals, or tolerability differences.[13]

The increase in prescription volume for cardiovascular drugs rose from 230.56 million in 2006/7 to 246.25 million 2007/8 (for the period April – September in both years), a 6.9% increase.[14] The greatest effect on volume were drugs affecting the renin-angiotensin system, which increased by 5.7 million items over the year to September 2007; this accounts for one third of the overall increase in volume of drugs to treat the cardiovascular system. After publication of the NICE Clinical Guideline for the management of hypertension in adults the number of prescriptions for beta-blockers fell by 3.4% whilst the increase in those for ACE Inhibitors rose by 13.6% (year to September 2007).[14]

Drugs costs can vary with the time and place of prescribing. The drug costs in this document have come from the Drug Tariff, January 2008. Category M drugs are reviewed on a quarterly basis and therefore the prices may change in the future.

Blood pressure lowering

Randomised trials lasting a few years have shown that blood pressure lowering can produce rapid reductions in vascular disease risk, and even greater differences in risk are likely to be produced by prolonged differences in blood pressure.[15] For example, a 10mmHg reduction in SBP or 5mmHg reduction in DBP would, in the long term, be associated with about 40% lower risk of stroke death and about 30% lower risk of death from ischaemic heart disease (IHD) or other vascular causes. Even a 2mmHg reduction in SBP would involve about 10% lower stroke death and about 7% lower death from IHD or other vascular causes in middle age.[15]

ACE Inhibitors and AIIAs seem to have similar long term effects on blood pressure in individuals with essential hypertension.[16] A systematic review (of 61 studies) by Matcher el al[16] could not discern any differential effect of ACE Inhibitors versus AIIAs with respect to death or major cardiovascular events in the included studies due to the low number of events occurring. There were also no consistent differential effects on important risk factors such as lipid levels, progression to type 2 diabetes, markers of diabetic control, measures of left ventricular mass or function and progression of renal disease, because relatively few studies assessed these outcomes over the long term. Quality of life studies also did not show a difference between ACE Inhibitors and AIIAs. The review does not support the hypothesis that ACE Inhibitors and AIIAs have clinically meaningful differences in benefits or harms for patients with hypertension. There are several limitations with the literature used in the systematic review (which can also be applied to the studies in this document). Follow-up exceeded 6 months in only one-third of the head-to-head studies; many reported limited data on patient characteristics and under-represented black patients. Study protocols had substantial differences such as doses used and if additional antihypertensive therapies were permitted. Assessment of outcomes also varied; some studies reported final blood pressure, others reported changes. Outcomes such as death, vascular events and angioedema were often not mentioned.

ACE Inhibitors

The benefits for hypertension (and heart failure) are likely to be class effects, so there are no primary reasons for preferring individual drugs.[13;17] For specific indications, the drugs licensed for those should be used (see table 2).

Lisinopril, ramipril and perindopril have the widest product licenses (as does captopril, but its 2-3 daily doses may affect compliance and it is generally not recommended first line[17]). There are differences in the licenses for these three ACE Inhibitors, with respect to use for diabetic nephropathy and cardiovascular risk reduction, and it may be prudent to use them accordingly. As already stated, the benefits in patients with hypertension are likely to be class effects so the choice of an ACE Inhibitor as an antihypertensive may then be based on cost, in which case lisinopril or ramipril would be suitable.

AIIAs

Expert opinion suggests that 20% of patients started on an ACE Inhibitor would be switched to an AIIA because of the inability to tolerate the ACE Inhibitor.[1] The incidence of ACE Inhibitor-induced cough has been reported to be in the range of 5-20%; in the systematic review the rates of cough ranged from 0% to 13% with AIIAs (mean 3%, median 1%), compared with 0% to 23% with ACE Inhibitors (mean 10%, median 9%).[16] The only uniformly effective intervention for ACE Inhibitor-induced cough is to stop ACE Inhibitor therapy.[2] If there is a compelling reason to treat with an ACE Inhibitor, then a repeat trial may be attempted. If ACE Inhibitor therapy cannot be stopped then pharmacologic therapy aimed at suppressing cough should be attempted.[2] In patients in whom persistent or intolerable ACE Inhibitor-induced cough occurs, therapy should be switched to an AIIA.[2]

It is reasonable to base choice of therapy on the licence, the evidence available and cost.[18] Trials assessing the effects of AIIAs on clinically important cardiovascular outcomes are limited but in general they have blood pressure lowering effects similar to ACE Inhibitors (see Appendix). It is difficult to give a precise figure of how many patients are truly intolerant of ACE Inhibitors, but for heart failure a figure of 10% has been quoted.[18]

When the cost is based on the WHO Daily Defined Doses (DDD) for hypertension, candesartan (at a dose of 8mg/day) is the least expensive AIIA. A higher dose of 16mg/day may be required[19], making the cost/year £165.23. Although this then brings it on par with the cost of other AIIAs at their WHO DDD, what should be taken into account is that higher doses of the other AIIAs may be required to control hypertension, which will be at a higher cost. As with the choice of ACE Inhibitor, for more specific indications, the drugs licensed for those should be used.

For relatively low-risk individuals with essential hypertension, any differences between ACE Inhibitors and AIIAs in major events or changes in risk factors are likely to be small.[16]

Relative efficacy

Relative efficacy based on the studies in Appendix I is difficult to produce. Not all the trials will have compared 'like with like' antihypertensive doses. For example, candesartan 8mg (low maintenance dose) has been compared with olmesartan 20mg (high maintenance dose).

Efficacy in the table below is crudely based on blood pressure reductions and responders, over the time of the study, from the studies in Appendix I. No information giving comparative doses of AIIAs/AIIAs and AIIAs/ACE Inhibitors were found.

When switching antihypertensive medications in patients it is essential that blood pressure is closely monitored. Even if rough estimations of equivalent dosing are made, it is prudent to compare where in the dosing range the current antihypertensive medication is (see Table 1) and start at a similar dose for the new product, e.g. bottom, middle or top of the dosing range. The dose of the drug is usually increased every 2-4 weeks, but can be increased weekly, depending on the severity of the hypertension and how well the patient tolerates the dose increases.[17]

Table 3: Relative efficacy based on the trials in Appendix 1

Drug	More effective in lowering BP than:	Less effective than lowering BP than:	Similar efficacy
Candesartan 4-8mg		Lisinopril 10mg	Enalapril 10-20mg
Candesartan 8-16mg	Losartan 50-100mg Enalapril 10-20mg	Olmesartan 20mg	Enalapril 10-20mg
Candesartan 16mg		Perindopril 4mg	
Candesartan 16-32mg	Losartan 50-100mg		
Eprosartan 400-600mg	Enalapril 5-20mg		
Eprosartan 600mg	Losartan 50mg		Enalapril 20mg
Eprosartan 400-800mg	Enalapril 10-40mg		
Irbesartan 75mg			Enalapril 10mg
Irbesartan 150mg			Valsartan 80mg Enalapril 20mg
Irbesartan 150-300mg	Losartan 50-100mg Enalapril 10-20mg		
Losartan 50mg		Valsartan 80-160mg Telmisartan 40mg	
Losartan 50-100mg	Captopril 25-50mg bd	Eprosartan 600mg Irbesartan 300mg Irbesartan 150mg Olmesartan 10-20mg Telmisartan 40mg	
Olmesartan 5mg	Captopril 25mg		
Olmesartan 10-20mg	Losartan 50-100mg		
Olmesartan 20mg	Candesartan 8mg		
Telmisartan 20-80mg			Enalapril 5-20mg
Telmisartan 40-80mg	Losartan 50-100mg Ramipril 2.5-10mg	Valsartan 40mg	
Valsartan 80mg	Telmisartan 40mg Losartan 50mg		Irbesartan 150mg Captopril 50mg Enalapril 20mg Lisinopril 10mg
Valsartan 160mg	Losartan 100mg		
Olmesartan > Candesartan > Losartan Valsartan > Telmisartan > Losartan Valsartan = Irbesartan > Losartan Eprosartan > Losartan			

Economic considerations and patent expiry

In the following table the prices are for the generic product unless the branded name is shown after the drug name, in which case the price is for the branded product. All prices have come from the Drug Tariff (January 2008, except for moexipril) and do not take into consideration any local price agreements. None of the AIIAs are available as generic products at the time of writing. NB: The Drug Tariff prices may change each month.

Table 4: Drug Tariff prices for ACE INHIBITORs and AIIAs.

ACE Inhibitor	Drug Tariff price Jan 2008[12]	Patent expiry[20]†	AIIA	Drug Tariff price Jan 2008[12]	Patent expiry[20]†
Captopril*	56x12.5mg: £0.68 56x25mg: £0.99 56x50mg: £1.32	Expired	**Candesartan (Amias)**	7x2mg: £2.99 28x4mg: £8.15 28x8mg: £9.89 28x16mg: £12.72 28x32mg: £16.13	2012
Cilazapril (Vascace)	28x1mg: £6.01 28x2.5mg: £7.64 28x5mg: £13.28	Expired	**Eprosartan (Teveten)**	28x300mg: £11.63 56x400mg: £15.77 28x600mg: £14.31	2012
Enalapril*	28x2.5mg: £0.41 28x5mg: £0.48 28x10mg: £0.59 28x20mg: £0.69	Expired	**Irbesartan (Aprovel)**	28x75mg: £10.29 28x150mg: £12.57 28x300mg: £16.91	2013
Fosinopril*	28x10mg: £3.08 28x20mg: £3.89	Expired	**Losartan (Cozaar)**	28x50mg: £12.80 28x100mg: £16.18	September 2009
Imidapril (Tanatril)	28x5mg: £6.78 28x10mg: £7.66 28x20mg: £9.20	May 2008	**Olmesartan (Olmetec)**	28x10mg: £10.95 28x20mg: £12.95 28.40mg: £17.50	2017
Lisinopril*	28x2.5mg: £0.45 28x5mg: £0.73 28x10mg: £0.78 28x20mg: £1.32	Expired	**Telmisartan (Micardis)**	28x20mg: £9.25 28x40mg: £11.34 28x80mg: £14.18	2017
Moexipril (Perdix)[3]	28x7.5mg: £7.55 28x15mg: £8.70	Expired	**Valsartan (Diovan)**	7x40mg: £4.11 28x80mg: £16.44 28x160mg: £21.66	2011
Perindopril	30x2mg: £11.36 30x4mg: £11.36 30x8mg: £11.36	Expired	*** = Category M drug:** Price determined by Secretary of State based on information submitted by manufacturers.		
Quinapril*	28x5mg: £1.10 28x10mg: £1.81 28x20mg: £2.51 28x40mg: £3.26	Expired	† The basic patent is rarely the only protection involved and other processes, chemical form or formulation patents may be relevant. These may all extend the effective patent life of a product. The date listed is for the SPC, or Supplementary Protection Certificate: this is a mechanism to guarantee a certain marketing exclusivity period for medicines throughout the EU, to allow for the extended development period they require. Current patents in the EU are valid for 20 years; an SPC applies from the date of first marketing of a product within the EU, and extends the effective patent life for up to 5 years, to allow up to a maximum of 15 years exclusivity.		
Ramipril*	28x1.25mg C: £0.65 28x1.25mg T: £1.82 28x2.5mg C: £0.86 28x2.5mg T: £1.98 28x5mg C: £1.11 28x5mg T: £2.81 28x10mg C: £1.46 28x10mg T: £3.54	Expired			
Trandolapril (Gopten)	14x500mcg: £1.40 28x1mg: £6.86 28x2mg: £6.86 28x4mg: 11.64	Expired			

Appendix 1:

Comparative efficacy: AIIAs

The following studies, comparing AIIAs with other AIIAs or with ACE Inhibitors, vary in design, size, inclusion and exclusion criteria, and in some primary endpoints, and therefore cannot be easily compared. Most studies were relatively brief (8-12 weeks) and may not imply changes that occur over months and years of treatment. With a drug that is taken in the morning, the end of the dosing interval is a critical period. The last 6-hours of the dosing interval is a time that correlates with the early morning period, during which there is the greatest risk of cardiovascular and cerebrovascular events. Some studies used this as the primary endpoint.

Some studies included the trough/peak ratio as a measure of efficacy. The trough/peak ratio is a measure of how well the blood pressure reduction is maintained during a dosage interval. It has been argued that this ratio should exceed 0.5, i.e. the effect at trough should be at least 50% of that at peak. A high peak/trough ratio would ensure a sustained efficacy in the event of missed dose.[21]

There are few outcome studies for AIIAs in hypertension. The LIFE study compared losartan 50mg with atenolol 50mg (n=9,193). Losartan more effective than atenolol in reducing the primary composite end point of cardiovascular mortality, stroke and MI, primarily due to a 26% relative risk reduction in stroke with losartan. There was not a statistically significant difference between the groups with regard to the cardiovascular mortality.[22] In the VALUE study valsartan <160mg/day was compared with amlodipine <10mg/day (n=15,245). There was not a statistically significant difference between the groups in the primary composite outcome of cardiac mortality and morbidity. There was a higher relative risk reduction of MI in the amlodipine group (19%) and a 23% lower incidence of new-onset diabetes in the valsartan group.[22]

Please refer to the table below for usual doses of the antihypertensives. The doses used in the trials may not always be comparing 'like with like'.

ACE Inhibitors (trade name)	Initial dose[3]*	Maintenance low dose[3]*	Maintenance high dose[3]*	Maximum dose[3]*
Captopril (Capoten)	12.5mg bd	25mg bd	50mg bd	50mg tds
Enalapril (Innovace)	5mg od	10mg od	20mg od	40mg od
Lisinopril (Zestril)	10mg od	20mg od	40mg od	80mg od
Perindopril (Coversyl)	4mg od	4mg od	8mg od	8mg od
Ramipril (Tritace)	1.25mg od	2.5mg od	5mg od	10mg od
Angiotensin II receptor antagonists	**Initial dose[3]***	**Maintenance low dose[3]***	**Maintenance high dose[3]***	**Maximum dose[3]***
Candesartan (Amias)	8mg od	8mg od	16mg od	32mg od
Eprosartan (Teveten)	600mg od	600mg od	800mg od	800mg od
Irbesartan (Aprovel)	150mg od	150mg od	300mg od	300mg od
Losartan (Cozaar)	50mg od	50mg od	100mg od	100mg od
Olmesartan (Olmetec)	10mg od	10mg od	20mg od	40mg od
Telmisartan (Micardis)	40mg od	20-40mg	40mg	80mg od
Valsartan (Diovan)	80mg od	80mg od	160mg od	160mg od

Table A1: Comparative efficacy: AIIAs vs. AIIAs for mild-moderate essential hypertension

Candesartan			
Comparator AIIA	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Responders: defined as having DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Losartan[21]	• Randomised, multicentre, double-blind, placebo controlled 8 wk study (n=337). • Dose: candesartan 8mg or 16mg, or losartan 50mg, or placebo, od. • Primary endpoint: change from baseline in trough sitting DBP after 8 wks.	• Inclusion: Adults 20-80yrs, with sitting DBP 95-114 mmHg. • Exclusion: MI, CABG, stroke or TIA in previous 6 months, angina, congestive heart failure, arrhythmias or other serious disease.	• Mean differences between treatments in reductions in 24hr sitting SBP/DBP were -3.4/-2.3 mmHg (candesartan 8mg vs. losartan) and -4.6/-3.7 mmHg (16mg vs. losartan) p=0.013, candesartan 16mg vs. losartan, for DBP only. • The response rates were 50% (candesartan 8mg), 57% (candesartan 16mg) and 46% (losartan), p<0.001 candesartan vs. losartan. • Trough/peak ratios for SBP and DBP were 0.99 and 1.10 (8mg), 0.88 and 0.87 (16mg) and 0.72 and 0.72 (losartan). This indicates a shorter duration of action of losartan compared with candesartan. • New adverse events were reported in 48.2% (placebo), 37.8% (candesartan 8mg), 38.1% (candesartan 16mg) and 49.4% (losartan). • Withdrawals due to adverse events: 3 (3.5%, placebo), 3 (3.6%, candesartan 8mg), 1 (1.2%, candesartan 16mg) and 4 (4.8%, losartan). • Candesartan 16mg was more effective than losartan in reducing trough DBP.
Losartan[23]	• Randomised, multicentre, double-blind 8 wk CLAIM II Trial (n=611). • Dose: candesartan 16mg for 2 wks then 32mg for 6 wks vs. losartan 50mg for 2 wks then 100mg for 6 wks od. • Primary endpoint = mean change from baseline to wk 8 in trough DBP.	• Inclusion: Adults 18-80 yrs, with DBP 95-114 mmHg. • Major exclusion criteria: SBP ≥180 mmHg or DBP ≥115 mmHg, secondary hypertension, severe liver/ significant renal impairment or valvular heart disease, angina, recent MI, coronary revascularisation procedures, strokes or TIAs.	• Mean trough sitting SBP/DBP lowered by 13.4/10.5 mmHg (candesartan) and by 10.1/9.1 mmHg (losartan), p<0.05. • Peak sitting BP reduction was 15.5/12.9 mmHg (candesartan) and 12.0/9.5 mmHg (losartan), p<0.005. Peak BP 6±2.5hrs post dose. • Mean BP reduction 48 hours post-dose was 10.5/9.9 mmHg (candesartan) and 5.9/7.0 mmHg (losartan), p<0.0005. • Incidence of adverse events was similar in each group: 45.6% (candesartan) and 44.7% (losartan) reported adverse events. • Withdrawals due to adverse events: 9 (2.9%, candesartan) and 6 (2.0%, losartan). • Responders: 58.8% (candesartan) and 52.1% (losartan).
Losartan[24]	• Double-blind, placebo-controlled, multicentre, forced titration 8 wk study (n=268). • Dose: candesartan 8mg, losartan 50mg or placebo, od. Dose doubled after 4 wks of treatment in all patients for an additional 4 weeks. • Primary endpoint: not stated. • Study purpose: to determine differences in the anti-hypertensive effects between candesartan and losartan.	• Inclusion: Adults 20-80 yrs with previous treatment for hypertension or recently diagnosed. • Exclusion: concomitant medications that would affect BP, and night-time workers.	• Both significantly reduced SBP and DBP compared with placebo, but candesartan 16mg was more effective than losartan 100mg in reducing day- and night-time SBP, p<0.05, and controlling SBP and DBP after a missed dose, p<0.001. • Candesartan 16mg was significantly better at controlling SBP compared with losartan 100mg, p<0.05 for all SBP measurements. • Mean differences in DBP reduction between candesartan 8mg (7.6 mmHg, daytime and 6.5 mmHg night-time) and losartan 50mg (6.0 mmHg and 4.8 mmHg) were not significant. • Adverse events were reported in 46% (placebo), 43% (candesartan) and 45% (losartan). • One patient in each group withdrew because of adverse events. • The percentages of responders were 66% (candesartan) and 56% (losartan).

Olmesartan[25]	• Randomised, double blind, multicentre, parallel group 8 wk study (n=643). • Dose: olmesartan 20mg or candesartan 8mg, od. • Primary endpoint: mean change from baseline to wks 1, 2 and 8 in daytime DBP.	• Inclusion: Adults >18yrs with sitting trough DBP 100-120 mmHg and SBP >150 mmHg. • Exclusion: secondary or malignant hypertension, significant cardiac, cardiovascular or cerebrovascular disease, hepatic, renal, gastrointestinal or haematological disease, poorly controlled diabetes.	• Mean reductions in daytime DBP at wks 1, 2, and 8 were 6.7, 8.4 and 9.3 mmHg (olmesartan) compared with 5.3, 6.0 and 7.8 mmHg (candesartan). • Mean reductions in trough sitting SBP/DBP were 21.2/15.8 mmHg (olmesartan) and 21.1/15.1 mmHg (candesartan). • The mean decreases from baseline were significantly greater with olmesartan than candesartan for 24 hr DBP (all time points), daytime SBP at all time points and 24-hr SBP (wks 1 and 2). • Adverse events were reported in 9.4% (olmesartan) and 12.3% (candesartan). • One patient in the olmesartan group and 3 in the candesartan group withdrew because of adverse events. • Decreases in night-time SBP/DBP were numerically greater with olmesartan than candesartan.
Losartan			
Comparator AIIA	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Response: defined as DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Eprosartan[26]	• Comparative trial (n=60). • Dose: losartan 50mg or eprosartan 600mg, od. • Primary endpoint not stated.	• Inclusion: Adults with DBP 95-114 mmHg.	• Mean reductions in SBP/DBP were 10.9/9.6 mmHg (losartan) and 12.7/12.4 mmHg (eprosartan). • Response was 53% and 73% respectively. • The study was not powered to compare differential antihypertensive effects between agents.
Irbesartan[27]	• Double-blind, placebo-controlled, multicentre, 8 wk comparator trial (n=567). • Dose: losartan 100mg, irbesartan 150mg or irbesartan 300mg, od. • Primary endpoint: Change from baseline in trough sitting DBP at wk 8.	• Inclusion: Adults >18 yrs with established history of mild-to-moderate hypertension. • Exclusion: concomitant diseases that would present safety hazards and concomitant medications that might affect efficacy or safety.	• Sitting SBP/DBP reductions were 3.7/4.9 mmHg (placebo), 11.3/8.7 mmHg (losartan 100mg), 12.1/9.7mm/Hg (irbesartan 150mg) and 16.4/11.7 mmHg (irbesartan 300mg, $p<0.01$ vs. losartan 100mg). • Response was seen in 33%, 56%, 60% and 63% of patients respectively at wk 8. • Adverse events possibly related to the study drug occurred in 21.2% (placebo), 27.5% (losartan), 21.3% (irbesartan 150mg) and 19.7% (irbesartan 300mg). • Withdrawals due to adverse events occurred in 3.4% (placebo), 3.6% (losartan), 2.1% (irbesartan 150mg) and 1.4% (irbesartan 300mg). • Irbesartan and losartan have antihypertensive effects that are significantly different at trough.

Irbesartan[28]	• Randomised, multicentre, double-blind 12 wk study. • 432 patients randomised to either losartan 50mg or irbesartan 150mg, od. • Doses doubled after 4 wks in non-responders. • Hydrochlorothiazide (HCZ) 12.5mg added at 8 wks in non-responders. • Primary endpoint: Comparison in the change in trough sitting DBP from baseline to wk 8.	• Inclusion: Adults over 18yrs, with mild-to-moderate hypertension (mean sitting DBP 95-115 mmHg). • Exclusion: concomitant diseases that might present health hazards and concomitant medications that might affect efficacy or safety.	• Mean reductions in DBP at wk 8 were 10.2 mmHg (irbesartan) and 7.9 mmHg (losartan), p<0.02. • Mean reductions in DBP/SBP at wk 12 were 18.0/13.8 mmHg (irbesartan) and 13.9/10.8 mmHg (losartan), p<0.002. • Monotherapy normalisation (sitting DBP to 90 mmHg) achieved in 60% (irbesartan) and 52% (losartan) of patients at wk 12. • At wk 12 response rates achieved in 78% (irbesartan) and 64% (losartan), p<0.01. • At wk 12, 35% were on irbesartan 150mg, 25% on 300mg and 40% on 300mg plus HCZ. 32% were on losartan 50mg, 20% on 100mg and 48% on 100mg plus HCZ. • No significant difference in adverse event rates between treatment groups, • Withdrawals due to adverse events were 9 patients (4.2%, irbesartan) and 13 patients (5.9%, losartan). • The antihypertensive effects of irbesartan monotherapy were significantly greater than those of losartan monotherapy.
Olmesartan[29]	• Randomised 12 wk study (n=316). • Dose: losartan 50mg or olmesartan 10mg od. • Dose increased at wk 4 in non-responders. • Study extended by a further 12 wks, when HCZ could be added. • Primary endpoint not stated.	• Inclusion: Adults with DBP 95-114 mmHg.	• Mean reductions in sitting SBP/DBP were 14.9/10.6 mmHg (olmesartan) and 11.6/8.5 mmHg (losartan). [95% CI: -6.0, -0.6 and -3.6, -0.5 for SBP and DBP respectively]. • Responder rates at 12wks were 63% (olmesartan) and 52% (losartan). • Fewer patients required a higher olmesartan dose (41.8% vs. 63.2%). • Results at wk 24 still showed superiority for olmesartan but the differences were no longer significant. • Fewer patients in the olmesartan group required HCZ (34.8% vs. 48.0%).
Losartan			
Comparator AIIA	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Response: defined as DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Telmisartan[30]	• Meta-analysis of 2 randomised, double-blind, multi-centre 8 wk trials (n=720). • Dose: telmisartan 40mg or losartan 50mg, od. • Doses doubled after 4 wks in non-responders. • Primary endpoint: Change from baseline in mean ambulatory DBP during the last 6hrs of the 24hr dosing interval after 8 wks.	• Inclusion: Adults aged ≥18 yrs with sitting DBP 95-109 mmHg. • Exclusion: night-shift workers, secondary hypertension, hepatic or renal dysfunction, bilaterial renal artery stenosis, kidney transplant or single kidney, biliary obstructive disorders, congestive heart failure or other significant cardiovascular disorders, angioedema.	• After 8 wks, mean SBP/DBP reductions during the last 6 hours of the dosing interval were 9.9/6.6 mmHg (telmisartan) and 7.8/5.1 mmHg (losartan), p=0.01 for SBP, p<0.01 for DBP. • After 8 wks mean sitting SBP/DBP reductions were 10.8/8.0 mmHg (telmisartan) and 9.0/7.2 mmHg (losartan). • DBP response was achieved by 37.8% (telmisartan) and 34.9% (losartan). • Responders were 45% and 41.1% of the telmisartan and losartan groups, p=0.29. • Titration to the higher dose was needed in 60.1% (telmisartan) and 69.5% (losartan) of patients, p=0.01. • Adverse events occurred in 22.8% (telmisartan 40mg), 20.2% (telmisartan 80mg), 22.2% (losartan 50mg) and 23.3% (losartan 100mg). • Telmisartan consistently produced greater reductions in BP compared with losartan.

Telmisartan[31]	• Randomised, multicentre, open-label, blinded endpoint 6wk study (n=597). • Dose: telmisartan 40mg or 80mg, or losartan 50mg od, all with HCZ 12.5mg. • Primary endpoint: Change from baseline in ambulatory BP derived mean DBP over last 6 hrs of the dosing period after 6 wks of treatment. • Primary comparison between telmisartan 40mg and losartan 50mg	• Inclusion: Adults ≥18 yrs; Mean sitting DBP ≥90 and ≤109 mmHg; Mean 24hr DBP ≥85 mmHg. • Exclusion: mean sitting SBP≥180 mmHg; secondary hypertension; severe renal, hepatic or peripheral vascular disease.	• After 6 wks the mean reductions in ambulatory DBP during the last 6 hours of the dosing intervals were 11.4 mmHg (telmisartan 40mg, p<0.05 vs. losartan), 12.1 mmHg (telmisartan 80mg, p<0.001 vs. losartan) and 9.7 mmHg (losartan). Reductions in SBP were significantly greater with telmisartan 40mg (p<0.05) and 80mg (p<0.01) vs. losartan. • Adverse events considered related to study medication were reported by 19 patients (10%, telmisartan 40mg/HCZ), 13 patients (7%, telmisartan 80mg/HCZ) and 9 (5% , losartan 50mg/HCZ). • Withdrawals due to adverse events were: 3 patients on telmisartan 40mg/HCZ, 2 on telmisartan 80mg/HCZ and 1 on losartan 50mg/HCZ. • Mean reductions in ambulatory DBP over the 24 hr period were significantly greater with telmisartan 80mg compared with losartan (p<0.001).
Telmisartan[9]	• Randomised, double-blind, double-dummy, multicentre, placebo-controlled 6 wk study (n=223). • Dose: telmisartan 40mg or 80mg or losartan 50mg, or placebo, od. • Primary endpoint: Change from baseline in ambulatory SBP and DBP after final dosing over the 18-24 hr post-dose interval.	• Inclusion: Adults 18-75 yrs with DBP 95-114 mmHg and SBP 140-200 mmHg with mean ambulatory DBP ≥85 mmHg. • Exclusion: secondary hypertension, hepatic or renal disease, cardiovascular disease, type 1 diabetes.	• Mean SBP/DBP reductions during the 18-24 hours post-dose period were 10.7/6.8 mmHg (telmisartan 40mg), 12.2/7.1 mmHg (telmisartan 80mg) and 6.0/3.7 mmHg (losartan), p<0.05 for both telmisartan doses vs. losartan. • Telmisartan 80mg produced greater BP reductions than losartan during all evaluation periods; telmisartan 40mg produced greater BP reductions for both SBP and DBP in the night-time and DBP in the morning. • BP was normalised in 46.2% (telmisartan 80mg), 32.7% (telmisartan 40mg) and 28% (losartan). The differences were not statistically significant. • The overall incidence of adverse events was comparable between the groups. • Withdrawals due to adverse events were: 1 patient (1.8%, telmisartan 40mg), 5 patients (8.8%, losartan 50mg) and 1 (1.8%, placebo). • The sustained 24hr controlled provided by telmisartan may be due to a more prolonged half life.
Valsartan / Telmisartan[32]	• 4-way randomised, double-blind, crossover study with 2-wk washout between treatments (n=30). • Dose: losartan 50mg, telmisartan 40mg, valsartan 80mg or placebo, od for 4 wks. • Primary endpoint: Comparison of the anti-hypertensive efficacy, particularly the time of onset and homogenicity of BP control.	• Inclusion: Adults aged 40-60 yrs with sitting DBP 95-115 mmHg. • Exclusion: secondary hypertension, heart failure, major arrhythmias, MI or stroke within previous 6 months, renal or hepatic insufficiency, terminal or severe chronic diseases.	• Mean 24 hr DBP readings after 4 wks were 83.3 mmHg (losartan), 83.3 mmHg (telmisartan) and 81.5 mmHg (valsartan), all drugs vs. placebo p<0.001, valsartan vs. losartan and telmisartan p<0.05. • Daytime and night-time SBP and DBP readings were significantly lower with valsartan than with losartan and telmisartan at both 2 (p<0.01) and 4 (p<0.05) wks. • Mean trough/peak ratios at 4 wks for SBP/DBP were 0.50/0.56 (losartan), 0.66/0.61 (valsartan) and 0.54/0.64 (telmisartan). • No patient withdrew due to adverse events. • Differences between valsartan and losartan/telmisartan were more marked after 2 wks of therapy than after 4 wks, indicating earlier responses to valsartan.
Valsartan[33]	• Randomised, open-label, crossover 4 wk study, with 2-wk washout between 4 wk treatments (n=40). • Dose: losartan 50mg or valsartan 80mg, od. • Primary endpoint: Not stated. Aim – to compare the two anti-hypertensives with respect to their effects on 24 hr ambulatory BP.	• Inclusion: Adults (aged not specified) with DBP 96-114 mmHg. • Exclusion: secondary hypertension, heart failure, major arrhythmias, MI or stroke within the previous 6 months, renal or hepatic insufficiency, terminal or severe chronic diseases.	• Both drugs significantly reduced SBP and DBP compared with placebo (p<0.001). • Mean 24-hr BP, day and night-time SBP and DBP were significantly lower with valsartan (24-hr BP: 133.6/81.0 mmHg at 4 wks) than losartan (135.6/82.7 mmHg) (p<0.01). • At wk 4 mean trough/peak ratio for SBP/DBP were 0.52/0.57 (losartan) and 0.65/0.62 (valsartan, p<0.05 vs. losartan). • Valsartan was more effective in controlling 24hr ambulatory BP than losartan.

Valsartan[34]	• Randomised, double-blind, placebo controlled 8 wk study (n=1369). • Dose: losartan 50mg, valsartan or placebo od. Dose doubled after 4 wks. • Primary endpoint: Change from baseline in trough mean sitting DBP.	• Inclusion: Adults 18-80 yrs with mean sitting DBP 95-115 mmHg. • Exclusion: overt heart disease or angina, history of MI or heart failure, inability to tolerate the absence of antihypertensives during the run in period.	• Both drugs significantly reduced mean sitting DBP compared to placebo ($p<0.001$). Mean reductions from baseline were 10.5 mmHg (valsartan 160mg), 9.7 mmHg (losartan 100mg). • No significant difference between the losartan and valsartan. • Valsartan showed a slightly greater response rate than losartan at the end of 8 wks (61.6% compared to 54.5%, $p=0.021$). • Adverse events occurred in 87 patients (32.0%, placebo), 174 patients (31.6%, valsartan) and 159 patients (29.3%, losartan). • Adverse events that were serious or led to trial discontinuation occurred in 13 patients (2.3%, valsartan), 13 patients (2.4%, losartan) and 7 patients (2.6%, placebo). • Both treatments were as effective as each other, but response rates were higher with valsartan at the higher dose.
Irbesartan			
Comparator AIIA	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Response: defined as DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Valsartan[35]	• Randomised, open-label, crossover study (n=40). • Dose: irbesartan 150mg or valsartan 80mg od for 4wks, followed by a 2wk washout then 4wks of the alternate drug. • Primary endpoint: Not stated. Objective was to compare the two anti-hypertensives using 24hr ambulatory BP monitoring.	• Inclusion: Adults 31-60 yrs with sitting DBP 96-114 mmHg. • Exclusion: secondary hypertension, heart failure, major arrhythmias, stroke or MI within previous 6 months, renal or hepatic insufficiency, terminal or severe chronic conditions	• Mean 24-hr SDB/DBP reductions were 10.5/9.7 mmHg (irbesartan) and 10.5/9.5 mmHg (valsartan). • There were no significant differences between the two drugs for daytime and night-time readings. • Mean trough/peak ratios for SBP/DBP were 0.57/0.69 (irbesartan) and 0.65/0.62 (valsartan). • Despite the differences in pharmacology, both drugs maintained their antihypertensive effect throughout 24 hrs.

Table A2: Comparative efficacy: AIIAs vs. ACE Inhibitors for mild-moderate essential hypertension

Candesartan			
Comparator ACEI	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Response: defined as DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Enalapril[36]	• Randomised, double-blind, parallel-group 12-wk study (n=429). • Dose: candesartan 8mg or enalapril 10mg [or hydrochlorothiazide (HCZ) 12.5mg], od. • Dose doubled after 6 wks in non-responders. • Primary endpoint: Quality-of-life variable – difference in change in dry cough from baseline to 12 wks.	• Inclusion: women 40-69 yrs of age with sitting DBP 95-115 mmHg. • Exclusion: secondary hypertension, sitting SBP >200 mmHg, MI, stroke, CABG or TIA within previous 6 months, angina, valve stenosis, heart failure, arrhythmias, type 1 diabetes, severe concomitant diseases that might affect assessments.	• After 12 wks candesartan reduced sitting SBP/ DBP by 19/11 mmHg, compared with 13/9 mmHg (enalapril) and 13/8 mmHg (HCZ), p<0.01. • Higher doses were used in 47% of candesartan, 65% of enalapril and 63% of HCZ recipients. • Quality of life questionnaire showed that patients experienced significantly more discomfort from dry cough with enalapril than the candesartan (p<0.001). • Adverse events occurred in 06% (candesartan) and 67% (enalapril). • Candesartan was more effective at lowering BP, and the favourable effect on SBP is of interest, as mean SBP increases in postmenopausal women and is a strong predictor for cardiovascular events.
Enalapril[37]	• Randomised, double-blind, multicentre 8 wk study (n=227). • Dose: candesartan 4mg or enalapril 10mg. Doses doubled after 4 wks in non-responders. • Primary endpoint: not stated.	• Inclusion: Adults 18-70 yrs with sitting DBP 95-109 mmHg. • Exclusion: none stated.	• Mean reductions in sitting SBP/DBP were 12.3/10.1 mmHg (candesartan) and 15.0/10.5 mmHg (enalapril). • Dosage doubling was necessary in 36.7% (candesartan) and 28.2% (enalapril). • Adverse reactions were lower in the candesartan group (11.3% vs. 23.5%). • Adverse events occurred in 7 patients (15.9%, placebo), 9 patients (11.3%, candesartan) and 19 patients (23.5%, enalapril). • 3 patients on enalapril experienced cough, compared with none in the candesartan group. • 3 patients in the enalapril group withdrew due to adverse events. • Candesartan and enalapril provided similar BP lowering efficacy.
Enalapril[38]	• Randomised, double-blind, placebo controlled multicentre 12 wk study (n=364). • Dose: candesartan 4, 8 or 12 mg, or enalapril 10mg. • Primary endpoint: not stated but aim of study was to compare the efficacy of candesartan vs. enalapril.	• Inclusion: Adults 18-70 yrs with sitting DBP 95-114 mmHg.	• Mean reductions in sitting DBP after 12 wks were 8.4 mmHg (candesartan 4mg), 10.5 mmHg (candesartan 8mg), 10 mmHg (candesartan 12mg) and 10.6 mmHg (enalapril 10mg). • Overall response rates were 53% (candesartan 4mg), 69.1% (candesartan 8mg) and 69% (enalapril). Response rates for candesartan 12mg were not stated. • Adverse events occurred in 23% (placebo), 28-33% (candesartan groups) and 35% (enalapril). • 11 patients withdrew due to adverse events (treatment not specified). • There were no significant differences in sitting DBP in patients treated with candesartan 8mg or 12mg, or enalapril 10mg.

Lisinopril[39]	• Randomised, double-blind, multicentre 26wk study (n=355). • Dose: candesartan 8mg or lisinopril 10mg, od, each with HCZ 12.5mg, od. • Primary endpoint: Change in sitting DBP from baseline to wk 26.	• Inclusion: Adults 20-80 yrs with sitting DBP 95-115 mmHg. • Exclusion: recent significant cardiovascular events, concomitant drugs that affect BP, severe concomitant disease.	• Mean changes from baseline to wk 26 in sitting SBP/DBP were 16.2/9.8 mmHg (candesartan) and 18.4/10.3 mmHg (lisinopril). • Although BP changes were numerically greater in the lisinopril group for both sitting and standing BP, they were not statistically significant. • The proportion of responders was 54.4% (candesartan) and 62.1% (lisinopril). • Adverse events occurred in 68.9% (candesartan) and 79.5% (lisinopril, p=0.02). • Withdrawal due to adverse events occurred in 5.9% (candesartan) and 12.0% (lisinopril). • Cough was more common in the lisinopril group (23.1% vs. 4.6%). • Candesartan has similar antihypertensive effects to lisinopril but is better tolerated.
Perindopril[40]	• Randomised, double-blind, 12months study in 96 patients with type 2 diabetes. • Dose: perindopril 4mg or candesartan 16mg od. • Objective: Effects on haemodynamics and metabolic parameters.	• Inclusion: Adults with type 2 diabetes and DBP 91-104 mmHg. • Exclusion: secondary hypertension, angina, MI within the previous 6 month, liver or renal insufficiency, contraindications to ACEIs or AIIAs.	• Both treatments significantly reduced BP, with effects seen after 1 month of treatment. • SBP/DBP reductions at month 12 were 13/11 mmHg (perindopril) and 12/8 mmHg (candesartan). • Fasting plasma glucose was reduced more with perindopril at 12 months (-9.7% vs. -5.0%, p<0.05). • Dry cough occurred in 2 perindopril-treated patients. • No patient withdrew due to adverse events. • The inclusion/exclusion criteria could limit the ability to extrapolate this data to the general population.
Eprosartan			
Comparator ACEI	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Response: defined as DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Enalapril[41]	• Randomised, prospective, multi-centre, double-blind, double-dummy 10 wk study (n=118). • Dose: eprosartan 200mg bd or enalapril 10mg od. Doses could be titrated to 400mg bd or 40mg od in non-responders. HCZ 25mg could be added in non-responders taking the maximum doses. • Primary endpoint: mean change from baseline in trough sitting DBP in the ITT population.	• Inclusion: Adults >18 yrs with sitting DBP 115-125 mmHg – severe hypertension. • Exclusion criteria: malignant hypertension, secondary hypertension, hypertension due to contraceptive use, MI, CVA within previous 90 days, angina treated with nitrates, beta blockers or calcium channel blockers, unstable diabetes mellitus.	• Mean reductions in trough sitting DBP were 20.1 mmHg (eprosartan) and 16.2 mmHg (enalapril). • The mean change in trough sitting DBP in Caucasian patients was greater with eprosartan than enalapril (p<0.05, difference of 5.7 mmHg) • Mean reductions in trough sitting SBP were significantly higher in the eprosartan group (p=0.025). • Eprosartan was more effective in lowering sitting SBP in patients <65 yrs, females and Caucasian, (p<0.05), and in patients with baseline sitting DBP <120 mmHg or not receiving a thiazide diuretic at baseline. • At study endpoint in the eprosartan group 25% of patients were on 400mg/day, 17% on 600mg/day, 19% on 800mg/day and 39% were taking HCZ as well; in the enalapril group 10% were on 10mg, 22% on 20mg, 31% on 40mg and 37% also took HCZ. • Adverse events occurred in 35 patients (59.3%, eprosartan) and 36 (61.0%, enalapril). 41 were considered treatment related (20 with eprosartan, 21 with enalapril). Cough occurred at the same incidence in both groups. • Withdrawal due to adverse events: 3 (5.1%, eprosartan) and 2 (3.4%, enalapril). • The response rate at study endpoint was 69.5% (eprosartan) and 54.2% (enalapril), p=0.07.

Enalapril[42]	• Randomised, multicentre, parallel-group, double-blind, placebo-controlled 6wk study in 136 patients with hypertension who developed a persistent, non-productive cough whilst on enalapril. • Dose: eprosartan 300mg bd, enalapril 20mg od or placebo. • Primary endpoint: persistent, non productive cough.	• Inclusion: Adults >18 yrs with a history of cough from ACEI treatment and DBP 95-114 mmHg. • Exclusion criteria included: emphysema or chronic bronchitis with daily cough, asthma with dry cough, URTI within previous 2 weeks, secondary hypertension, cardiovascular diseases, renal or hepatic insufficiency.	• Both active treatments reduced sitting DBP significantly more than placebo, but did not differ from each other. • 53% (eprosartan) and 42% (enalapril) of patients responded to treatment. • Adverse events occurred in 22 patients (48.9%, placebo), 26 patients (56.5%, eprosartan) and 29 patients (64.4%, enalapril). • Cough was seen in 2.6% of eprosartan-treated patients and 25% of enalapril-treated patients (p=0.008). • Withdrawals due to adverse events occurred in 1 patient treated with eprosartan and 4 treated with enalapril. • Eprosartan is comparable to enalapril in terms of BP reduction but has a lower incidence of cough.
Enalapril[43;44]	• Randomised, double-blind, multicentre 26 wk study (n=528,). • Dose: enalapril 5mg od or eprosartan 200mg bd – doses titrated over 18 wks to 20mg od or 300mg bd, then 8 wk maintenance. • Non-responders after 12wks had HCZ 12.5mg-25mg added. • 40 patients in the study were black. • Primary endpoint: Definite cough of interest – persistent, non-productive dry cough associated with treatment.	• Inclusion: Adults >18 yrs old, with essential hypertension. • Exclusion: sitting SBP >200 mmHg, advanced atrioventricular conduction defects, arrhythmias, prior MI or CVA within last 90 days, heart failure treated with ACEIs, renal or hepatic insufficiency.	• Sitting SBP/DBP reduction in the overall study population was 15.5/12.9 mmHg (eprosartan) and 14.7/11.9 mmHg (enalapril). • Reductions in the black population at 12 wks were 15.4/9.4 mmHg (eprosartan) and 3.4/5.4 mmHg (enalapril). • Mean reductions in the black population at study endpoint were 18.8/10.5 mmHg (eprosartan) and 10.5/9.6 mmHg (enalapril). • 52.4% (eprosartan) and 26.3% (enalapril) of the black patients responded to monotherapy and 66.7% and 42.1% responded to dual therapy. • Cough occurred in 1 black patient in the eprosartan group (4.8%) and 2 black patients in the enalapril group (10.5%). • The overall incidence of cough in all patients was significantly higher in the enalapril group (5.4% vs. 1.5%, p=0.018). • Eprosartan monotherapy was generally more effective than enalapril monotherapy in black patients.
Enalapril[44;45]	• Study design as above. • 125 patients were ≥65 years, 63 on eprosartan and 62 on enalapril. • Primary endpoint: Definite cough of interest – persistent, non-productive dry cough associated with treatment.	• Inclusion: Adults ≥18 yrs old, with essential hypertension. • Exclusion: sitting SBP >200 mmHg, advanced atrioventricular conduction defects, arrhythmias, prior MI or CVA within last 90 days, heart failure treated with ACEIs, renal or hepatic insufficiency.	• Mean SBP/DBP reductions at endpoint in pts ≥65 yrs were 18.9/13.9 mmHg (eprosartan) and 15.3/12.2 mmHg (enalapril). • BP response rates in the elderly patients were 87.3% (eprosartan) and 77.4% (enalapril). • Both drugs showed a similar reduction in BP with no evidence of an age-related response. • In the main study, significantly more patients on eprosartan (81.7%) responded to treatment compared with enalapril (73.4%, p=0.018).
Enalapril[26]	• Randomised, double-blind 26wk study (n=528). • Dose: eprosartan 400-600mg daily or enalapril 5-20mg od. HCZ 12.5 or 25mg could be added in non-responders after 12 wks. • Primary endpoint: not stated.	• Inclusion: Adults with sitting DBP 95-114 mmHg.	• Sitting SBP/DBP reduced by 15.5/12.9 mmHg (eprosartan) and 14.7/11.9mHg (enalapril). • Significantly more patients responded to eprosartan monotherapy (70.3% vs. 62.6%, p<0.05). • Response rates at study endpoint were 81.7% (eprosartan) and 73.4% (enalapril), p<0.018. • Maximum doses were used in 52% (eprosartan) and 57% (enalapril) of patients. Similar amounts in each group required HCZ.

Irbesartan			
Comparator ACEI	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Response: defined as DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Enalapril[46]	• Randomised, double-blind, multicentre 12wk study (n=238). • Dose: irbesartan 150mg or enalapril 10mg od. • Doses doubled in non-responders at wk 4 and or at wk 8. • Primary endpoint: Reduction in 24 hr DBP after 12 wks.	• Inclusion: Adults with DBP 90-109 mmHg or SBP 140-179 mmHg. • Exclusion: renal impairment, papilloedema, coronary heart disease or cardiac failure in the previous 3 months, any severe concomitant disease.	• Mean reductions in SBP/DBP were 14.7/9.4 mmHg (irbesartan) and 12.6/8.8 mmHg (enalapril). • Response rates were seen in 36% (irbesartan) and 34.8% (enalapril) of patients (as assessed by clinic measurements). Daytime BP control was achieved by 40.5% and 33.9% respectively as, assessed by ambulatory BP measurements. • Adverse events considered treatment related were more frequent in the enalapril group (24.6%) than the irbesartan group (9.2%), p=0.026. • Withdrawals due to adverse events occurred in 2 patients treated with irbesartan (1.7%) and 3 treated with enalapril (2.4%). • Cough was more prevalent in the enalapril group (8.1% vs. 0.9%). • Irbesartan was as effective as enalapril for controlling BP, but was better tolerated.
Enalapril[47]	• Randomised, double-blind 12 wk study (n=182). • Dose: irbesartan 150mg or enalapril 20mg od; in non-responders doubled after 1 wk and additional antihypertensives (hydrochlorothiazide then nifedipine then atenolol) added after 4 wks. • Primary endpoint: Reduction in trough sitting DBP (24±3hrs) from baseline at wk 12.	• Inclusion: Adults >18yrs, with DBP 115-130 mmHg. • Exclusion: concomitant diseases or medications that would affect assessments.	• SBP/DBP reductions after 12 wks were 40.1/29.6 mmHg (irbesartan) and 39.3/30.5 mmHg (enalapril). • Reductions in trough sitting BP tended to occur earlier with irbesartan. • Response rates were 100% (irbesartan) and 98% (enalapril). • At week 12 9% of patients on irbesartan and 7% on enalapril were on monotherapy, whilst 24% and 18% received additional HCZ. More than 3 antihypertensives were needed in 67% and 75% respectively. • More adverse events occurred in the enalapril group (64%) than the irbesartan group (55%). • Cough was more prevalent in the enalapril group (13.1% vs. 2.5%), p=0.007. • Irbesartan was as effective as enalapril at maximum doses.
Enalapril[48]	• Randomised, double-blind, crossover 12 wk study (n=21). • Dose: irbesartan 100mg or enalapril 20mg od. Doses were randomly allocated to the morning or the evening for 6 wks according to a crossover design. • Primary endpoint: Not stated. Objective – to compare the acute and sustained renal haemodynamic effects.	• Inclusion: Adults 35-70 yrs, with DBP 95-115 mmHg. • Exclusion: none stated.	• In the morning dose group reductions in 12hr daytime ambulatory SBP/DBP were 11.1/6.8 mmHg (irbesartan) and 13.8/8.7 mmHg (enalapril) and in 12hr night-time ambulatory SBP/DBP 4.2/4.6 mmHg (irbesartan) and 6.1/2.7 mmHg (enalapril). • For the evening dose group the daytime reductions were 9.8/6.9 mmHg (irbesartan) and 11.1/9.1 mmHg (enalapril), and the night-time reductions were 7.4/4.6 mmHg (irbesartan) and 7.5/6.8 mmHg (enalapril). • The differences between the treatments were not statistically significant. • This was a small study in which the antihypertensive effect was not the main endpoint, but it did show comparable effects of irbesartan and enalapril. • The reduction in 24hr ambulatory blood pressure was similar irrespective of whether the dose was given in the morning or the evening.

Enalapril[49]	• Randomised, double-blind, multicentre 12wk study (n=200). • Dose: irbesartan 75mg or enalapril 10mg od. Doses were doubled at wk 4 and wk 8 in non-responders to a max of 300mg or 40mg respectively. • Primary endpoint: Not stated. Objective – to compare the anti-hypertensive efficacy, safety and tolerability of the two drugs.	• Inclusion: Adults ≥18 yrs with sitting DBP 95-110 mmHg. • Exclusion: concomitant diseases or medications that would present safety hazards or interfere with assessments.	• Both treatments resulted in statistically significant decreases in trough SBP and DBP, with no significant differences between the two drugs. • DBP was reduced by ~15 mmHg within 4 wks in patients on irbesartan 75mg or enalapril 10mg, with no further changes at wks 8 or 12. • DBP was reduced by 13 mmHg in patients on irbesartan 150mg or enalapril 20mg. • DBP was reduced by 11 mmHg (enalapril 40mg) and 8 mmHg (irbesartan 300mg). • At wk 12, 66% (irbesartan) and 63% (enalapril) had DBP <90 mmHg. • At wk 12, 42% and 36% were taking irbesartan 75mg and enalapril 10mg respectively, whilst 28% and 24% respectively were taking 300mg and 40mg respectively. • Adverse events occurred at a similar incidence in both groups (43% enalapril, 45% irbesartan). • Withdrawals due to adverse events occurred in 1 patient in the irbesartan group (1%) and 3 in the enalapril group (2.9%). • Cough was reported by 10% of patients on irbesartan and 17% on enalapril. • Irbesartan was as effective as enalapril in reducing BP.

Losartan

Comparator ACEI	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Response: defined as DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Captopril[50]	• Randomised, double-blind, multicentre 12 wk study (n=396). • Dose: following placebo washout, losartan 50mg od or captopril 25mg bd. Doses were doubled after 6 wks in non-responders. • Primary objective: to compare the antihypertensive efficacy of losartan with captopril.	• Inclusion: Adults with sitting DBP 90-115 mmHg. • Exclusion: concurrent medical conditions or treatment that might affect BP, malignant/ secondary hypertension, significant cardiovascular, cerebrovascular, renal, hepatic, gastrointestinal, pulmonary or neurologic disorders, uncontrolled diabetes.	• Mean sitting SBP/DBP changes were 15.4/11.5 mmHg (losartan) and 12.2/9.3mmgHg (captopril), p=0.023 for SBP and p=0.010 for DBP. • Titration to higher doses was required in 59% (losartan) and 58% (captopril). • Response was achieved in 60% (losartan) and 54.7% (captopril). • Drug-related adverse events were more common in the captopril group (13%) than the losartan group (10%). • Withdrawals due to adverse events occurred in 5 patients in the losartan group (3%) and 12 in the captopril group (6%). • Cough occurred in more patients treated with captopril (4.4%) than losartan (2.6%). • BP changes were statistically superior with losartan compared with captopril, though similar proportions of patients in each group achieved BP control.
Enalapril[51]	• Randomised, multicentre, double blind, parallel group 12 wk study (n=75). • Dose: losartan 50mg or enalapril 20mg od. In non responders, at wk 2 doses were doubled, at wk 4 HCZ 25mg added, at wk 6 atenolol 50mg-100mg added, at wk 8 calcium channel blocker added. • Primary endpoint: change from baseline in trough BP and hypertensive response.	• Inclusion: Adults 23-74 yrs, with sitting DBP 115-130 mmHg. • Exclusion: secondary hypertension, serious heart, liver or renal disease, any medical condition or treatment that might affect BP.	• Mean reductions in trough SBP/DBP were 33.4/29 mmHg (losartan) and 39.6/32.4 mmHg (enalapril). • By wk 12, in the losartan group 6% were still on monotherapy, 34% were on 2 antihypertensives, 46% were on 3 and 14% were on 4. The corresponding percentages for the enalapril group were 16%, 0%, 68% and 16% respectively. • Similar reductions in sitting SDP/DBP were achieved in both black and non-black patients (36.6/28.4 and 31/27.1 mmHg with losartan, and 39.5/31.6 and 44.9/30.4 mmHg with enalapril). • At wk 12 98% (losartan) and 100% (enalapril) had achieved antihypertensive response. • Adverse events occurred in 35 patients in the losartan group (70%) and 19 in the enalapril group (76%). No patients withdrew due to adverse events. • Cough was more common in the enalapril group (12% vs. 8%). • Enalapril-based therapy appeared to be more efficacious but additional agents were used to achieve target blood pressure.

Enalapril[52]	• Randomised, double-blind, multicentre, parallel-group 12 wk study (n=268). • Dose: losartan 50mg od, HCZ 12.5mg added at 8 wks if necessary, or enalapril 5mg od, increased to 10mg od at 4 wks, then HCZ 25mg added at 8wks, if necessary. • Primary endpoint: Change in mean sitting DBP from baseline to wk 12.	• Inclusion: Adults ≥21 yrs with mean sitting DBP 90-115 mmHg. • Exclusion: previous ACEI or AIIA use or sensitivity / intolerance, angioedema, heart failure, secondary hypertension, arrhythmias, MI, angioplasty, CVA.	• Mean reductions in DBP at wk 12 were 10.3 mmHg (losartan) and 9.8 mmHg (enalapril, p=0.31). • Higher doses or HCZ were required in 53% (losartan), 29% (enalapril 10mg) and 47% (enalapril 10mg plus HCZ). • More patients in the losartan group achieved goal blood pressure (68% vs. 60%, p=0.16). • Mean decreases in DBP were significantly greater with losartan than enalapril in black patients (10.0 mmHg vs. 8.0 mmHg, p=0.02) and elderly patients (12.7 mmHg vs. 8.7 mmHg, p=0.03). • Drug-related adverse events occurred in 35 patients taking losartan (27%) and 36 taking enalapril (36%). • Withdrawals occurred in 3 patients taking losartan (2%) and 7 taking enalapril (5%). • Cough was more prevalent in the enalapril group (12% vs. 7%). • Losartan provides comparable BP lowering effects to enalapril, with better results in some patient subgroup.

Olmesartan

Comparator ACEI	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Response: defined as DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Captopril[29]	• Randomised 12 wk study (n=291). • Dose: captopril 12.5mg bd or olmesartan 5mg od. • Dose increased at wks 4 and 8 in non-responders to captopril 25mg then 50mg bd, or olmesartan 10mg then 20mg od, respectively. • Primary endpoint: Not stated.	• Inclusion: Adults with DBP 95-114 mmHg.	• Mean reductions in SBP/DBP at wk 12 were 14.7/9.9 mmHg (olmesartan) and 7.1/6.8 mmHg (captopril). • Significantly more patients responded to olmesartan (53%) than captopril (38%), p<0.01. • Fewer patients required the highest olmesartan dose (25%) than the highest captopril dose (54.9%). • Target blood pressure was achieved with a lower dose of olmesartan than captopril.

Telmisartan

Comparator ACEI	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Response: defined as DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Enalapril[53]	• Randomised, multicentre, double-blind, parallel-group 26 wk study (n=278). • Dose: telmisartan 20mg or enalapril 5mg od. Doses doubled every 4 wks to telmisartan 40mg then 80mg, or enalapril 10mg then 20mg. HCZ 12.5mg added in wk 12 to those not responding to the third dose increase, or to non-responders after wk 16. • Primary endpoint: Change from baseline in trough supine SBP and DBP.	• Inclusion: Adults ≥65 yrs with mean morning supine DBP 95-114 mmHg. • Exclusion: secondary hypertension, hepatic or renal dysfunction, bilateral renal artery stenosis or post renal transplant, NYHA class III or IV heart failure, arrhythmias.	• Mean reductions in trough SBP/DBP were 22.1/12.8 mmHg (telmisartan) and 20.1/11.4 mmHg (enalapril). • By wk 12, 57% (telmisartan) and 49% (enalapril) had achieved DBP <90 mmHg. • Mean reductions in supine DBP in patients <75 yrs were 13.2 mmHg (telmisartan) and 10.7 mmHg (enalapril), and in patients ≥75 yrs were 11.9 mmHg (telmisartan) and 13.6 mmHg (enalapril). • More patients ≥75 yrs responded to enalapril (72% vs. 63%). • HCZ was taken by 36% (telmisartan) and 38% (enalapril). • Drug-related adverse events occurred in 35 patients in the telmisartan group (25%) and 52 in the enalapril group (37%). • Cough was more prevalent in the enalapril group (16% vs. 6.5%). • Overall more patients responded to telmisartan (71%) than enalapril (68%).

Ramipril[54]	• Randomised, multicentre, parallel-group, forced-titration 14 wk study (n=812). • Dose: Telmisartan 40mg or ramipril 2.5mg od; doses increased at wk 2 to 80mg and 5mg od, then at wk 8 ramipril increased to 10mg od. • Primary endpoint: Changes from baseline in the last 6 hrs mean DBP and SBP as measured by ambulatory BP at 8 wks and 14 wks.	• Inclusion: Adults ≥18 yrs with mean sitting DBP 95-109 mmHg and a 24hr mean DBP ≥85 mmHg. • Exclusion criteria included: mean sitting SBP≥180 mmHg or mean sitting DBP ≥110 mmHg, secondary hypertension, congestive heart failure or stroke within the previous 6 months, PTCA within 3 months, night-shift workers.	• After 8 and 14 wks, significantly greater decreases in mean ambulatory BP during each period of the 24-hr administration interval* were seen with telmisartan compared with ramipril (p<0.0001). *Mean last 6-hr, 24-hr, morning, daytime and night-time. • Mean decreases in last 6-hr ambulatory SBP/DBP at wk 14 were 12.7/8.8 mmHg (telmisartan) and 7.9/5.4 mmHg (ramipril), p<0.0001. • Cough was more prevalent in the ramipril group (8.1% vs. 0.2%). • Telmisartan was consistently significantly more effect than ramipril in controlling BP during the entire 24-hr dosing interval.
Valsartan			
Comparator ACEI	**Trial design and primary endpoint**	**Inclusion / exclusion criteria**	**Results** Response: defined as DBP decreased to <90 mmHg, or decreased by 10 mmHg or more
Captopril[55]	• Randomised, open-label, multicentre, 8 wk study (n=197). • Dose: valsartan 80mg od or captopril 25mg bd or placebo. • Primary endpoint: Change in mean sitting DBP from baseline to wk 8.	• Inclusion: Adults >18 yrs with mean sitting DBP 96-114mmHg. • Exclusion: heart failure, MI, CVA, CABG or PCTA within the previous 6 months, heart block, angina, arrhythmias, secondary hypertension, renal or hepatic impairment, poorly controlled type 1 diabetes.	• Mean reductions in SBP/DBP were 21.8/12.5 mmHg (valsartan) and 18.4/12.2 mmHg (captopril). • More patients had a DBP <90 mmHg in the valsartan group (45% vs. 34%), but more patients in the captopril group had a reduction of ≥10 mmHg in DBP (71% vs. 69%). • There were 27 adverse events in the captopril group and none in the valsartan group. • Six patients in the captopril group withdrew because of adverse events. • Cough was more prevalent in the captopril group (21.6% vs. 0%). • Valsartan was as effective as captopril in controlling BP.
Enalapril[56]	• Randomised, double-blind, parallel group, placebo controlled multicentre, 8 wk study (n=348). • Dose: valsartan 80mg or enalapril 20mg od. • Primary endpoint: Change from baseline in mean sitting DBP at wk 8. • Primary comparison was valsartan vs. placebo. Enalapril was used as a positive control.	• Inclusion: Adults 20-79 yrs with sitting DBP 95-115 mmHg. • Exclusion: heart failure, CVA in previous 6 months, MI in previous 3 months, renal or hepatic impairment, concomitant medication that might affect assessments.	• Mean reductions in sitting SBP/DBP were 12.4/9.5 mmHg (valsartan), 13.1/9.4 mmHg (enalapril) and 5.7/4.5 mmHg (placebo). Both active treatments were significantly better than placebo (p<0.001 and p=0.003 respectively) but there was no significant difference between them. • Response rates with valsartan (54%) and enalapril (58%) were significantly better than placebo (20%), p<0.001 but there was no significant difference between the 2 active treatments. • Adverse events occurred in 20 patients in the valsartan group (15%), 24 in the placebo group (17%) and 9 in the enalapril group (13%). • One patient in the valsartan group and 3 in the placebo group withdrew because of adverse events. • Cough was reported by 4.3% of patients on enalapril compared with 0.7% on valsartan. • Although the study did not compare valsartan with enalapril, no statistically significant therapeutic differences were found between them.

Lisinopril[57]	• Randomised, multicentre, double-blind, parallel-group, placebo controlled 12 wk study (n=734). • Dose: valsartan 80mg or lisinopril 10mg od. Doses doubled after wks in non-responders to valsartan 80mg bd or 160mg od, or lisinopril 20mg od. • Primary endpoint: Change from baseline in mean sitting DBP at wk 12.	• Inclusion: Adults 21-80 yrs with sitting DBP 95-115 mmHg. • Exclusion: heart failure, MI, hypertensive encephalopathy or CVA within previous 6 months, arrhythmias, valvular disease, hepatic or renal impairment and type 1 diabetes, concomitant medication that could affect assessments.	• Mean reductions in sitting DBP were 8.29 mmHg (valsartan od), 8.67 mmHg (valsartan bd) and 9.97 mmHg (lisinopril). • All 3 treatment groups showed comparable efficacy with no significant differences between them in lowering DBP and SBP. All were significantly better than placebo ($p<0.001$). • There was no difference between the valsartan od and bd groups in the reductions in DBP (7.76 mmHg and 7.9 mmHg respectively). • Significantly more patients responded to lisinopril than valsartan (59.3% vs. 46.3% (od)). 49.4% responded to valsartan bd. • Drug-related adverse events occurred in 27.8% taking lisinopril and 22.8% taking valsartan. • Cough was more prevalent in the lisinopril group (8.0% vs. 1.1%); 3 patients in the lisinopril group withdrew due to cough compared with valsartan. • Valsartan showed similar efficacy to lisinopril.

Appendix 2:

Comparative efficacy: ACE Inhibitors

Captopril and lisinopril are the only ACE Inhibitors that do not require hepatic activation to an active metabolite.[58] All the others are prodrugs that increase bioavailability, rate of absorption or duration of activity. The prodrugs are usually esters of the active form and rapidly hydrolysed in the liver by first pass metabolism.[58]

All currently available ACE Inhibitors are licensed for the treatment of hypertension and can potentially reduce mean blood pressure to the same extent for a finite period of time.[58] The antihypertensive duration of action for ACE Inhibitors depends on each drugs pharmacokinetics and dosage. Captopril, moexepril and quinapril have the shortest duration of action of all the ACE Inhibitors; with the exception of captopril all the ACE Inhibitors can be given once a day though the efficacy of moexipril and quinapril may be increased if given twice daily.[58]

The CKS Guidance on Hypertension recommends enalapril, lisinopril, perindopril, ramipril, and trandolapril.[17] Other ACE Inhibitors are not included because there are fewer trial data on their use. Captopril has a shorter half-life than other ACE Inhibitors; it needs to be taken in divided doses, and is no longer recommended as a first-line ACE Inhibitor. All ACE Inhibitors are licensed for use in hypertension and there is probably a drug-class effect.

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