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ACE INHIBITORS AND ANGIOTENSIN II ANTAGONISTS FOR THE TREATMENT OF HYPERTENSION: DRUG SELECTION BY MEANS OF THE SOJA METHOD

ACE inhibitors have proved to be effective blood pressure lowering agents with an excellent tolerability profile. The family of ACE inhibitors is still expanding, necessitating the definition of selection criteria in order to choose the "right ACE inhibitor".

In this article the ACE inhibitors available in the Netherlands as well as the angiotensin II antagonist losartan are scored by means of the System of Objectified Judgement Analysis (SOJA) method, which is a model for rational drug selection. The relevant selection criteria for a certain group of drugs are defined and judged by a panel of experts and each selection criterion is given a relative weight. The more important that a selection criterion is considered, the higher the relative weight that is given to it. The ideal properties for each selection criterion are determined and each drug is scored as a percentage of the score of the ideal drug for all selection criteria.

The following selection criteria were used (relative weight): number of formulations (20), number of registrations (20), variation in bioavailability (40), interactions (40), trough/peak ratio diastolic blood pressure lowering effect (20), efficacy (360), side-effects (150), dosage frequency (100), acquisition cost (100) and documentation (150). Ramipril shows the highest score, followed by lisinopril, enalapril and captopril. These are the most attractive ACE inhibitors for formulary inclusion. The other drugs show lower scores.

KEY WORDS: Hypertension, ACE inhibitors, angiotensin II inhibitors, SOJA, drug selection

INTRODUCTION

ACE inhibitors have proved to be effective blood pressure lowering agents with an excellent tolerability profile, while some of them are also standard drugs in the therapy of heart failure. The family of ACE inhibitors is still expanding, necessitating the definition of selection criteria in order to choose the "right ACE inhibitor" [1].

The System of Objectified Judgement Analysis (SOJA) method is a model for rational drug selection. The relevant selection criteria for a certain group of drugs are defined and judged by a panel of experts and each selection criterion is given a relative weight. The more important that a selection criterion is considered, the higher the relative weight that is given to that criterion. The ideal properties for each selection criterion are determined and each drug is scored as a percentage of the score of the ideal drug for all selection criteria.

In this article the ACE inhibitors available in the Netherlands as well as the angiotensin II antagonist losartan are scored by means of the SOJA method.

The following drugs were included in the score:
Benazepril
Captopril
Cilazapril
Enalapril
Fosinopril
Lisinopril
Perindopril
Quinapril
Ramipril
Trandolapril
Losartan

The selection criteria and the relative weights that are assigned by the authors are shown in Table 1.

SELECTION CRITERIA

Formulations

To facilitate flexible dosing it is important to have more than one dosage strength available. This is also true for a liquid or dispersible formulation in patients with swallowing problems. An injectable formulation of ACE inhibi-

Formulations	20
Number of registrations	20
Variation in bioavailability	40
Interactions	40
Trough/peak ratio diastolic blood pressure effect	20
Efficacy	360
Side effects	150
Dosage frequency	100
Acquisition cost	100
Documentation	150
Number of DB comparative studies	25
Number of patients in these studies	25
Number of years marketed	25
Number of patient days worldwide	25
Survival studies	50
Total	1000

Table 1: Selection criteria for ACE inhibitors

tors is not used to any great extent and is not scored. This criterion was scored as follows:

one oral form	50%
more oral tablet/capsule strengths	75%
liquid/dispersible oral form	25%

Number of registrations

From a formulary point of view it may be relevant to include ACE inhibitors which are approved for more than one single indication. Although it seems unlikely that there will be major differences in efficacy or tolerance between different ACE inhibitors, not all ACE inhibitors are approved for more indications than just hypertension. This was scored as follows:

hypertension	60%
congestive heart failure (any form)	20%
diabetic nephropathy	20%

Pharmacokinetics

A wide variety of pharmacokinetic properties may be used for drug selection of ACE inhibitors, but only a few have any clinical relevance. Factors such as protein binding, volume of distribution, route of elimination and lipophilicity have little or no impact on efficacy and tolerability of ACE inhibitors, although a combined renal and metabolic elimination may be advantageous in patients with renal disease. Dose adaptation of ACE inhibitors in renal disease is usually relatively simple, so this is not clinically relevant in the treatment of hypertension, although it might be of more importance in the treatment of heart failure or after myocardial infarction [1–6]. The elimination half-lives of ACE inhibitors and losartan are quite different. Elimination half-life as such was not used as a selection criterion, as this criterion is incorporated in the criteria dosage frequency and peak-trough ratio of antihypertensive effect. Moreover, half-life is probably of less importance than the kinetics of binding to ACE.

Most ACE inhibitors are prodrugs, which have to be metabolized into the active "prilate". It is a theoretical advantage if a drug is not a prodrug, as this may result in less variable serum concentrations of the active compound. We have chosen to combine the criteria prodrug and bioavailability in one single criterion: variability of the serum concentration of the active substance. This was scored as follows:

Variation in bioavailability

SD of AUC in healthy volunteers:

<10%	100%
10–20%	80%
20–30%	60%
30–40%	40%
40–60%	20%
> 60%	0%

Interactions

Drug interactions usually occur in a small minority of patients, but are relevant from a formulary point of view in order to reduce the incidence and severity of these interactions.

A drug exhibiting a high incidence of drug interactions may complicate therapy. The lower the incidence and severity of drug interactions with each individual drug, the higher the score for this criterion.

Trough/peak ratio diastolic blood pressure effect

The US Food and Drug Administration has suggested a definite and comprehensive index of the antihypertensive effect. The trough effect (at the end of the dosage interval) should be at least 50% of the peak effect, once appropriate adjustment has been made for placebo effect and the circadian rhythm. If the net peak effect is limited (5 mmHg) the trough effect should be at least 66% of the peak effect [7]. This was scored as follows:

Trough/peak ratio	
> 0.75	100%
0.66–0.75	80%
0.5–0.65	60%
0.4–0.49	40%
0.25–0.39	20%
< 0.25	0%

Efficacy

Clinical efficacy is by definition a very important selection criterion for each group of drugs. The relative efficacy of ACE inhibitors and losartan was determined from double-blind comparative studies between these drugs. The extent of blood pressure reduction in mmHg was used for comparison as well as the number of patients who show normalization of blood pressure (% responders) after treatment with the drugs.

Side-effects

The relative tolerance was determined from double-blind comparative studies between ACE inhibitors and/or losartan. For every 1% difference in tolerance, 3% of the maximum score was deducted for the least tolerated drug. If one drug has an incidence of adverse reactions which is 5% higher than that of another ACE inhibitor, the score for the drug with the poorest tolerance will be 15% (3 x 5%) lower.

Dosage frequency

A low dosage frequency is of great importance in lifelong treatment such as that of hypertension. Patient compliance is at its best with once-daily dosing, although the difference between once- and twice-daily dosing is not impressive. Patient compliance drops significantly at higher dosage frequencies. This was scored as follows:

once daily	100%
once–twice daily	90%
twice daily	80%
twice–thrice daily	60%
thrice daily	40%

Acquisition cost

The cost of drugs plays an increasing role as a selection criterion. Ideally, pharmacoeconomic studies, in which all treatment related costs and outcome are included, should be included in the SOJA score, but these are not available. Therefore, acquisition cost for the patient was used for cost comparison. The dosages of the ACE inhibitors were compared by means of the internationally (World Health Organization) standardized Defined Daily Dosages (DDD) for ACE inhibitors. This was scored as follows:

cheapest ACE inhibitor in the Netherlands (on the basis of DDD)	100%
every % increase in cost	-1%

Documentation

The clinical documentation and the clinical experience with drugs are important selection criteria. Documentation was divided into five subcategories, of which the first two reflect clinical efficacy and tolerability and the third and fourth are indicative of the clinical experience with the drug in question. The data on the number of patient-days experience on a worldwide level were obtained from the respective pharmaceutical companies.

The last criterion (survival studies in patients with heart failure) does not reflect their use in hypertension, but is included as a criterion reflecting clinical documentation of the drug in question.

1. Number of double blind comparative studies

The number of double blind comparative clinical studies with other antihypertensive agents is an important determinant of the clinical documentation. This was scored as follows:

> 20	100%
15–20	80%
11–14	60%
6–10	40%
3–5	20%
0–2	0%

2. Number of patients in these studies

Besides the number of clinical studies, the number of patients who were treated with the drug in question must also be taken into consideration.

This was scored as follows:

> 1000	100%
750–1000	80%
500–750	60%
250–500	40%
150–250	20%
0–150	0%

3. Number of years marketed

The number of years that a product has been marketed in any country in the world provides information on the clinical experience with the drug. If a product has been on the market for more than 10 years it is very unlikely that serious adverse reactions will be observed which have not been seen in the first decade after its introduction. This was scored as follows:

> 10	100%
6–10	75%
2–5	50%
1–2	25%
< 1	0%

4. Number of patient-days worldwide

Besides the number of years that a product is on the market, the number of patient days experience with the drug also plays a role. This was scored as follows:

> 100 million	100%
50–100 million	80%
20–50 million	60%
10–20 million	40%
5–10 million	20%
< 5 million	0%

5. Survival studies

No studies are yet available which have shown that the use of ACE inhibitors for the treatment of hypertension results in a reduction of cardiovascular mortality. Studies are available, however, on the reduction of mortality and morbidity when ACE inhibitors are used for congestive heart failure or post-myocardial infarction. These studies are of great importance as reduction of mortality and morbidity is the primary endpoint for treatment with these drugs. Although these studies have no direct relationship with their use in hypertension, they contribute very much to the overall documentation of ACE inhibitors. The relative weight of the survival studies in heart failure in this SOJA score for their use in hypertension (in which these studies contribute to overall documentation only) is lower than if a SOJA score was prepared for their use in congestive heart failure or post-myocardial infarction, where this is the most important criterion. This was scored as follows:

Demonstrated reduction in mortality and morbidity in:	
congestive heart failure	50%
prophylaxis after myocardial infarction	50%

RESULTS

Formulations

None of the ACE inhibitors is available as a liquid or dis-

persible formulation. Ramipril is available as a capsule formulation, which can easily be dispersed in water, apple juice or apple sauce without affecting its bioavailability or pharmacodynamic effects [8]. This drug scores 100%. All other drugs are available in more than one tablet strength and these score 75%. Losartan scores 50%, as only a 50 mg tablet is available.

Number of registrations

Most ACE inhibitors (benazapril, enalapril, lisinopril, perindopril, quinapril, ramipril and trandolapril) are approved for both hypertension and congestive heart failure (as such or occurring after myocardial infarction). These drugs score 80%. Captopril is also approved for diabetic nephropathy, and this drug scores 100%. Cilazapril, fosinopril and losartan are only approved for hypertension. These drugs score 60%.

Pharmacokinetics

The pharmacokinetic properties of the ACE inhibitors and losartan are summarized in Tables 2 and 3. Trandolapril shows the lowest variability in the area under the serum concentration-time curve (AUC) of the active compound and scores 100%. Ramipril, captopril and perindopril also show little variability in the serum levels of the active compounds and score 80%. The highest variability is seen with lisinopril, cilazapril and quinapril, these drugs score 40%. The other drugs score 60%.

Interactions

The pharmacokinetic drug interactions which may occur with ACE inhibitors have been extensively reviewed by Shionori [29].

Interactions with cardiovascular drugs

No major pharmacokinetic interaction is seen with diuretics, but hyperkalaemia may occur in patients taking potassium supplements or potassium-sparing diuretics, especially in patients with renal disease. Addition of ACE inhibitors to diuretic therapy may result in hypotension. There appear to be no differences in the extent of these interactions between ACE inhibitors. No major interactions (apart from the intended additive blood pressure lowering effect) are observed when ACE inhibitors are combined with beta-blockers or calcium antagonists. Additive blood pressure lowering effects are also seen with alpha-blockers and central alpha$_2$ adrenoceptor agonists. Although data are incomplete and sometimes conflicting, there seems to be no clinically relevant effect of ACE inhibitors on the pharmacokinetics of digoxin [29]. An interaction between captopril and digoxin (25% increase of digoxin levels) was observed in patients with severe heart failure, whereas no interaction was found in patients with hypertension [30].

Interactions with other drugs

Concomitant intake of antacids reduces the absorption of captopril by about 35%. There are few data on the other

	Variability (% standard deviation of the AUC)	Score (%)
Benazepril	23%	60%
Captopril	13%	80%
Cilazapril	31%	40%
Enalapril	26%	60%
Fosinopril	24%	60%
Lisinopril	38%	40%
Perindopril	19%	80%
Quinapril	31%	40%
Ramipril	11%	80%
Trandolapril	8%	100%
Losartan	26%	60%

From references 9–28.

Table 3: Variability of the serum concentration of the active compound

	Prodrug	Bioavailab. (%)	Bioav. act.met	Effect of food	T 1/2	Clearance
Benazepril	yes	37–50	12	–	10–11	Renal/hep
Captopril	no	75–85	75–85	25–50%	2–3	renal
Cilazapril	yes	40–75		15%	30–50	renal
Enalapril	yes	60–70		–	11	renal
Fosinopril	yes	36	30	–	11	renal/hep
Lisinopril	no	25–30	25–30	–	12	renal
Perindopril	yes	80	16	30%	25	renal
Quinapril	yes*	60	35	–	3	renal
Ramipril	yes	50–60		–	13–17	renal/hep
Trandolapril	yes	40–60	–	–	16–24	renal/hep
Losartan	no#	33	33	–	2 6–9 (met)	renal/hep

From references: 1, 4, 5 and 6.

* Quinapril also has ACE inhibitory effects, comparable to captopril

\# Losartan also has characteristics of a prodrug as its major metabolite is more active than the parent compound

Table 2: Pharmacokinetics of ACE inhibitors

ACE inhibitors. No pharmacokinetic drug interaction is observed when ACE inhibitors are combined with cimetidine. No major kinetic interactions are observed between ACE inhibitors and antihyperglycaemic drugs, allopurinol, probenecid or lipid lowering drugs such as the HMG-CoA reductase inhibitors. ACE inhibitors may affect the clearance of lithium, resulting in higher serum concentrations of lithium. It is not clear whether there are relevant differences between ACE inhibitors in the extent of this interaction. In general the interaction appears to be of limited importance [30].

The blood pressure lowering effect of ACE inhibitors may be decreased to some extent by non-steroidal anti-inflammatory drugs (NSAIDs). There seem to be no differences between ACE inhibitors with respect to this interaction. Perindopril showed similar antihypertensive activity in patients treated with NSAID,s and in patients who were not receiving NSAID treatment [31]. There are insufficient data on the potential interactions between ACE inhibitors and cyclosporin or rifampicin. Food has limited or no effects on the absorption of most ACE inhibitors and losartan: only the bioavailabilities of captopril, cilazapril and perindopril are decreased to any significant extent.

There are few clinically relevant drug interactions between ACE inhibitors and other drugs, apart from the (intended) additive blood pressure lowering effects of combinations with diuretics, beta-blockers or calcium antagonists. There are no conclusive data to show whether differences are observed between ACE inhibitors in the extent of interaction with antacids, although this interaction appears to be absent with ramipril.

An interaction with food has been described for captopril, cilazapril and perindopril. These drugs score 80%. All other drugs score 90% for this criterion.

Trough/peak ratio

In the studies included in this section, the trough/peak ratio (TPR) was calculated by subtracting the blood pressure following drug treatment from that following placebo. The peak is defined as the time point of the lowest blood pressure and the trough as the time point of the highest blood pressure [32].

	No. of patients	Dose range	Trough/peak (%)	Score (%)
Benazepril	13	10–20 qd	40	40
Captopril	17	25–100 bid	25	20
Cilazapril	85	2,5–5 qd	59–62	60
Enalapril	95	5–20 qd	40–79	60
Fosinopril	64	10–40 qd	32–44	40
Lisinopril	144	10–80 qd	30–70	40
Perindopril	21	4–8 qd	35	20
Quinapril	49	10–40 qd	30–40	20
Ramipril	84	5–10 qd	50–63	60
Trandolapril	84	1–2 qd	50–100	100
Losartan	79	50 qd	60	60

From references 33–37.

Table 4: Trough/peak ratios for diastolic blood pressure calculated from 24 hour blood pressure monitoring

The most relevant data concerning the TPR of ACE inhibitors are summarized in Table 4. The data in this table are extracted from a review by Zannad [33], who collected data using the same methodology (patients with mild to moderate hypertension untreated for at least 2 weeks prior to the study, ACE inhibitor monotherapy for at least 2 weeks, 24-hour ambulatory blood pressure monitoring with hourly mean values of systolic and diastolic blood pressure). For three drugs (cilazapril, fosinopril and losartan) data were collected from other studies. For several drugs (captopril, perindopril and ramipril) higher TPRs were found in studies using different methodologies from those of Zannad [33, 34, 38]. As there are many differences in study methodology and the clinical relevance of this criterion is still unclear [39, 40], we have given a low relative weight of 20 points to this criterion.

Relatively high doses were used for several drugs, such as benazepril, captopril, lisinopril and ramipril. This makes it difficult to draw any definite conclusions from these data. The results for TPRs are not always consistent for all studies. Trandolapril shows the highest TPR and scores 100%. Cilazepril, enalapril, ramipril and losartan score 60%, benazepril, lisinopril and fosinopril score 40%, captopril, perindopril and quinapril score 20%.

Efficacy

A large number of comparative clinical studies has been performed between ACE inhibitors. The results of these studies are summarized in Table 5. Not all drugs have been directly compared with each other. The number of comparative studies of fosinopril with other ACE inhibitors is quite low. Most ACE inhibitors have been compared with captopril and enalapril and, to a lesser extent, also with lisinopril. The size of most studies was insufficient to exclude type II errors, but in general most drugs appear to have quite similar antihypertensive efficacy. All drugs score 70% for this criterion.

Side effects

ACE inhibitors are usually well tolerated. Their most important side effects include: cough, headache, dizziness, weakness, nausea and skin reactions [1–4, 86–95]. Almost all studies have failed to show any relevant differences in the incidence and severity of adverse reactions between ACE inhibitors. Cough is their most common and "most irritating" side-effect: the incidence of cough is highly variable and ranges from 3% to more than 50% [30]. The incidence of cough is often underestimated [96]. There seem to be few, if any, differences between ACE inhibitors in the incidence of cough.

There are some indications that the incidence of cough with fosinopril may be lower than that of other ACE inhibitors [97, 98]. The number of comparative studies with fosinopril is, however, too small to allow definite conclusions.

In contrast with ACE inhibitors, losartan does not induce cough to any relevant extent. The incidence of cough in most studies is comparable with that of placebo. The

	Dose (mg)	Type	No. of patients	Effect on DBP	% responders	Ref
Ben	10 qd	MM	90	-10	49	31
Cap	50 bid		84	-7	36	
Ben	10 mg qd	MM	75	-12	58	31
Cap	50 mg qd		73	-10	51	
Ben	10 qd	MM	59	-15	83	31
Ena	20 qd		58	-16	89	
Cap	25–50 bid	MM	62	-7	26	42
Cil	2.5–5 qd		132	-8	37	
Cap	25–50 bid	MM	15	-13	63	43
Cil	2.5–5 qd		15	-17	83	
Cap	50–100 qd	MM	66	-16	78	44
Ena	10–20 qd		69	-14	79	
Cap	25–100 bid	MM	75	-8		45
Ena	5–20 bid		74	-11		
Cap	25–50 tid	MS	82	-16	60	46
Ena	5–20 bid		79	-16	66	
Cap	25–100 tid	MS	16	-16	75	47
Ena	5–20 bid		16	-18	75	
Cap	25–50 bid	MS	34	-21	97	48
Ena	20–40 qd		35	-26	100	
Cap	25–100 bid	MM	46	-15		49
Lis	10–40 qd		45	-17		
Cap	25–100 bid	MM	35	-6		50
Lis	10–40 qd		35	-10		
Cap	50–100 bid	MM	63	-10	81	51
Lis	20–40 qd		54	-12	76	
Cap	12.5–50 bid	MM	46	-12	72	52
Lis	10–40 qd		45	-16	80	
Cap	50 mg qd	MM	154	-12	67	53
Lis	20 mg qd		150	-14	80	
Cap	25–50 bid	MM	79	-12	49	54
Per	4–8 qd			80	-17	49
Cap	25–50 bid	MM	54	-14	47	55
Per	4–8 qd			54	-14	67
Cap	12.5–50 bid	MM	19	-14	53	56
Qui	10–40 qd		21	-18	62	
Cap	25–100 bid	MS	84	-15	75	57
Qui	10–40 bid		88	-19	78	
Cap	25–75 bid	MM	102	-9	55	58
Qui	10–40 qd		98	-8	52	
Qui	10–20 bid		102	-9	62	
Cap	25–100 bid	S	48	-10	44	59
Qui	5–20 bid		40	-12	58	
Cap	50 bid	MM	111	–14	65	60
Ram	10 qd		121	-15	65	
Cap	50 bid	MM	30	-12	84	61
Ram	5 qd		30	-8	71	
Cap	50 bid	MM	83	-10	44	62
Tra	4 qd		86	-14	61	
Cap	50–100 qd	MM	34	-6	29	63
Los	50–100 qd		109	-9	50	
Cil	0.5–4 qd	MM	157		70	64
Ena	2.5–20 qd		153		68	
Ena	5–10 qd	MM	116	-10	52	65
Fos	10–20 qd		115	-9	50	
Ena	10–20 qd	MM	97	-11		66
Fos	20–40 qd		98	-11		
Ena	5–40 qd	MM	48	-16	98	67
Lis	10–40 qd		49	-17	96	
Ena	10 qd	MM	14	-6		68
Lis	10 qd		14	-7		
Ena	10 qd	MM	36	-7	42	69
Lis	10 qd		37	-11	70	
Ena	20 qd	MM	29	-9	70	
Lis	20 qd		29	-7		
Ena	5–20 qd	MM	125		56	71
Per	2–8 qd		125		69	
Ena	10–40 qd	MM	130	-16	80	72
Qui	10–40 qd		128	-14	90	
Ena	10–40 qd	MM	27	-17	67	73
Qui	10–40 qd		27	-19	78	
Ena	10–20 qd	MM	26	-17	74	
Qui	10–20 qd		23	-17		
Ena	10–20 qd	MM	86	-11	59	75
Ram	5–10 qd		88	-11	55	

Table 5: Double-blind comparative studies between ACE inhibitors in hypertension

	Dose (mg)	Type	No. of patients	Effect on DBP	% responders	Ref
Ena	10 qd	MM	48	-16	58	76
Ena	10 qd		49	-17	63	
Ram	5 qd		51	-16	71	
Ram	10 qd		45	-17	71	
Ena	5 qd	MM	26	-5		77
Ena	10 qd		26	-7		
Ena	20 qd		27	-7		
Ram	2,5 qd		28	-5		
Ram	5 qd		26	-6		
Ran	10 qd		25	-8		
Ena	16 qd	MM	20	-15	60	78
Lis	13 qd		20	-13	65	
Qui	15 qd		20	-14	75	
Ram	3 qd		20	-12	75	
Ena	2.5–10 qd	MM	155		45	79
Tra	0.5–2 qd		131		41	
Ena	20 qd	MM	78	76		80
Tra	4 qd		81	57		
Ena	10 qd	MM	18	-10		81
Los	50 qd		20	-10		
Ena	20 qd	MM	79	-11		82
Los	25 qd		75	-7		
50 qd			76	-10		
100 qd			80	-10		
Ena	20 qd	MM	199	-11	59	83
Los	50 qd		200	-8	51	
Lis	10 qd	MM	21	-10		84
Qui	10 qd		21	-20		
Lis	5 qd	MM	55	-2	0	85
Lis	10 qd		34	-11	49	
Ram	2.5		58	-15	67	

MM mild to moderate hypertension
MS moderate to severe hypertension
S severe hypertension

\# Various definitions were used for the percentage responders, such as reaching a diastolic blood of lower dan 90 mm Hg or a lowering of the diastolic blood pressure by at least 10 mm Hg

Table 5: Continued

overall incidence of adverse reactions with losartan in comparison with that of ACE inhibitors such as captopril and enalapril is usually slightly lower, although the number of comparative studies is still limited. The tolerability of losartan ranged from identical to captopril [63] to better than that of enalapril [83]. The incidence of cough in a group of patients with previous ACE inhibitor-associated cough [29] was similar to that of hydrochlorothiazide (34%) and lower than that of lisinopril (72%) [99].

Another well known side effect of ACE inhibitors is first-dose hypotension, which occurs especially in patients with congestive heart failure. Although some (small scale) studies suggest that there may be differences in the incidence of this reaction between ACE inhibitors, this needs to be studied in more detail [30]. All ACE inhibitors score 80%. Losartan, which does not induce cough (total incidence of side effects is approximately 3% lower than that of ACE inhibitors) scores 89%.

Dosage frequency

Most drugs can be given once daily: fosinopril, lisinopril, losartan, perindopril, quinapril, ramipril and trandolapril. These drugs score 100%. All other agents are given once or twice daily, and these drugs are awarded 90%.

	Daily dose	Daily cost	Score (%)	Daily cost of double dose
Benazepril (Cibacen®)	7.5 mg*	0.94	99	1.42
Captopril (Capoten®)	50 mg	1.09	83	1.77
Cilazapril (Vascase®)	2.5 mg	0.95	98	1.89
Enalapril (Renitec®)	10 mg	1.04	88	1.46
Fosinopril (Newace®)	15 mg❖	1.35	55	2.43
Lisinopril (Zestril®)	10 mg	0.95	98	1.42
Perindopril (Coversyl®)	4 mg	1.40	50	2.80
Quinapril (Acupril®)	15 mg❖	1.24	48	2.41
Ramipril (Tritace®)	2.5 mg	0.93	100	1.32
Trandolapril (Gopten®)	2 mg	1.14	78	2.28
Losartan (Cozaar®)	50 mg	1.63	25	3.26

* The price of the 10 mg tablet was taken for cost comparison as the price of 1.5 tablet of 5 mg is higher than that of a 10 mg tablet

❖ The price of the 20 mg tablet was taken for cost comparison as the price of 1.5 tablet of 10 mg is higher than that of a 20 mg tablet

Table 6: Acquisition cost (official Dutch prices, "KNMP Taxe" December 1996)

Acquisition cost

The acquisition cost of ACE inhibitors and losartan in the Netherlands is depicted in Table 6. There are no major differences in cost between the drugs. Ramipril is the cheapest drug, closely followed by benazepril, cilazapril and lisinopril. The most expensive drugs are fosinopril, perindopril and losartan.

Documentation

The clinical documentation of the drugs is summarized in Table 7. For calculation of the number of studies and the number of patients involved in these studies, the studies included in Table 5 were taken into account as well as published double-blind comparative studies with other antihypertensive agents, such as diuretics, beta-blockers or calcium antagonists. These data were collected from reviews on each individual drug, plus recently published studies.

Captopril, enalapril, lisinopril, cilazapril and quinapril are the best documented agents concerning these four subcriteria.

Survival studies

So far, no effects of ACE inhibitors on survival, when used for the treatment of hypertension, have been published. On the other hand, a variety of studies has been published showing beneficial effects of ACE inhibitors on mortality and morbidity when they are used for the treatment of congestive heart failure or after myocardial infarction. The results from these studies are summarized in Tables 8 and 9.

	Studies	Patients	Years	Patientdays million
Benazepril	14	844	5	> 100
Captopril	> 20	> 1000	>10	> 100
Cilazapril	> 20	> 1000	6	> 100
Enalapril	> 20	> 1000	>10	> 100
Fosinopril	5	242	5	> 100
Lisinopril	> 20	> 1000	8	> 100
Perindopril	14	805	7	> 100
Quinapril	> 20	> 1000	7	> 100
Ramipril	15	> 1000	7	> 100
Trandolapril	7	686	3	> 100
Losartan	7	990	2	50–100

Table 7: Documentation

LARGE TRIALS IN HEART FAILURE		
Trial	Consensus	SOLVD
Reference	100	101
N patients	253	2569
NYHA class	IV	II–III (90%)
Drug	Ena	Ena
2.5 qd–20 bid	2.5–10 bid	
Control	Placebo	Placebo
Duration	20 months	4.8 y
Follow-up	188 d	41 m
Mortality		
Overall	27%	16%
Cardiovasc	31%	18%
No. of patients treated to save one life	7	22
Morbidity		
Infarct		23%
Serious heart failure	–	43%
Hospitalization or death due to heart failure	50%	26%

Table 8: Survival studies with ACE inhibitors

The Consensus study showed a clear reduction of overall and cardiovascular mortality of enalapril on a high risk group of patients with heart failure when compared with placebo [100].

The SOLVD study involved patients with a left ventricular ejection fraction of <25%. The study included in the table was the group of patients in the treatment group with complaints of heart failure. This study also showed a significant reduction in cardiovascular and overall mortality, infarction and the development of serious heart failure [101].

Several trials have studied the use of ACE inhibitors after myocardial infarction. The Consensus II trial started within 24 hours after myocardial infarction. The lack of a beneficial effect on mortality in Consensus II may have been caused by a variety of reasons, such as increased myocardial ischaemia due to blood pressure lowering effect and a potential role of angiotensin II in the healing process immediately after myocardial infarction [108]. Trandolapril reduced overall mortality in post myocardial infarction patients with left ventricular dysfunction [107]. The number of patients that has to be treated to save one life varies widely between the studies, also because of the different patient populations [109].

Both captopril and ramipril significantly reduced mortality and morbidity after myocardial infarction [103, 104] in patients with symptomatic heart failure.

Enalapril scores 50% for the reduction in mortality in heart failure, but it does not score for its application after myocardial infarction as the Consensus 2 study did not result in a positive treatment outcome. Captopril, ramipril, lisinopril and trandolapril score 50% for their ability to reduce post-myocardial mortality.

The SOJA score

The SOJA score is shown in Table 10. The selection criteria for ACE inhibitors may be divided into "intrinsic" criteria (bioavailability, drug interactions, TPR, efficacy and side effects) which do not change with time and are valid for all countries; and "extrinsic" criteria (number of formulations, number of indications, dosage frequency, acquisition cost and documentation) which may vary from country to country and are also time-dependent (especially documentation and acquisition cost).

This score is specific for the Dutch situation as the extrinsic criteria may be different in other countries. The SOJA score is also time-dependent as acquisition cost, documentation and survival studies may change when the results of new studies become available. New ACE inhibitors or angiotensin II antagonists should be included in the score after their introduction on the market.

Trial	Consensus II	SAVE	AIRE	GiSSI 3	ISIS 4	TRACE
Reference	102	103	104	105	106	107
No. patients	6090	2231	2005	19394	58058	1749
Inclusion	BP>100/60	LVEF < 0.4	Mild to moderate HF	MI	MI	Ventricular dysfunction
Drug	Ena 1 mg i.v. then 5–40 mg qd for 180 d	Cap 6.25–50 tid	Ram 2.5–5 bid	Lis 10 mg qd	Cap 50 mg bid	Tra 4 mg qd
Timing	< 24 h	3–16 d	3–10 d	< 24 h	< 24 h	3–7 d
Control	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Duration	1.5 y	5 y	2.5 y	6 weeks	4 weeks	2–4 y
Follow-up	41–180 d	42 m	15 m			
Reduction in mortality						
Overall	–	19%	27%	11%	7%	22%
Cardiovasc	–	21%	–			
No. of patients treated to save one life	–	24	17	125	200	13
Reduction in morbidity						
Reinfarct		25%	7%			
Serious heart failure	–	36%	–			

Table 9: Large trials after myocardial infarction

DISCUSSION

The relative weight that is given to each selection criterion is the result of consultation of a panel of experts on ACE inhibitors, but will always be a matter of discussion. An interactive program for a personal computer will be available shortly in which the user of the program is allowed to determine his own relative weight to each selection criterion.

The criteria clinical efficacy and side effects, although being the most important selection criteria, are not discriminating for this group of drugs as all ACE inhibitors and losartan show very similar clinical efficacy and tolerance (except the absence of cough for losartan).

Besides the criteria mentioned in Table 1, a variety of other criteria could be applied to ACE inhibitors, but their relevance was questioned by the panel of experts. This was the case for criteria such as whether the ACE inhibitor is a prodrug or not (included in variability of the serum level of the active compound), elimination half-life (included in peak/trough ratio) and potency (no relationship to clinical efficacy or tolerance).

Lipophilicity may affect the rate of intracellular penetration and differences in lipophilicity may cause differences in tissue ACE inhibition. This may be an important selection criterion, but human data are lacking and animal data are limited [101–112] and even absent for most drugs [1]. ACE inhibitors are able to significantly reduce left ventricular hypertrophy (LVH) in hypertensive patients. The LVH reduction appears to be greater than that of other classes of antihypertensive agents. It is, however, unclear whether there are any relevant differences in the LVH reduction by each individual drug. As far as it is known, this appears to be a class-related effect, with little or no relevant differences between the ACE inhibitors [1].

Another criterion discussed was the effect of ACE inhibitors on the vascular endothelium. Although this might be of importance, there are insufficient comparative data between the various ACE inhibitors to include this as a criterion. The best studied ACE inhibitors in this respect are perindopril and quinapril [113, 114].

Ramipril shows the highest overall score, followed by lisinopril, enalapril and captopril. These are the most attractive ACE inhibitors for formulary inclusion on the basis of this score. The other drugs show lower scores. Losartan does not score well at all in comparison with ACE inhibitors, due to the limited documentation and

	Benaz	Capto	Cilaz	Enala	Fosin	Lisin	Perin	Quina	Rami	Trando	Losart
Formul	15	15	15	15	15	15	15	15	20	15	10
Indic	16	20	12	16	12	16	16	16	16	16	12
Bioav	24	32	16	24	24	16	32	16	32	40	24
Interact	36	32	32	36	36	36	32	36	36	36	36
Trough/peak	8	4	12	12	8	8	4	4	12	20	12
Efficacy	252	252	252	252	252	252	252	252	252	252	252
Side-eff	120	120	120	120	120	120	120	120	120	120	134
Dosage freq	90	90	100	90	100	100	100	100	100	100	100
Acq cost	99	83	98	88	55	98	50	48	100	78	25
Patients	20	25	25	25	5	25	20	25	25	15	20
Studies	15	25	25	25	5	25	15	25	20	10	10
Pat days	25	25	25	25	25	25	25	25	25	25	20
Years	13	25	19	25	13	19	19	19	19	13	6
Survive	0	25	0	25	0	25	0	0	25	25	0
Total	733	773	751	778	670	780	701	701	802	765	661

Table 10: SOJA score for ACE inhibitors

	Aus	Bel	Fin	Fra	Ger	Ire	Spa	Swi	UK
Benazepril	–	670	–	679	689	643	629	660	–
Captopril	764	742	764	774	713	757	740	757	731
Cilazapril	654	754	741	731	748	701	737	723	717
Enalapril	785	789	771	751	784	750	784	771	746
Fosinopril	664	652	–	718	704	–	617	667	–
Lisinopril	777	771	764	752	776	711	782	777	764
Perindopril	707	684	699	701	745	671	652	707	699
Quinapril	704	683	671	739	721	654	662	687	671
Ramipril	797	798	802	798	796	802	773	750	802
Trandolapril	–	–	–	774	784	724	714	779	–
Losartan	680	–	646	677	684	644	630	680	646

Aus	Austria	Ire	Ireland
Bel	Belgium	Spa	Spain
Fin	Finland	Swi	Switzerland
Fra	France	UK	United Kingdom
Ger	Germany		
–	not available in this country		

Table 11: SOJA scores for other countries

the relatively high acquisition cost, whereas its only objective advantage is the lower incidence of cough, which is a clinical problem in only a small minority of patients treated with ACE inhibitors. Losartan is, therefore, not the drug of first choice, but may be an attractive alternative to ACE inhibitors in patients who are intolerant of these drugs.

The criteria clinical efficacy and side effects, although being the most relevant selection criteria, are not discriminating for this group of drugs as all ACE inhibitors and losartan show very similar clinical efficacy and tolerance. The criterion acquisition cost then becomes the most important discriminating factor for drug selection of ACE inhibitors and losartan. Losartan is the most expensive drug. The relative scores of the other drugs are less dependent on this criterion. The dosages included in the score were derived from the internationally valid defined daily doses (DDD). Although these dosages reflect the most usual dosages for these drugs, considerable variation exists in the dosages applied in clinical practice. If a double dose was given for all drugs, the relative differences become even more pronounced. The double-strength formulations are relatively inexpensive in the case of ramipril, benazepril, enalapril and lisinopril, whereas this results in doubling the cost for the expensive drugs such as perindopril, trandolapril and losartan. If the criterion acquisition cost was excluded from the analysis, very small changes were observed for the "top four" (ramipril, lisinopril, enalapril and captopril).

In conclusion, ACE inhibitors and losartan were compared on the basis of a large number of criteria, which may be divided into "intrinsic" (substance-related, such as bioavailability, interactions, efficacy, etc.) and "extrinsic" (acquisition cost and documentation). Drugs in this group can hardly be distinguished on the basis of intrinsic criteria. However, inclusion of extrinsic criteria, which are obviously time-dependent, does result in a distinction of the drugs.

A summary of total SOJA scores of ACE inhibitors and losartan in other countries is presented in Table 11. Relatively few differences are observed between the results from the Netherlands and other European countries. The criterion acquisition cost is the most important discriminating factor. In most countries, ramipril shows the highest score, again followed by lisinopril, enalapril and captopril. Trandolapril performs relatively well in Switzerland and Germany, mostly because of the relatively low price in these countries.

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