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Risk-Benefit Ratio of Angiotensin Antagonists versus ACE Inhibitors in End-Stage Renal Disease

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Abstract

The effective treatment of hypertension is an extremely important consideration in patients with end-stage renal disease (ESRD). Virtually any drug class – with the possible exception of diuretics – can be used to treat hypertension in the patient with ESRD. Despite there being such a wide range of treatment options, drugs which interrupt the renin-angiotensin axis are generally suggested as agents of choice in this population, even though the evidence in support of their preferential use is quite scanty.

ACE inhibitors, and more recently angiotensin antagonists, are the 2 drug classes most commonly employed to alter renin-angiotensin axis activity and therefore produce blood pressure control. ACE inhibitor use in patients with ESRD can sometimes prove an exacting proposition. ACE inhibitors are variably dialysed, with compounds such as catopril, enalapril, lisinopril and perindopril undergoing substantial cross-dialyser clearance during a standard dialysis session. This phenomenon makes the selection of a dose and the timing of administration for an ACE inhibitor a complex issue in patients with ESRD.

Furthermore, ACE inhibitors are recognised as having a range of nonpressor

effects that are pertinent to patients with ESRD. Such effects include their ability to decrease thirst drive and to decrease erythropoiesis. In addition, ACE inhibitors have a unique adverse effect profile. As is the case with their use in patients without renal failure, use of ACE inhibitors in patients with ESRD can be accompanied by cough and less frequently by angioneurotic oedema. In the ESRD population, ACE inhibitor use is also accompanied by so-called anaphylactoid dialyser reactions.

Angiotensin antagonists are similar to ACE inhibitors in their mechanism of blood pressure lowering. Angiotensin antagonists are not dialysable and therefore can be distinguished from a number of the ACE inhibitors. In addition, the adverse effect profile for angiotensin antagonists is remarkably bland, with cough and angioneurotic oedema rarely, if ever, occurring. In patients with ESRD, angiotensin antagonists are also not associated with the anaphylactoid dialyser reactions which occur with ACE inhibitors. The nonpressor effects of angiotensin antagonists – such as an influence on thirst drive and erythropoiesis – have not been explored in nearly the depth, as they have been with ACE inhibitors. Although ACE inhibitors have not been compared directly to angiotensin antagonists in patients with ESRD, angiotensin antagonists possess a number of pharmacokinetic and adverse effect characteristics, which would favour their use in this population.

Patients receiving long term maintenance haemodialysis have an age-adjusted death rate several times higher than that of the general population.[1] The large majority of patients with end-stage renal disease (ESRD) begin renal replacement therapy with a disproportionate burden of cardiovascular disease risk factors.[2] Thus, it is not at all surprising that cardiovascular disease is a leading cause of death in ESRD, accounting for 30 to 50% of all deaths.[1-4] Hypertension, an important contributing factor to the progression of renal failure, also features significantly in the cardiovascular event rate in the patient with ESRD.[2,5]

Hypertension is a complex multifactorial process in ESRD.[2] Volume expansion has long been held as perhaps the single most important factor in the development and maintenance of hypertension in patients receiving dialysis.[6-7] Recently, the critical role of volume in ESRD-related hypertension has been re-examined.[8-9] Although control of volume expansion remains an important element in the effective treatment of ESRD-related hypertension, a number of other factors are now recognised as important contributors to this condition. Such factors include a relative to absolute increase in renin-angiotensin-aldosterone axis activity,[10,11] increased sympathetic activity,[12,13] endothelial abnormalities[14-16] and/or hyperparathyroidism.[17]

1. Treatment of Hypertension in End-Stage Renal Disease

The treatment of hypertension in the patient with ESRD is complicated. A cornerstone of therapy remains the efficient management of salt and water balance. Obstacles to this approach include:[5]

- the absence of an accepted operational definition of dry weight and methods to assess it
- patient noncompliance with dietary salt and fluid restriction
- intradialytic hypotension secondary to overly aggressive ultrafiltration during the relatively short duration of haemodialysis treatments.

An additional concern in the treatment of ESRD-related hypertension is that casual blood pressure readings obtained in the immediate predialysis period poorly reflect the true blood pressure load experienced during an interdialytic period.[7,8] Although ambulatory blood pressure monitoring may better define blood pressure load in the patient with ESRD, this procedure is not routinely available,

forcing the clinician to rely instead on casual blood pressure readings.[9,18]

ESRD-related hypertension has been effectively treated with any of a number of antihypertensive drug classes. In particular, drugs that interrupt the renin-angiotensin-aldosterone axis have been proposed as being well tolerated and effective agents in the treatment of hypertension in ESRD. A number of drug classes can interfere with renin-angiotensin-aldosterone axis activity, including β-blockers, ACE inhibitors and angiotensin antagonists (AT_1 receptor antagonists), with ACE inhibitors being most frequently used to achieve this goal in the ESRD population.[19,20]

Unfortunately, despite a lengthy legacy of use of ACE inhibitors in the treatment of ESRD-related hypertension, a number of problems exist with ACE inhibitors, fueling the search for alternative therapies. One such alternative therapy involves the use of angiotensin antagonists, compounds that specifically block the effect of angiotensin II at the AT_1 receptor. Several angiotensin antagonists are either currently marketed or are in various stages of development. These compounds are mechanistically distinct in their action, being devoid of any effect on bradykinin metabolism, which distinguishes them from ACE inhibitors. They also differ pharmacokinetically from many of the ACE inhibitors in that they have a predominantly nonrenal mode of elimination. Use of angiotensin antagonists has been limited; thus, comments concerning this class of drugs must be viewed cautiously. This review will specifically address treatment considerations in ESRD-related hypertension and, by inference, congestive heart failure, as well as the risk-benefit ratio that attends the use of each of these drug classes.

2. Pharmacokinetics

2.1 ACE Inhibitors

In the treatment of essential hypertension, the pharmacokinetics of the ACE inhibitors are rarely a consideration unless they are being given to patients with renal insufficiency.[21] In that condition, since the mode of elimination of these compounds is primarily renal, systemic accumulation will ensue unless dosage adjustment has occurred.[22] The exceptions to this are fosinopril and trandolapril. Each of these compounds undergoes a combination of both renal and hepatic clearance and thereby accumulate to a lesser degree in renal failure.[23]

Table I. ACE inhibitor properties and dialysability in patients with end-stage renal disease

Drug	Protein binding (%)	Molecular weight (parent/diacid)	CL_{HD} (ml/min) [% removed]
Benazeprilat[25]	>95	461/396	NA
Captopril[26-29]	30	217	80-120 [35]
Enalaprilat[30-32]	60	493/384	40-70 [60]
Fosinoprilat[33,34]	>95	585/436	<10
Lisinopril[35]	10	442	60 [50]
Moexipril[36]	50	499/471	NA
Perindopril[37,38]	20	368/340	50-70 [50]
Quinaprilat[39,40]	>95	475/410	<10
Ramiprilat[41]	>60	417/388	20-30
Trandolapril[42]	80	431/402	NA

CL_{HD} = haemodialysis clearance; **NA** = data not available.

In ESRD, the otherwise mundane pharmacokinetics of ACE inhibitors become more confusing. Repetitive administration of a renally cleared ACE inhibitor, in the undialysed state, will inevitably result in significant drug accumulation and thereby prolonged pharmacological effect. Once dialysis is superimposed on a particular administration schedule, variable dialytic clearance of a compound will occur in relationship to compound-specific features such as molecular weight, protein binding and volume of distribution, as well as compound-independent features such as membrane surface area, dialyser blood flow and duration of dialysis. The most important of these features is protein binding, since in the presence of extensive protein binding (>90%) all other considerations for dialytic clearance of a compound are superfluous. The fact that several ACE inhibitors are not heavily protein-bound means that a substantial mass of drug can be removed during a haemodialysis session (table I).[24]

If ESRD-related blood pressure values are particularly renin-dependent, they can rise during a

Table II. Elimination characteristics of ACE inhibitors in haemodialysis

Drug	Dialysable[a]	Accumulation	Post-dialysis supplementation[b]
Captopril	Yes	Yes	Yes
Enalaprilat	Yes	Yes	Yes
Lisinopril	Yes	Yes	Yes
Perindopril	Yes	Yes	Yes
Ramiprilat	Yes	Yes	Yes
Fosinopril	No	No	No
Quinapril	No	Yes	Yes
Benazepril	NA	Yes	Yes
Moexipril	NA	Yes	Yes
Trandolapril	NA	No	No

a 'Yes' indicates drug removed during dialysis.

b Postdialysis dosage supplementation or routine administration within 4h postdialysis is considered when >30% drug removal has occurred and blood pressure levels warrant treatment.

NA = data not available.

haemodialysis session in the absence of the dampening influence of an ACE inhibitor. Administration of antihypertensives in ESRD is most commonly dictated not by interdialytic readings, but rather by readings obtained in the peridialytic period. A common approach to the treatment of ESRD-associated hypertension is to withhold drug treatment for the several hours immediately before a dialysis session in the hope that peak drug effect will not coincide with the vasodepressor effect of haemodialysis and lead to intradialytic hypotension. Whether intradialytic hypotension can be effectively minimised by this approach remains to be determined.

The dialysis clearance values for ACE inhibitors in table I should be viewed cautiously. These clearance values were typically determined under what might be currently viewed as contrived study conditions; that is, dialyser blood flow rate was typically 150 to 200 ml/min and dialyser size $\leq 1.2 m^2$. It is highly likely that dialyser clearances for those ACE inhibitors that are dialysable will be considerably higher than the values reported in table I, since blood flow rates and dialyser size are now more typically 400 ml/min and $\geq 2.0 m^2$, respectively. Accordingly, assessments of ACE inhibitor effect on any of the pharmacodynamic parameters cited in this review should take into account the year(s) in which the study was conducted and the prevailing dialysis practice at that time. Current dialysis conditions should result in considerably lower postdialysis blood concentrations for dialysable ACE inhibitors than values observed in the 1980s. Thus, much of the early literature from the 1980s concerning ACE inhibitor dialysability is no longer directly applicable.

A final consideration in assessing the differential pharmacokinetics of ACE inhibitors in ESRD relates to their mode of systemic elimination. As previously mentioned, the ACE inhibitors fosinopril and trandolapril are systemically eliminated by both renal and hepatic mechanisms.[22,23] This aspect of the elimination profile of an ACE inhibitor must be factored into their intradialytic elimination behaviour. Thus, ACE inhibitors are dialysable or nondialysable and accumulating or nonaccumulating. To start a patient with ESRD on an ACE inhibitor is not as simple as 'randomly' selecting one of the several drugs in this class. The selection process requires a thorough understanding of drug kinetics and dialysability (table II), and if correctly performed can influence outcome.

2.2 Angiotensin Antagonists

Angiotensin antagonists have only been available for the treatment of hypertension since 1995, at which time the first such compound, losartan potassium, was released. Since then several additional compounds have either been released for general use or will soon be available (table III). Angiotensin antagonists are distinguishable in that these

Table III. Angiotensin antagonist properties and dialysability in patients with end-stage renal disease

Drug	Protein binding (%)	Molecular weight	CL_{HD} (ml/min)
Losartan potassium [43]	98.7	461	0
E-3174[43]	99.8	437	0
Irbesartan[44]	90.0	429	0
Valsartan[45]	95.0	436	NA
Eprosartan[46]	98.0	521	11
Candesartan cilexetil [47]	99.0	611	0
Telmisartan[48]	99.5	515	0

CL_{HD} = haemodialysis clearance; **NA** = not applicable.

drugs are all heavily protein-bound (>90%), which precludes significant dialysability. Thus, the process of treating renin-dependent forms of hypertension in ESRD is likely to be simplified. Table III provides information useful for estimating the potential for an angiotensin antagonist to be dialysed. Where data are available, actual clearance values are reported; otherwise the potential for dialytic clearance of an angiotensin antagonist can be inferred from the pharmacological features of the compound.

The likelihood of an angiotensin antagonist accumulating with repetitive administration has been examined only for losartan potassium and irbesartan. However, marked accumulation is unlikely with these drugs, since they all undergo a significant degree of nonrenal clearance (table IV).

Table IV. Mode of elimination of angiotensin antagonists

Drug	Relative clearance (%)	
	renal	hepatic
Candesartan cilexetil[47]	60	40
Eprosartan[49]	30	70
Irbesartan[44]	1	99
Losartan potassium[50]	10	90
E-3174[50]	50	50
Telmisartan[48]	1	99
Valsartan[45]	30	70

3. Pharmacodynamics

3.1 Hypertension

A number of studies have established both ACE inhibitors[20,30,31,35,38,40,41] and angiotensin antagonist[51-54] as effective therapies in the treatment of ESRD-related hypertension. Unfortunately, there have been few pharmacological studies that have determined the concentration-effect relationship for blood pressure reduction with either ACE inhibitors or angiotensin antagonists. It can be presumed that if the form of hypertension expressed by a patient with ESRD is renin-dependent there will be a steep concentration-effect relationship at low doses of an ACE inhibitor and/or an angiotensin antagonist.[20,29-41] Thus, the pharmacological features of an ACE inhibitor or an angiotensin antagonist, such as dialysability and/or mode of systemic elimination, will be of lesser concern.

Alternatively, if the form of hypertension expressed by a patient with ESRD is more volume-sensitive, albeit with less renin-dependency, higher concentrations of an ACE inhibitor or an angiotensin antagonist may well become an important determinant of response. In this regard, a compound that is not dialysable but undergoes some degree of nonrenal clearance (to limit excessive systemic accumulation) may be favoured. The ACE inhibitors fosinopril and trandolapril are compounds with such characteristics and may well be the most suitable compounds for use in patients with ESRD.[23,33] The angiotensin antagonists also possess the pharmacological characteristics of nondialysability and an absence of systemic accumulation – similar to fosinopril and trandolapril – which facilitates their use in the treatment of hypertension in ESRD.[55] Nonetheless, until specific studies are performed in the ESRD population to determine the concentration-effect relationship of specific ACE inhibitors or angiotensin antagonists, the impact of drug dialysability and/or systemic accumulation on blood pressure control will remain conjectural.

3.2 Congestive Heart Failure

ACE inhibitors and angiotensin antagonists as therapy for congestive heart failure have been studied in a rather cursory fashion in the ESRD population. To date, in this population no long term outcome studies have been conducted with either of these drug classes. In addition, no studies have been conducted that compare individual ACE inhibitors and/or angiotensin antagonists in a head-to-head fashion. Heart failure management in ESRD is a complicated issue with multiple aetiological factors being present. Although ACE inhibitors can be presumed to be 'effective' in the management of congestive heart failure found in the setting of ESRD, this is by inference alone from congestive heart failure studies completed in non-ESRD populations; for angiotensin antagonists, even fewer such studies exist in the non-ESRD population.

There is no doubt that the alteration in angiotensin II effect from either ACE inhibitor or angiotensin antagonist therapy should offer some therapeutic benefit to the patient with ESRD and congestive heart failure, although the exact nature of such benefit remains to be determined, particularly for the angiotensin antagonists.

A series of recent studies have suggested a greater benefit in heart failure management from high rather than low dosages of ACE inhibitors,[56,57] and current practice guidelines for the management of congestive heart failure recommend therapy with high dosages of ACE inhibitors for optimal symptomatic and survival benefits. A question yet to be resolved is whether the benefits of ACE inhibitor therapy in congestive heart failure management are also drug concentration–dependent for the ESRD population. If a parallel exists for congestive heart failure treatment in the ESRD population, then the pharmacological features of either an ACE inhibitor or an angiotensin antagonist may dictate therapeutic success. For example, dialysable compounds would provide a less sustained exposure to the presumed positive effects of an agent that interrupts the renin-angiotensin-aldosterone axis. The opposite would logically apply to a nondialysable compound. Furthermore, the tentative nature of postdialysis administration of antihypertensive medication would also lessen exposure to a dialysable ACE inhibitor. A further and final confounding variable in the ESRD population is that of the inter-relationship between blood pressure and dose titration of an ACE inhibitor. Because of intradialytic blood pressure changes, it is rare that the dosage of ACE inhibitors is titrated to maximal effect in the ESRD population.

4. Adverse Effects

4.1 Thirst

In polydipsic haemodialysis patients, angiotensin II levels rise after a dialysis session, in part in relationship to the degree of volume removal.[58] Angiotensin II levels can remain elevated in the interdialytic period, despite the progressive volume expansion that characterises this period. High plasma levels of angiotensin II have been associated with excessive thirst, mediated by either central or peripheral thirst promoting mechanisms.[58-60]

An important practical implication of these observations is that drugs that decrease activity in the renin-angiotensin-aldosterone axis may alleviate the polydipsia observed in these patients.[61-63] In an early nonblind trial using captopril, interdialytic bodyweight gain and thirst were diminished in 4 patients.[61] In a more extensive set of studies employing a double-blind, placebo-controlled, crossover design, enalapril therapy was accompanied by significant reduction in interdialytic bodyweight gain, thirst and oral intake of fluid.[62] These changes directly paralleled decreased levels of angiotensin II. Unfortunately, the effect of ACE inhibitors on thirst drive in patients with ESRD has not been uniformly observed.[62]

This suggests that this phenomenon may be more heterogeneous than first thought. Multiple factors exist as determinants of a slackening of thirst drive with ACE inhibitors, and, no doubt, additional clarifying studies will be required. To date, angiotensin antagonists have not been studied in patients with ESRD as to their effect on thirst drive.

4.2 Anaemia

In 1984, 9 out of a group of 12 hypertensive patients on maintenance haemodialysis displayed a decrease in haemoglobin concentration, haematocrit and red blood cell mass while receiving long term treatment with captopril. After discontinuation of captopril, haematocrit values returned to pretreatment levels.[64] In follow-up studies, it was demonstrated that this phenomenon was associated with reduced circulating concentrations of angiotensin II[65] that paralleled a suppression of erythropoietin production.[66] The observed anaemia in these patients was successfully treated with androgenic steroids despite little change in erythropoietin levels, suggesting an element of 'erythropoietin resistance' to the process.[67]

ACE inhibitor–related anaemia seems to be a class effect[68] and has been observed to occur in

patients on haemodialysis[64,65,67] and continuous ambulatory peritoneal dialysis.[69] The exact mechanism(s) of ACE inhibitor–related anaemia in ESRD remain poorly defined. It was originally believed that ACE inhibitor administration, by increasing renal blood flow and decreasing tissue hypoxia, removed a hypoxic stimulus to erythropoietin release and thereby decreased red blood cell mass.[70] Subsequent studies have suggested that ACE inhibitor–related anaemia in ESRD cannot be explained simply by decreasing erythropoietin levels,[71,72] although this so-called 'erythropoietin resistance' has not been universally observed.[73,74]

Recent observations point to 2 possible mechanisms by which ACE inhibitors might suppress erythropoiesis.[75,76] First, ACE inhibitors reduce circulating insulin-like growth factor–I and thereby curb erythropoiesis.[75] Second, ACE inhibitors increase the plasma levels of the natural stem cell regulator N-acetyl-seryl-aspartyl-lysyl-proline, which prevents the recruitment of pluripotent haemopoietic stem cells.[76]

The potential for angiotensin antagonist therapy to retard red blood cell production is still poorly defined. For example, the angiotensin antagonist losartan potassium has been observed to decrease haemoglobin concentration in patients with post-transplant erythrocytosis, a pattern similar to that observed with ACE inhibitors.[77,78] Alternatively, losartan potassium has been variably associated with the development of anaemia in ESRD.[79,80] The carefully performed studies of Schiffl and Lang,[80] in particular, suggest that the partial resistance to recombinant erythropoietin observed with captopril was not seen with losartan.

Whether true differences exist between ACE inhibitors and angiotensin antagonists in their ability to affect erythropoiesis remains to be determined. Unless contraindications to their use exist, ACE inhibitors should remain the preferred compounds for suppression of erythropoiesis.

4.3 Angioneurotic Oedema

Angioneurotic oedema is a potentially fatal adverse effect that occurs with ACE inhibitors. Surveys have indicated that angioedema occurs in from 0.1 to 1% of ACE inhibitor recipients.[81-83] Multiple causal mechanisms have been invoked for the development of angioedema, with the most plausible being that of a reduced degradation of bradykinin as a direct class effect of ACE inhibitors.[83] It was originally thought that angiotensin antagonists would not be associated with the development of angioneurotic oedema, since they do not interfere with bradykinin metabolism.[84] Recent information suggests that this thinking requires re-examination, since losartan potassium and valsartan have now been associated with the development of angioneurotic oedema.[85-89]

The frequency of angiotensin antagonist–related angioneurotic oedema is unknown. The majority of the reported cases have involved the use of losartan potassium, although this may simply be a reflection of its being the first angiotensin antagonist introduced and therefore its gaining the widest patient exposure. Of those individuals that have developed losartan potassium-related angioneurotic oedema, a high number had previously developed angioneurotic oedema during the use of an ACE inhibitor.[89] This observation suggests that a proclivity for the development of angioneurotic oedema may exist in certain patients with hypertension, irrespective of the agent in use. The mechanism of angiotensin antagonist–related angioneurotic oedema is not established at this time.[89] It is unlikely that this process involves bradykinin excess. To date, angioneurotic oedema has been rarely reported in patients with ESRD receiving an angiotensin antagonist.[88] Although ACE inhibitor–associated angioneurotic oedema is not considered a formal contraindication to the use of an angiotensin antagonist, it may be advisable not to prescribe them in patients with a history of ACE inhibitor–related angioedema until its exact pathogenesis has been established.

4.4 Cough

Cough is one of the most frequent adverse effects associated with ACE inhibitors.[81,85,90] Whether cough is more frequent in patients with ESRD be-

ing treated with ACE inhibitors is currently not known. It is, though, fairly well accepted that cough frequency with angiotensin antagonists is little different from that observed with placebo.[91-93] This applies to the use of angiotensin antagonists in either essential hypertension[91-93] or ESRD.[54] The markedly lower incidence of cough with angiotensin antagonists is one of the unquestioned advantages of this drug class over ACE inhibitors.

4.5 Anaphylactoid Dialyser Reactions

In 1990, the first cases were described of anaphylactoid dialyser reactions occurring in patients dialysed with AN69 dialyser membranes.[94] These reactions were distinctive, occurring at the start of a haemodialysis session in patients being concomitantly treated with an ACE inhibitor. Since the original description of this entity a number of corroborating reports have appeared that further define the nature of this phenomenon.[24,95-98]

Anaphylactoid reactions present as immediate hypersensitivity reactions and anaphylaxis, both of variable severity. These reactions have not been dialyser- or dialysate-specific, although they do occur more frequently with AN69 (polyacrylonitrile) membranes.[99,100] Reactions have ranged from mild itching to life-threatening systemic reactions characterised by bronchospasm, hypotension and cardiopulmonary collapse.[98] These reactions are abrupt, occurring within seconds to minutes of blood contact with the dialyser and often occur repetitively.[24,94] These reactions are class-specific since they have been described with virtually all ACE inhibitors.[24,94,96] Although not specifically demonstrated to be a dose-dependent phenomenon, these anaphylactoid reactions are likely to be so.[101] The inability to show convincing ACE inhibitor dose dependency for this phenomenon probably relates to different administration times predialysis and/or pharmacokinetic differences between the culpable ACE inhibitors.

The aetiology of this process is probably related to ACE inhibitor–mediated perturbations in the bradykinin system.[95,101] Polyacrylonitrile membranes are highly negatively charged, which permits contact activation of Hageman factor at a greater rate than might be seen with a cuprophane membrane. Hageman factor then facilitates conversion of prekallikrein to kallikrein. Under these conditions of kallikrein activation, an earlier and more intense generation of bradykinin occurs upon contact exposure of blood to polyacrylonitrile membranes. This process is simply amplified in the presence of an ACE inhibitor.[24,95,101] The association of this process with bradykinin has now been convincingly shown in that it can be completely prevented by the prior administration of the bradykinin B_2 receptor antagonist icatibant.[101]

To date, the phenomenon of dialyser-related anaphylactoid reactions has not been convincingly demonstrated with the angiotensin antagonists.[54] Because of this, conventional practice in most dialysis units is to automatically convert ACE inhibitor–treated patients to an angiotensin antagonist if a polyacrylonitrile membrane is being used.

5. Conclusions

Hypertension and cardiovascular disease are common accompanying features to ESRD, often requiring targeted therapy for the disease state.

ACE inhibitors have long been thought to be the agents of choice for the patient with ESRD, since it is commonly believed that ESRD-related hypertension is a uniformly high renin state. This belief is not supported by currently available information; thus, concrete evidence in support of a specific superiority of ACE inhibitors over other antihypertensive medications is currently lacking. If similar treatment logic is applied to the angiotensin antagonist class of drugs as has evolved for ACE inhibitors in ESRD, then angiotensin antagonist use should increase significantly in the coming years.

Part of the appeal of ACE inhibitor use relates to a perception, albeit somewhat flawed, that these drugs are both efficacious and lacking in significant adverse effects in patients with ESRD. ACE inhibitor use in patients with ESRD is an exacting proposition. Their use requires a working knowledge of both an individual compound's pharmacokinetics as well as the across-dialyser clearance.

The latter varies widely among the various ACE inhibitors. The dilemma of dialytic clearance of drug is not an issue with the angiotensin antagonists because of their extensive protein binding. In addition, angiotensin antagonists are free of many of the troublesome adverse effects that accompany ACE inhibitor use. Thus, angioneurotic oedema, which occurs with ACE inhibitors, occurs much less frequently with angiotensin antagonists. In addition, anaphylactoid reactions can occur when ACE inhibitor–treated patients are dialysed with polyacrylonitrile membranes; this phenomenon is rarely (if ever) observed with angiotensin antagonists.

Thus, it appears that the angiotensin antagonists can be viewed as being similar to ACE inhibitors in their actions as well as being free from many of the troubling adverse effects observed with ACE inhibitors in the treatment of ESRD-related hypertension and/or cardiovascular disease. The pharmacokinetic characteristics of the angiotensin antagonists are quite similar, in that they are predominantly cleared by the hepatic route and they are uniformly nondialysable. Accordingly, if an angiotensin antagonist is considered as therapy in a patient with ESRD, cost issues may well become the driving forces behind the selection of a particular product. Alternatively, pharmacokinetic features, dialysability and cost are considerations with the use of an ACE inhibitor.

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