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20 Antihypertensive drugs

GENERAL

Updated guidance on the management of hypertension in adults in the UK offers new advice, including recommendations on the treatment of very elderly people (over 80 years old), who should be offered the same treatment as patients aged 55–80 years, while taking into account co-morbidities [1S]. Previous guidance has acknowledged that while elderly people may accrue benefits from lowering of blood pressure, treatment could potentially lead to more adverse events, such as syncope and falls. However, the most recent evidence challenges this position. Other useful recommendations consider the risk of adverse drug reactions in therapy; for example, the recommendation that patients should not have a combination of an angiotensin converting enzyme (ACE) inhibitor and an angiotensin II receptor antagonist to treat hypertension, based on trial evidence of increased rates of adverse events with this treatment combination. Furthermore, in view of the propensity for black people of African or Caribbean family origin to develop angioedema from ACE inhibitors, angiotensin II receptor antagonists should be used in preference to ACE inhibitors.

Reviews of the pharmacotherapy of chronic pediatric hypertension [2R] and the management of hypertension in pregnancy [3R] have also been published.

Nervous system The risk of falls associated with various antihypertensive drug classes has been studied in a self-controlled case series using The Health Improvement Network primary care database in the UK [4C]. The researchers analysed 9862 individuals over 60 years of age and estimated incidence rate ratios for falls during periods of exposure and non-exposure adjusted for age. The highest incidence rate ratio for first fall within 3 weeks of medication use was with thiazide diuretics (IRR = 2.80; 95% CI = 1.70, 4.57). Beta-adrenoceptor antagonists were associated with an increased incidence of falls from day 22 onwards in the first episode of medication (IRR = 1.23; 95% CI = 1.02, 1.48) and in subsequent episodes (IRR = 1.21; 95% CI = 1.02, 1.42). The implications of this analysis, given the usual limitations of prescription database research, insofar as what is recorded may not always reflect actual exposure, is that clinicians who issue prescriptions of thiazide diuretics for older people should be alert to the possibility of an increased risk of falls early in therapy.

Musculoskeletal Some antihypertensive drugs are associated with changes in bone metabolism. A large prospective cohort study of hypertensive patients beginning treatment with a single antihypertensive drug has therefore been conducted using health-care utilization data to determine the risk of a typical *osteoporotic fracture* [5C]. The fracture rate in the cohort of 376 061 patients was on average 35 fractures per 1000 patient-years, but rates varied across antihypertensive drug classes. When adjusted for co-morbidities and co-medications, the fracture risk was reduced for angiotensin receptor blockers (HR = 0.76; 95% CI = 0.68, 0.86) and thiazide diuretics (HR = 0.85; 95% CI = 0.76, 0.97) compared with calcium channel blockers.

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ANGIOTENSIN CONVERTING ENZYME (ACE) INHIBITORS *[SED-15, 226; SEDA-32, 379; SEDA-33, 416; SEDA-34, 321]*

Combination studies While dual blockade of the renin–angiotensin–aldosterone system (RAAS) by a combination of angiotensin converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists has been advocated for some patients with chronic kidney disease, a study has shown that hemodialysis patients may be at increased risk of cardiovascular death when agents in these classes are used in combination [6C]. After adjustment for baseline cardiovascular risk factors, the cardiovascular mortality in 701 patients who took combined ACE inhibitors and angiotensin II receptor antagonists (HR = 1.45) or 6866 patients taking combinations of ACE inhibitors and non-angiotensin II receptor antagonists (HR = 1.27) was greater compared with 1758 patients taking an angiotensin II receptor antagonist and a non-ACE inhibitor second agent. While a randomized trial would be required to confirm these findings, the benefit of combination therapy with ACE inhibitors and angiotensin II receptor antagonists remains unclear for many clinical circumstances.

Respiratory *Dry cough* is a common and annoying adverse reaction to all ACE inhibitors. In a study of the rates of cough reported in the literature compared with the rates reported in the Physicians' Desk Reference (PDR, a drug reference manual used in the USA) or the drug label, articles that reported randomized controlled trials of ACE inhibitors with at least 100 patients and at least 3 months of follow up and reported the incidence or withdrawal rates due to cough were assessed [7C]. The pooled weighted incidence of cough for enalapril was 11% (95% CI = 9.5, 13%), which was nine times greater than the reported rate in the PDR or drug label (1.3%). The pooled weighted withdrawal rate for enalapril was 2.6% (95% CI = 2.4, 2.7%), which was 31 times greater than the reported rate in the PDR or drug label (0.1%). Over most of the ACE inhibitors examined, the incidence of cough and the withdrawal rate due to cough is significantly greater by several times in the literature than reported in the PDR and the drug label. These results suggest that prescribers should be aware that there is often a gap between the data available from the literature and those that are presented in official drug reference sources for this and possibly other adverse reactions.

Drug–druginteractions ***Intravenous immunoglobulin*** In a retrospective case–control study using the French Pharmacovigilance database the risk of renal failure caused by intravenous immunoglobulin (IVIg) has been quantified [8c]. Adults with renal failure caused by intravenous immunoglobulin were matched with controls with other immunoglobulin-induced adverse reactions, taking into account the sucrose content of the formulation, the time of the adverse event, and age. A number of independent predictors of immunoglobulin-induced renal failure were found, including age, chronic kidney disease, and diabetes mellitus. Exposure to ACE inhibitors, angiotensin II receptor antagonists, and diuretics were also independent predictors, but in the final multivariate model, exposure to ACE inhibitors and/or angiotensin II receptor antagonists was the sole independent predictor associated with immunoglobulin-induced renal failure (OR = 7.9, 95% CI = 1.3, 49). This suggests that temporary interruption of therapy with ACE inhibitors and angiotensin II receptor antagonists should be considered at the time of infusion of intravenous immunoglobulin to reduce the risk of renal failure.

ACE inhibitors and angioedema

Several studies have covered the association of ACE inhibitors with angioedema [SEDA-31, 352; SEDA-32, 380; SEDA-33,

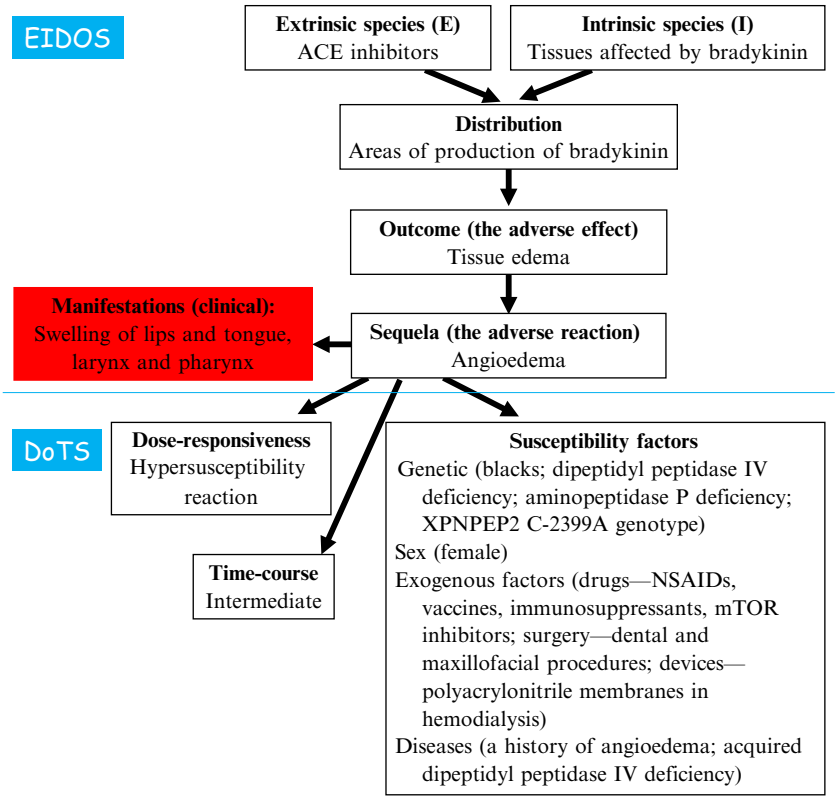

Figure 1 The EIDOS and DoTS descriptions of angioedema due to ACE inhibitors.

417; SEDA-34, 322]. The EIDOS and DoTS descriptions of this adverse reaction are shown in Figure 1.

Clinical features *Angioedema during ACE inhibitor therapy has been widely described, and a common approach is to substitute an angiotensin II receptor antagonist. However, recurrent angioedema is also well recognized with the angiotensin II receptor antagonist class [SEDA-32, 387; SEDA-33, 418; SEDA-34, 325]. An observational study of long-term follow up of over 100 patients with ACE inhibitor-related angioedema has produced evidence that the large majority of patients who apparently relapsed because of angiotensin II receptor antagonists may in fact continue to relapse independently from the antihypertensive treatment [9C]. Of 111 patients who discontinued ACE inhibitors because of angioedema, 51 had further recurrences of angioedema mostly within a month of withdrawal. Switching to a different antihypertensive drug (which included calcium channel blockers, beta-adrenoceptor antagonists, and other drugs, as well as angiotensin II receptor antagonists) had no effect on the frequency of recurrence of angioedema.*

While most cases of angioedema involve the skin or mucous membranes of the nose and/or mouth, visceral angioedema of the bowel has been less frequently recognized and reported. In cases of bowel angioedema the presentation is often of unexplained abdominal pain or ascites, and it is usually diagnosed on the basis of cross-sectional imaging, which reveals the segmental bowel wall thickening typical of visceral angioedema. There have been four individual case

reports of small bowel angioedema, all of which were considered to be related to lisinopril [10[A]–13[A]].

A case of delayed recurrent angioedema during treatment with enalapril has been reported [14[A]].

- *A 63-year-old man with hypertension and chronic obstructive pulmonary disease had two episodes of angioedema 3 years and 5 years after beginning treatment. On both occasions tracheotomy was narrowly avoided.*

Other cases of probable trandolapril-induced angioedema [15[Ar]] and probable ramipril-induced angioedema [16[Ar]] have been reported, including reviews of management.

Severe angioedema can sometimes cause airway compromise, requiring intubation, as in a case of angioedema secondary to enalapril with impressive localized tongue swelling [17[A]]. Despite treatment with diphenhydramine, methylprednisolone, and adrenaline, the patient required nasotracheal intubation for 24 hours until the edema had resolved after withdrawal of the ACE inhibitor.

Cases in children *Angioedema has rarely been described in children. In a retrospective chart review of 42 children who were discharged from intensive care with a diagnosis of angioedema, three were due to antihypertensive agents, enalapril, lisinopril, and amlodipine [18[A]]. In all three cases upper airway obstruction was involved, which probably related to intensive care admission, but in all cases symptoms resolved after the antihypertensive agents were withdrawn. The authors concluded that with the increasing use of antihypertensive agents in children, clinicians should be alert to the possibility of angioedema with upper airway obstruction as a potential lethal adverse reaction.*

Another case of angioedema has been reported in a 2-year-old infant [19[A]].

- *A 2-year-old girl with renal failure secondary to hemolytic–uremic syndrome developed secondary hypertension and was initially treated with furosemide. Her blood pressure remained poorly controlled and enalapril 0.05 mg/kg/day was started. However, 2 days later she developed persistent isolated tongue swelling, which was initially controlled by intravenous methylprednisolone 1 mg/kg. The symptoms totally resolved when enalapril was replaced with nicardipine.*

Susceptibility factors ***Genetic*** *Over the last few decades, the mechanisms underlying ACE inhibitor-induced angioedema have been further characterized. The main mechanism of angioedema during treatment with ACE inhibitors is thought to be by defective degradation of substance P and bradykinin, vasoactive peptides that are normally inactivated by dipeptidyl peptidase IV (DPPIV) and aminopeptidase P (APP). A genetic polymorphism in an X-linked gene encoding membranous APP, the XPNPEP2 C-2399A genotype, has been described [20[E]] and this SNP and serum APP activity have been studied using blood and DNA samples previously extracted from patients with ACE inhibitor-induced angioedema and ACE-inhibitor exposed controls [21[c]]. APP activity was reduced in men compared with women, even after controlling for the polymorphic genotype. The XPNPEP2 C-2399A genotype associated with APP activity and the frequency of loss of function genotype was increased in men with ACE inhibitor-induced angioedema. The investigators noted that it is unlikely that variation in this X-linked gene accounts for the majority of cases, which occur in women. Multiple genetic and environmental factors affecting activity of the vasoactive peptides during ACE inhibition are likely to be involved.*

The association between ACE-inhibitor angioedema and solid organ transplantation has been investigated [22[c]]. Previously the use of mTOR (mammalian target of rapamycin) inhibitor immunosuppressants, such as sirolimus, has been associated with angioedema in patients taking ACE inhibitors. Two of 47 ACE inhibitor-treated patients with renal transplants and one of 36 ACE inhibitor-treated patients with cardiac transplants developed angioedema, which was significantly higher than the incidence in the control groups. The use of immunosuppressants, current smoking, and

having seasonal allergic disorders were associated susceptibility factors. The investigators also experimentally tested the effect of immunosuppressant drugs on DPPIV activity and found a significant reduction, particularly with sirolimus, which is probably the mechanistic reason for the association with ACE inhibitor-induced angioedema.

Management *While withdrawal of ACE inhibitor therapy usually leads to resolution of angioedema, several other treatments have been considered. One of the principal drugs considered for the treatment of ACE inhibitor-induced angioedema is icatibant, a bradykinin B_2 receptor antagonist, which is biologically plausible, given the pathophysiological mechanisms and given that it is effective for the similar condition of hereditary angioedema. A single dose of icatibant 30 mg has been studied in eight adults with probable ACE inhibitor-induced angioedema compared with 47 historical controls with similar presentations who received standard pharmacological therapy with methylprednisolone and clemastine [23[c]]. With icatibant, the time to first improvement of symptoms was on average 51 minutes, but no comparative data were provided; the average time to complete resolution of symptoms was 4.4 hours with icatibant compared to 33 hours in the historical control group. The authors acknowledged the limited scope of their data, but the rapid and stable relief of symptoms using icatibant shows promise, and we await the results of randomized comparisons.*

Captopril *[SED-15, 625; SEDA-32, 384; SEDA-33, 418; SEDA-34, 323]*

Urinary tract Reversible *acute renal failure* with hyperkalemia has been reported in a premature neonate with a double-outlet right ventricle and heart failure after 3 days of treatment with captopril 0.1 mg/kg every 8 hours; renal function and electrolytes completely resolved within a further 6 days after drug withdrawal [24[A]].

Enalapril *[SED-15, 1210; SEDA-32, 384; SEDA-33, 418; SEDA-34, 324]*

Urinary tract A small increase in serum creatinine concentration (up to 30% above baseline) is common in patients after the start of an ACE inhibitor, because of intraglomerular hemodynamic changes. If it occurs it will generally happen within the first 2 weeks. This rise in creatinine concentration is mechanistically distinct from spontaneously *worsening renal function.* Data from the Studies Of Left Ventricular Dysfunction (SOLVD) trials have been used to determine the relative prognostic importance of early worsening renal function in patients randomized to enalapril compared with placebo [25[c]]. Early worsening renal function in the enalapril group had no adverse prognostic significance (adjusted HR = 1.0, 95% CI = 0.8, 1.3), and in those who continued to take the study drug the survival advantage remained, despite worsening renal function (adjusted HR = 0.66; 95% CI = 0.5, 0.9). These results should reassure prescribers that when monitoring patients with heart failure starting on ACE inhibitors, small changes in renal function do not worsen the overall prognosis; however, the outcomes of continuing ACE inhibitors in patients with larger degrees of renal impairment remain unclear.

Skin Three patients with enalapril-induced *photoallergy* have been reported, one of whom had previously had a similar reaction with captopril [26[A]]. Photoallergy is a specific type of immunologically mediated form of delayed hypersensitivity that tends to occur after 24 hours of drug exposure and is characterized by an eczematous eruption, erythema, and blistering in sun-exposed sites.

Lisinopril *[SED-15, 2071; SEDA-32, 385; SEDA-33, 418; SEDA-34, 324]*

Liver A possible case of lisinopril-induced hepatotoxicity has been reported [27[A]].

- A 30-year-old woman developed fatigue and jaundice. She had hypertension and nephrotic

syndrome and had taken furosemide and lisinopril 10 mg/day for 8 months. She had previously taken enalapril, lisinopril, and quinapril without adverse reactions. The liver enzyme abnormalities continued to worsen and hepatic imaging suggested hepatocellular disease. A liver biopsy showed moderate chronic inflammatory cell infiltrates and interface hepatitis. Lisinopril was withdrawn and there was rapid clinical and biochemical improvement.

Fetotoxicity *Anhydramnios or oligohydramnios* has been reported with several ACE inhibitors. Anhydramnios in the third trimester has been reported in a 40-year-old nulliparous woman taking lisinopril for a dilated cardiomyopathy secondary to viral myocarditis and hypertension [28[A]]. The lisinopril was withdrawn and there was a normal liquor volume 1 week later, suggesting that fetal kidneys can recover from ACE inhibitor-related renal damage.

Ramipril *[SED-15, 3022; SEDA-32, 385; SEDA-34, 324]*

Respiratory The extent to which ACE inhibitor-induced *cough* varies in incidence between different agents in the class is largely unknown. The frequency and intensity of cough induced by ramipril 10 mg/day was reduced in a randomized study in 97 patients by substituting imidapril 20 mg/day or, if that was ineffective, by adding placebo-controlled indometacin 50 mg/day to inhibit prostaglandin synthesis [29[C]]. Self-rated cough intensity and frequency were significantly reduced by imidapril (in 24 of the 48 patients) and indometacin significantly reduced the mean score for cough intensity and frequency in both groups. The authors concluded that the incidence of cough is lower with imidapril than with ramipril and that the beneficial effects of indometacin suggest that imidapril-induced cough might be mediated by a mechanism independent of prostaglandin synthesis. However, the use of indometacin is not recommended in hypertensive patients who develop cough during treatment with ACE inhibitors, because of potential adverse reactions and an unfavorable effect on blood pressure control.

Liver Severe *hepatic encephalopathy* has been reported in a patient with liver cirrhosis when ramipril was added to treatment with losartan, both indicated for heavy proteinuria secondary to hepatoportal sclerosis and membranous nephropathy [30[A]].

- A 40-year-old man with hepatic cirrhosis and nephrotic syndrome who had taken losartan 50 mg/day and then, because of heavy proteinuria, ramipril 2.5 mg/day. After 12 hours he became unconscious with electroencephalographic evidence of toxic or metabolic encephalopathy. Previous oral treatment was withheld and he improved with lactulose, intravenous hydration, and branched-chain amino acids. When angiotensin blockade was re-introduced the encephalopathic symptoms recurred and neurological recovery occurred when losartan and ramipril were withdrawn.

The authors inferred that suppression of angiotensin II activity from the combination treatment modulated renal ammonia excretion, leading to an abrupt rise in serum ammonia concentration and encephalopathy.

Skin *Drug rash with eosinophilia and systemic symptoms* (DRESS) is a rare, life-threatening adverse reaction that has been described with various agents, including ACE inhibitors, including ramipril [31[A]].

Monitoring drug therapy The importance of monitoring renal function when starting treatment with ACE inhibitors has been highlighted by a report of a patient who developed acute renal impairment shortly after starting to take ramipril [32[A]].

- A 69-year-old woman with stable stage 3 chronic kidney disease and a background of tablet-controlled diabetes mellitus and recurrent urinary tract infections, was given ramipril 2.5mg/day for hypertension. She had a significant reduction in urine volume and an increased serum creatinine (865 μmol/l). The ramipril was withdrawn and no cause could be found other than ramipril-induced renal dysfunction.

ANGIOTENSIN II RECEPTOR ANTAGONISTS

[SED-15, 223; SEDA-32, 387; SEDA-33, 418; SEDA-34, 325]

Autacoids *Angioedema* of the lips and tongue with difficulty breathing has been reported in a 70-year-old woman who took losartan for hypertension [33[A]]. Angioedema in the oral floor and epiglottis due to valsartan has also been reported [34[A]]. In this case the patient had not previously taken ACE inhibitors but was taking multiple concurrent drugs, including some vasoactive drugs. The angioedema resolved on withdrawal of valsartan, but rechallenge was not performed so it is possible that the valsartan was not causative.

The role of angiotensin II receptor antagonists in patients who develop angioedema from ACE inhibitors has been explored in a systemic literature review [35[M]]. Taking data from two randomized controlled trials and one meta-analysis, the authors produced a conservative estimate of a 10% or less incidence of cross-reactivity in patients who take an angiotensin II receptor antagonist after developing angioedema from an ACE inhibitor. They concluded that angiotensin II receptor antagonists should be reserved in patients with ACE inhibitor-induced angioedema for those who have a high therapeutic need for angiotensin inhibition, and that if an angiotensin II receptor antagonist is used in these circumstances it should be started with careful observation, clear patient counseling, and proper emergency management if angioedema should occur. The EIDOS and DoTS descriptions of angioedema due to angiotensin II receptor antagonists are shown in Figure 2.

Fetotoxicity A series of cases of neonates with partially severe fetopathy has been reported and attributed to maternal angiotensin II receptor antagonist therapy [36[A]]. In seven cases in German teaching hospitals there had been exposure to angiotensin II receptor antagonists at different times in pregnancy, but none of the patients was taking therapy at around the time of delivery. Fetotoxic effects in all cases were *oligohydramnios* and *hyperechogenic fetal kidneys on ultrasound*. Four of the seven neonates did not survive beyond the first few days or weeks of life, because of *lung hypoplasia, hypotension*, and/or *renal insufficiency*; of the three who survived two had continuing renal impairment, in part requiring renal replacement therapy. Other birth

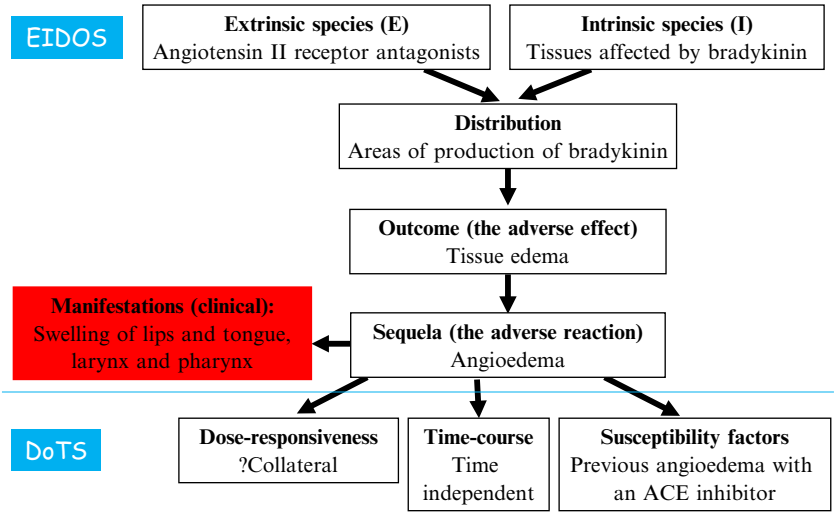

Figure 2 The EIDOS and DoTS descriptions of angioedema due to angiotensin receptor antagonists.

defects included *cranial ossification, flaccid paralysis of the hands and feet*, and *sensorineural deafness*. This case series does not demonstrate the size of the risk to the fetus from angiotensin II receptor antagonists, but it does underline the potentially hazards of using angiotensin II receptor antagonists during pregnancy.

Susceptibility factors *Dehydration* The concerns about using angiotensin II receptor antagonist in preschool children have been highlighted by examination of data from two published reports together with additional information obtained from the sponsoring companies [37M]. Among 183 hypertensive children aged from birth to 5 years old, there were three deaths (1.6%); two occurred in children known to be susceptible to drugs acting on the RAAS, that is, patients with nephrotic syndrome and acute gastroenteritis. Although relatively limited data were available about the exact causes of death, at least two of them occurred when dehydration and intravascular fluid depletion was apparent. Children must be carefully monitored when using these drugs and particular caution and probably withdrawal of the drugs is required during periods of acute illness associated with fluid depletion, such as diarrhea or other acute infectious episodes.

Azilsartan

Azilsartan differs structurally from candesartan only by replacement of candesartan's five-membered tetrazole ring with a five-membered oxo-oxadiazole ring. Azilsartan is formulated as an ester prodrug, azilsartan medoxomil, which is rapidly hydrolysed to the bioactive molecule during gastrointestinal absorption. It produces dose-dependent reductions in vascular smooth muscle contraction, peripheral resistance, and the synthesis and effects of aldosterone on the kidneys [38R]. Azilsartan has a half-life of about 11 hours and is metabolized in the liver mainly via CYP2C9 and is eliminated in both the urine and feces.

In a systematic review of the literature on azilsartan the adverse events noted in trials were similar to those of other angiotensin II receptor antagonists, including *headache, dizziness, urinary tract infections*, and *fatigue* [39M]. The most common adverse event leading to withdrawal was hypotension/orthostatic hypotension, which occurred in 0.4% of patients randomized to azilsartan 40 or 80 mg/day compared with no cases in placebo groups [40R]. Increases in serum creatinine concentration were also more common in the higher dose azilsartan groups (0.2%) compared with placebo (0%).

Candesartan *[SED-15, 612; SEDA-32, 386; SEDA-33, 419; SEDA-34, 326]*

In a systematic review of the use of candesartan in hypertensive patients, including those at higher risk, such as those with diabetes, metabolic syndrome, left ventricular hypertrophy, or microalbuminuria, the authors concluded that the drug is well tolerated across the whole spectrum of patients with hypertension [41R].

Teratogenicity While fetotoxic effects of angiotensin II receptor antagonists have been well described, adverse fetal reactions after exposure during the first trimester, and specifically very early in pregnancy, are unclear, especially when treatment is strongly indicated, such as in patients with diabetes mellitus and microvascular complications.

An analysis of women with type I diabetes mellitus exposed to candesartan or placebo as part of the DIRECT (Diabetic Retinopathy and Candesartan Trials) studies, who became pregnant during the trial (208 pregnancies in 178 women) but stopped taking the trial therapy at an estimated 8 weeks from their last menstrual period, has been undertaken [42R]. Rates of premature deliveries, spontaneous miscarriages, elective terminations, and other outcomes were similar between candesartan and placebo, and there was no difference in the rates of sick babies or malformations. The authors concluded that

the teratogenic risk of candesartan in babies born to mothers with type I diabetes mellitus may not be high if exposure is clearly limited to the first trimester of pregnancy and that these agents could be used in similar populations if drug administration is diligently stopped on planning or detection of pregnancy.

Eprosartan *[SED-15, 3311; SEDA-32, 388; SEDA-33, 419; SEDA-34,327]*

Respiratory In a meta-analysis of 22 studies of eprosartan in 6460 patients, data from five comparisons of eprosartan and enalapril showed a lower incidence of *cough* with the former (RR = 0.46; 95% CI = 0.33, 0.64) [43M].

Irbesartan *[SED-15, 1908; SEDA-32, 386]*

The authors of a review of irbesartan suggested that it has a "placebo-like" adverse reactions profile [44R].

The Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE 1) has reported its findings [45C]. Based on the hypothesis that angiotensin II receptor antagonists may prevent cardiovascular events and enhance maintenance of sinus rhythm in patients with intermittent atrial fibrillation by reducing blood pressure and specific RAAS blocking effects, the authors enrolled 9016 patients with either permanent or intermittent atrial fibrillation and other cardiovascular risk factors who were taking neither anticoagulants nor clopidogrel, and gave them either irbesartan (target dose 300 mg/day) or double-blind placebo and followed them for a mean of 4.1 years. There was no significant difference between the groups in the co-primary outcomes of myocardial infarction, stroke, or death from cardiovascular causes, and irbesartan did not prevent atrial fibrillation. Irbesartan produced greater reductions in blood pressure (mean difference 2.9/1.9 mmHg). Significantly more patients in the irbesartan group withdrew because of symptomatic *hypotension* (127 versus 64) and *renal dysfunction* (37 versus 34). The investigators concluded that irbesartan did not significantly reduce cardiovascular events in patients with atrial fibrillation, but they wondered whether more aggressive lowering of blood pressure would be effective in such patients. However, given that the baseline blood pressure in patients enrolled was high-normal and that there were significantly more adverse reactions with irbesartan, more aggressive treatment could cause more harm than benefit.

Losartan *[SED-15, 2168; SEDA-32, 387; SEDA-33, 419]*

Electrolyte balance A post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study has assessed the effect of losartan on *serum potassium concentrations* and renal outcomes [46c]. Higher serum potassium concentrations at 6 months were associated with higher risks of doubling the serum creatinine concentration or end-stage renal disease, particularly in those with serum potassium concentrations of 5.0 mmol/l or more (HR = 1.39; 95% CI = 1.07, 1.80) and further increased at serum potassium concentrations of 5.5 mmol/l or more (HR = 1.77; 95% CI = 1.22, 2.56). Patients who had a mean serum potassium concentration during follow up of 5.0 mmol/l or more also had a higher risk of doubling of serum creatinine concentration or end-stage renal disease (HR = 1.36; 95% CI = 1.11, 1.67) even after controlling for potential confounders. Therefore, while losartan had an overall renal protective effect in the RENAAL trial, the authors concluded that it can damage the kidneys in those who develop high serum potassium concentrations.

Skin *Psoriasis* has been attributed to losartan [47A].

Drug overdose The combination of an angiotensin II receptor antagonist and a calcium channel blocker in overdose can produce synergistic toxicity by limiting the effectiveness of endogenous and exogenously administered catecholamines. Prolonged refractory hypotension following combined ingestion of losartan and amlodipine was successfully treated with an infusion of metaraminol [48[A]].

Telmisartan *[SED-15, 3311; SEDA-32, 388; SEDA-33, 419; SEDA-34, 327]*

Management of adverse drug reactions Chemotherapy-induced cardiotoxicity is not uncommon, specifically with anthracyclines, through a combination of chronic inflammation, oxidative stress, and changes in the RAAS. In a phase II, placebo-controlled trial of telmisartan 40 mg/day for up to 12 months in the prevention of subclinical cardiac damage induced by epirubicin, cardiovascular toxicity was assessed by a combination of echocardiography with tissue Doppler and strain parameters and serum measurement of proinflammatory cytokine concentrations in 49 patients with tumors at different sites receiving epirubicin chemotherapy [49[C]]. Telmisartan prevented the increase in some proinflammatory cytokines and reactive oxygen species and overall reduced and later reversed epirubicin-induced cardiac abnormalities. These results confirm the protective effects of angiotensin blockade in anthracycline-induced toxicity.

Valsartan *[SED-15, 3593; SEDA-32, 388; SEDA-33, 420; SEDA-34, 327]*

According to a systematic review of valsartan more than 10 years since its initial approval, the most frequently reported adverse events are *malaise/fatigue, dizziness, headache*, and *nausea/vomiting*, with incidences similar to those observed with placebo [50[M]].

Nervous system In 261 hypertensive children and adolescents, aged 6–16 years, using a randomized, controlled, withdrawal design, three different dose ranges of valsartan were used—low dose, 10/20 mg/day; medium dose, 40/80 mg/day; high dose, 80/160 mg/day [51[C]]. *Headache* was the most common adverse reaction, but it did not appear to be dose-dependent, which suggests that it was not a true adverse reaction or that the study was too small to demonstrate dose-dependency, probably the former, since the study was large enough to show dose-related beneficial effects on blood pressure. *Dizziness* occurred with high-dose valsartan in seven patients and *orthostatic hypotension* in one. There is some evidence that high blood pressure causes headaches, and antihypertensive drugs reduce the incidence of headache in hypertensive patients [52[M]], so confounding by indication is possible.

DUAL ANGIOTENSIN II RECEPTOR ANTAGONISTS/ NEPRILYSIN ANTAGONISTS

LCZ696

Metabolism It has been suggested that increased natriuretic peptide availability through inhibition of neprilysin could affect human lipid metabolism, causing adverse effects, since natriuretic peptides stimulate lipolysis in human adipocytes through natriuretic peptide receptor-A activation [53[HE]]. LCZ696 could therefore augment lipid mobilization and lipid oxidation. This might be beneficial in overweight and obese patients, but excessive lipid mobilization could promote ectopic fat storage in muscle and liver and increase insulin resistance.

DIRECT RENIN INHIBITORS *[SEDA-32, 388; SEDA-33, 420; SEDA-34, 328]*

NON-PEPTIDE INHIBITORS

Aliskiren *[SEDA-32, 388; SEDA-33, 420; SEDA-34, 328]*

Several further reviews of the use of aliskiren in hypertension have been published [54R,55R].

Combination studies There is a strong focus on combination treatment with aliskiren in recent publications, including reviews of the rationale and scientific basis for combining a direct renin inhibitor with other antihypertensive drugs [56R] and specifically with inhibitors of the RAAS [57R]. In an open study of aliskiren + valsartan with or without hydrochlorothiazide for up to 18 months the combinations provided clinically useful blood pressure reductions [58c]. *Hyperkalemia* is a concern with dual RAAS blockade, and 3.6% of patients had a potassium concentration of over 5.5 mmol/l at some time during the study. In most cases the rise in potassium was transient, but two patients (0.1%) withdrew because of hyperkalemia. The time courses of the adverse biochemical effects were not mentioned, and details about monitoring were not included. Given the risk of hyperkalemia, a potentially serious but silent adverse effect of combination treatment, an appropriate and regular monitoring scheme is prudent.

In an analysis of patients taking aliskiren and losartan in the Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) study [59c] adverse events were most common in patients with stage 3 chronic kidney disease, with a trend towards a higher incidence of hyperkalemia (potassium concentration over 5.5 mmol/l) in those taking aliskiren (23%) compared with placebo (14%). Renal dysfunction may therefore modify the frequency of biochemical monitoring required if such combinations are used.

In a post-hoc subgroup analysis of the ALiskiren Observation of Heart Failure Treatment (ALOFT) study, in which aliskiren was added to multiple RAAS inhibitors (including an ACE inhibitor or angiotensin II receptor antagonist and an aldosterone antagonist), there was no statistically significant increase in pre-specified adverse events, such as new renal dysfunction or hyperkalemia, but only 101 patients were randomized to aliskiren when already on dual therapy [60c].

Combining aliskiren with a thiazide diuretic does not pose the same risk of hyperkalemia according to the results of an open, dose escalation study of combination treatment [61c]. Adverse events in those taking a combination of aliskiren and hydrochlorothiazide, such as headache, dizziness and nasopharyngitis, were similar to those in patients taking aliskiren alone.

Urinary tract Acute kidney damage has been reported in a 43-year-old man with co-existing chronic renal disease and dilated cardiomyopathy who started to take aliskiren [62A]. He was also taking several other drugs, including enalapril, furosemide, and spironolactone. The renal dysfunction failed to resolve on withdrawal of aliskiren, but renal function returned to normal on withholding enalapril. It is therefore not correct to attribute the adverse effect to aliskiren alone.

Susceptibility factors ***Age*** In four patients aged 5–18 years taking aliskiren in combination with losartan for persistent proteinuria in the context of chronic kidney disease, there were reductions in proteinuria, but three patients had adverse reactions requiring a change in the dose of aliskiren, and one child developed accelerated loss of kidney function, leading to a need for hemodialysis after only a short course of therapy [63A]. Both patients with a significant reduction in renal function were taking combination treatment with an ACE inhibitor and angiotensin II receptor antagonist when

aliskiren was started. These observations suggest that aliskiren should be used with extreme caution in children, particularly triple RAAS blockade in the presence of renal dysfunction.

Drug–drug interactions Several different drug interaction studies have been conducted with aliskiren in healthy volunteers. Aliskiren is a substrate for the Multidrug Resistance Transporter 1 (MDR1) P glycoprotein and also has moderate affinity for the Organic Anion Transporting Polypeptide (OATP) transporter; CYP-mediated drug–drug interactions are thought to be less important.

Ciclosporin Ciclosporin inhibits CYP3A4, MDR1, and OATP, and the combination of ciclosporin with aliskiren 75 mg has been examined in 14 subjects in single dosing studies [64[c]]. Ciclosporin 200 or 600 mg resulted in dose-independent increases in the AUC (4- to 5-fold) and C_{max} (2.5-fold) of aliskiren. Several subjects had adverse reactions, even in this single-dose study, probably related to increased aliskiren exposure. This suggests that aliskiren should be avoided in combination with ciclosporin.

Itraconazole Itraconazole is a potent inhibitor of P glycoprotein and CYP3A4, and combination with aliskiren has been studied [65[c]]. Itraconazole (first dose 200 mg then 100 mg bd for 5 days), followed by aliskiren 150 mg on day 3, increased the AUC of aliskiren 6.5-fold and the C_{max} 5.8-fold. This suggests that aliskiren should be avoided in combination with itraconazole.

Verapamil Verapamil is a moderate inhibitor of the P glycoprotein MDR1 and a weak inhibitor of CYP3A4. Verapamil 240 mg/day, followed by aliskiren 300 mg given on day 8, resulted in only a 2-fold increase in both the AUC and C_{max} of aliskiren [66[c]]. This suggests that concomitant administration of aliskiren with verapamil is acceptable without dosage adjustment.

Drug–food interactions ***Grapefruit*** In 28 healthy volunteers, concomitant administration of grapefruit juice with aliskiren reduced the AUC and C_{max} of aliskiren in [67[cE]]. In in vitro studies of aliskiren transport using cell-based uptake assays after either transient transfection (OATP1A2) or stable expression (OATP2B1) of these transport proteins in human embryonic kidney cells (HEK293), the uptake of aliskiren into OAT2B1 cells was similar to control cells, but uptake into OAT1A2 cells increased linearly with time. Naringin, a flavonoid that is found in grapefruit juice, reduced the accumulation of aliskiren in OAT1A2 cells, suggesting that inhibition of the gastrointestinal OATP1A2 uptake transporter partially explains the effect of grapefruit juice on aliskiren pharmacokinetics.

ENDOTHELIN RECEPTOR ANTAGONISTS *[SED-15, 1215; SEDA-32, 389; SEDA-33, 421; SEDA-34, 328]*

Ambrisentan *[SEDA-32, 389; SEDA-33, 421; SEDA-34, 328]*

Observational studies In an observational cohort study of ambrisentan in 13 patients with portopulmonary hypertension (POPH), based on significant falls in mean pulmonary artery pressure (from 55 to 41 mmHg) and pulmonary vascular resistance (from 445 to 174 dynes/second/cm^3), the authors argued that monotherapy with ambrisentan was safe and effective [68[c]]. However, there was no control group and no defined protocol for patient allocation to treatment. One patient was removed from the study after 2 weeks after *weight gain, bilateral periorbital bleeding*, and *peripheral edema*.

In a 24-week open trial of ambrisentan in 21 patients with sarcoidosis-associated pulmonary hypertension and no control group, there was no improvement in 6-minute walk distance, dyspnea, or quality of life. Eleven of the 21 patients dropped out of the study, because of “medical reasons”, dyspnea, or edema. The authors suggested possible

benefit in some patients, but the lack of statistical significance and the large number of patients who were unable to tolerate the treatment suggests otherwise [69^{c}].

Liver In a 24 week uncontrolled open study of ambrisentan in Japanese adults with pulmonary arterial hypertension there were similar pharmacokinetics to non-Japanese subjects and there were no clinically significant rises in serum aminotransferase activities [70^{c}]. Pre-registration and post-marketing data show only a low risk of liver damage [71^{R}]; the FDA's black box warning for liver disease has been removed.

Death The effects of ambrisentan in idiopathic pulmonary fibrosis have been examined in the ARTEMIS-IPF study [72^{C}]. It was hypothesized that endothelin blockade using ambrisentan would reduce disease progression, but the study was terminated by the Data Monitoring Board after recruitment of 75% (n = 492) of its target subjects, 329 of whom were taking ambrisentan and 163 placebo. Analysis showed a higher rate of progression of idiopathic pulmonary fibrosis with ambrisentan (27%) compared with placebo (17%), with statistically significant increases in mortality and hospitalization. In July of 2012, on the basis of initial reports of the trial, GlaxoSmithKline issued a direct health-care professional communication, with the agreement of the European Medicines Agency, noting that ambrisentan should be restricted to the treatment of pulmonary arterial hypertension, and not used in idiopathic pulmonary fibrosis [73^{S}].

Bosentan *[SED-15, 549; SEDA-32, 389; SEDA-33, 422; SEDA-34, 329]*

Observational studies In patients with pulmonary arterial hypertension associated with connective tissue disease bosentan (n = 32) and sitaxentan (n = 22) were of similar efficacy [74^{c}]. Two patients stopped taking sitaxentan because of *diarrhea* and *abdominal pain*, one because of *raised aminotransferase activities*, and one with other adverse reactions. Bosentan was withdrawn from seven patients because of raised aminotransferases. The authors argued that monthly liver enzyme testing is indicated with both drugs (see also Sitaxentan below). They also noted a fall in mean hemoglobin concentrations with both bosentan and sitaxentan and one patient taking bosentan required a blood transfusion, although it is notable that many of the patients were taking concomitant warfarin and drug interactions were not formally examined.

In a 5-year retrospective study of 101 children, mean age 9.7 years, with pulmonary arterial hypertension estimated survival was 96%, 89%, 83%, and 60% at 1, 2, 3, and 5 years respectively [75^{c}]. Seven children stopped taking bosentan and all survived. Liver function tests became abnormal in three patients, one of whom had aminotransferase activities three times the upper limit of normal. The authors suggested that adverse reactions to bosentan are unusual, but this was a retrospective study without a systematic method of collating suspected adverse reactions.

No clinically relevant or statistically significant changes in liver aminotransferases were found in a prospective study of the use of bosentan in 39 adults with congenital heart disease and pulmonary arterial hypertension, 10 of whom had Down's syndrome. There were no withdrawals because of suspected adverse reactions, of which *headache* (n = 10) and *lower-limb edema* (n = 4) were the most common [76^{c}].

In a retrospective study of 20 patients who took bosentan for pulmonary arterial hypertension there were few adverse reactions [77^{c}]. Recurrent *syncope* in one patient led to bosentan withdrawal, and three patients had transiently *increased aminotransferase activities*.

Placebo-controlled studies Interest in the role of the endothelin pathway in melanocyte physiology and in the pathogenesis of melanoma has led to studies of bosentan in stage IV metastatic melanoma. In 80 patients who were randomized to bosentan or placebo, in addition to dacarbazine, there was no effect on tumor progression. *Anemia, thrombocytopenia, vomiting*, and *lethargy*

were more common in those taking bosentan. Clinically relevant *increases in liver aminotransferase activities* occurred with a similar frequency to those seen in trials of bosentan in pulmonary arterial hypertension [78[C]].

Liver A patient with HIV-related pulmonary hypertension who took bosentan, with a good response, had *increased aminotransferase activities* [79[A]]. She was given sildenafil instead and died about 2 years later after bilateral pneumonia.

Severe drug-induced liver damage associated with bosentan been reported [80[A]].

- A 37-year-old woman with portopulmonary hypertension became jaundiced, with a 2–3 week history of fatigue, nausea, and poor appetite. Serum bilirubin, aspartate and alanine aminotransferase, and alkaline phosphatase were raised. Although she had taken spironolactone and bosentan for 18 months with good effect, bosentan was withdrawn. She further deteriorated for a week, until she was given prednisolone 40 mg/day, when she improved. When her pulmonary arterial hypertension worsened she was given sildenafil and ambrisentan, which were well tolerated.

It seems unlikely that bosentan was responsible for the liver damage in this case. However, the authors also reviewed the current literature on bosentan-associated liver damage, noting that ambrisentan is a nonsulfonamide propanoic acid derivative and that there is evidence that it is well tolerated in patients who have had earlier abnormal liver function tests with bosentan.

Darusentan *[SEDA-34, 329]*

Placebo-controlled studies The results of the Darusentan-Resistant Hypertension Trial, a randomized controlled trial of darusentan in almost 400 hypertensive patients treated with more than four antihypertensive drugs (including a diuretic) but without effective blood pressure control, have been the subject of further commentary, noting the unfavorable adverse reactions profile of the drug when used for blood pressure control, despite apparent efficacy [81[T]].

Sitaxentan *[SEDA-32, 390; SEDA-33, 423; SEDA-34, 329]*

In December 2010 sitaxentan was withdrawn voluntarily from worldwide markets. The decision was made after examination of a 2009 case in the UK and two cases from clinical trials in India and the Ukraine. Hepatic damage was not prevented by monitoring, did not resolve on withdrawal of the drug, and proved fatal [82[S]].

Another fatal case of liver damage has been described [83[A]].

- A 19-year-old woman with severe idiopathic pulmonary arterial hypertension taking sitaxentan 100 mg/day developed jaundice after 3 months. She had abnormal liver function (bilirubin 177 µmol/l, alkaline phosphatase 188 iu/l, aspartate aminotransferase 1300 iu/l, alanine aminotransferase 1259 iu/L). Hepatitis screens were negative. After withdrawal of sitaxentan she deteriorated and developed fulminant hepatic failure. A donor liver was found, but she died from refractory cerebral edema on day 13. Post mortem examination showed acute extensive necrosis and vigorous stem cell regeneration.

Hepatotoxicity associated with endothelin receptor antagonists, with particular reference to the withdrawal of sitaxentan, has been reviewed [84[T]].

DRUGS THAT ACT ON THE SYMPATHETIC NERVOUS SYSTEM *[SEDA-32, 391; SEDA-33, 424; SEDA-34, 329]*

PRESYNAPTIC ALPHA-ADRENOCEPTOR AGONISTS

Clonidine *[SED-15, 817; SEDA-32, 391; SEDA-33, 424; SEDA-34, 329]*

Cardiovascular A 44-year-old woman with few cardiovascular risk factors developed right coronary artery dissection possibly

secondary to clonidine 0.3 mg in a transdermal patch [85[A]].

Drug overdose A probable massive clonidine overdose followed the presumed inadvertent soft-tissue injection of clonidine and morphine during a routine refill of an implantable drug delivery device [86[A]]. This case highlights the risks and consequences of inadvertent soft tissue injections of clonidine and other analgesic agents, and suggests a number of strategies to reduce the risk of adverse events during implanted drug delivery device refills.

- A 51-year-old woman with a long history of complex regional pain syndrome of the right arm was fitted with an implanted drug delivery device delivering clonidine and morphine for intrathecal analgesia. Shortly after a routine refilling procedure she became confused, bradycardic, hypertensive, and drowsy and eventually required treatment for myocardial ischemia. The implanted device was reviewed on the day after it had been refilled, when there was minimal drug solution in the reservoir. It was presumed that the solution had been inadvertently injected into the soft tissues around the device.

Methyldopa *[SED-15, 2291; SEDA-32, 391; SEDA-33, 424; SEDA-34, 330]*

Pregnancy The effects of methyldopa and nifedipine on maternal and fetal hemodynamics have been prospectively studied in 56 women with mild gestational hypertension and 28 healthy controls during the third trimester in a cohort study [87[c]]. Uterine artery blood velocity waveform indices were improved only by nifedipine. Neither drug affected flow in the umbilical artery or the fetal middle cerebral artery.

NON-SELECTIVE α-ADRENOCEPTOR ANTAGONISTS

Tolazoline *[SED-15, 3443]*

Respiratory Episodes of apnea and skeletal muscle fasciculation were reported in mule deer after mistaken administration of excessive doses of intravenous tolazoline (mean dose 7.3 mg/kg versus protocol dose 4.6 mg/kg) to reverse the effects of xylazine as part of an external parasite research study [88[E]]. Normal breathing and chest expansion resumed spontaneously within 8–10 sec in all the animals. It is not known whether there was concomitant tachycardia, as heart rate monitoring was stopped before tolazoline administration. Apnea has not been attributed to non-selective alpha-blockers in humans. The mechanisms responsible are unknown.

POSTSYNAPTIC α-ADRENOCEPTOR ANTAGONISTS *[SEDA-32, 391; SEDA-33, 425; SEDA-34, 330]*

Sensory systems In a prospective observational study of cataract surgery the association of Intraoperative Floppy Iris Syndrome (IFIS) with pre-operative use of alpha-adrenoceptor antagonists (specific agents not specified) was confirmed [89[c]]. The incidence of IFIS during operative treatment of 439 eyes was 2.96% and alpha-adrenoceptor antagonists were associated with a 25-fold relative risk. There were no major intraoperative complications, and all cases of IFIS were managed with intraoperative adrenaline, by irrigation or injection into the anterior chamber. There was an increased risk of IFIS with a larger (3.2 mm) corneal incision compared with a 2.4 mm incision.

A meta-analysis of 17 trials covering 17 588 eye operations has explored the susceptibility factors for IFIS [90[M]]. There was an association between pre-existing hypertension and IFIS (OR = 2.2; 95% CI = 1.2, 4.2) and a strong association with all alpha-adrenoceptor antagonists (tamsulosin, alfuzosin, terazosin, and doxazosin) in a hierarchical manner, and a particularly large effect size with tamsulosin.

Alfuzosin *[SED-15, 74; SEDA-34, 330]*

Liver Recurrent hepatocellular damage, identified by deranged liver function tests during repeated exposure to alfuzosin, has been described [91[A]].

Doxazosin *[SED-15, 1188; SEDA-32, 392; SEDA-33, 426]*

Nervous system In an open, non-randomized 8-week study in 80 Taiwanese men taking a doxazosin gastrointestinal formulation (GITS) for benign prostatic hyperplasia, doxazosin was effective in terms of maximum urinary flow rate and prostatic symptoms, but 12 patients reported treatment-related *dizziness*; eight withdrew permanently because of dizziness and two because of other adverse reactions [92[c]].

Silodosin *[SEDA-31, 330]*

There is further evidence that silodosin, being a selective α_{1A}-adrenoceptor antagonist, may be beneficial in benign prostatic hyperplasia, while causing fewer hypotensive adverse reactions due to peripheral vasodilatation. The pharmacology and clinical uses of silodosin have been reviewed from the results in published phase III trials [93[R]]. The uroselectivity of silodosin leads to a lower incidence of *dizziness* than with other less selective agents, but more reported cases of ejaculatory disorders (particularly retrograde ejaculation) because of its effect on smooth muscle relaxation in the prostate, urethra, bladder neck, and vas deferens.

Sexual function In a parallel-group, randomized, placebo-controlled comparison of silodosin and tamsulosin in 955 patients, ejaculatory disorders emerged as important adverse reactions. [94[C]] Retrograde ejaculation occurred in (14%) of those who took silodosin (54 of 381), compared with 2.1% (8 of 384) and 1.1% (2 of 190) of those taking tamsulosin and placebo respectively.

Tamsulosin *[SED-15, 3303; SEDA-32, 392; SEDA-33, 426; SEDA-34, 331]*

Sensory systems In a retrospective review of phacoemulsification operations undertaken by ophthalmic surgical residents, recent use of tamsulosin (within 30 days preoperatively) compared with remote use (between 3 years and 30 days preoperatively) is associated with a higher risk of surgical complications, including IFIS [95[c]]. However, the authors did not detect a significant effect of duration of tamsulosin use on the risk of operative complications.

Tamsulosin is often used for the treatment of lower urinary tract symptoms in men, but has also found uses in various urological conditions in women. A prospective analysis of phacoemulsification eye operations in women taking tamsulosin was associated with IFIS in 11 of 19 eyes [96[c]]. Owing to careful intraoperative surgical strategies, there were no postoperative complications.

Sexual function Priapism has been described in a patient taking tamsulosin for empirical treatment of lower urinary tract symptoms [97[A]]. He was successfully treated by aspiration of the corpora and intracavernosal injection of adrenaline.

Drug–drug interactions ***Ketoconazole and paroxetine*** In 24 healthy men there was increased exposure to tamsulosin in the presence of paroxetine and even more so with ketoconazole, with increases in the AUC of 1.34 and 1.64 respectively [98[E]]. Pharmacodynamic testing was performed using forced orthostasis stress testing before and at 6 and 24 hours after tamsulosin. Despite the pharmacokinetic changes, co-administration of paroxetine or ketoconazole did not result in greater mean hemodynamic changes, although one individual did have mild postural dizziness after treatment with paroxetine and tamsulosin.

IMIDAZOLINE RECEPTOR AGONISTS

Moxonidine

The use of moxonidine in patients with arterial hypertension has been reviewed [99R].

DIRECT VASODILATORS

Diazoxide *[SED-15, 1188; SEDA-32, 393; SEDA-33, 427; SEDA-34, 331]*

Cardiovascular In a neonate who was treated with diazoxide for hyperinsulinemic hypoglycemia, mild pulmonary hypertension and re-opening of the ductus arteriosus occurred after 6 days and resolved soon after withdrawal of diazoxide [100A].

Hydralazine *[SED-15, 1701; SEDA-32, 393; SEDA-33, 428; SEDA-34, 331]*

Cardiovascular Anecdotal observations of excessive blood pressure reduction associated with the use of intravenous hydralazine prompted a prospective review of this treatment [101c]. Of 94 patients who received intravenous hydralazine, only four had evidence of a hypertensive emergency (based on target organ damage or symptoms). There were 16 adverse events in 16 patients, most of which were related to *hypotension*. Six had a greater than 65 mmHg reduction in systolic blood pressure, but there were no irreversible adverse events, such as stroke.

Skin Subacute cutaneous lupus erythematosus with associated C4 complement deficiency has been reported in a woman taking hydralazine [102A]. The authors suggested that before starting hydralazine it is prudent to obtain baseline C4 concentrations and avoid the drug in those who have low concentrations.

Minoxidil *[SED-15, 2354; SEDA-32, 297; SEDA-33, 428; SEDA-34, 332]*

Cardiovascular A drug-induced pericardial effusion has been reported in a patient with end-stage renal disease taking minoxidil for hypertension [103A].

Drug overdose Systemic overdose of topical minoxidil hair solution has been reported.

- A 2 year old infant drank 100 ml of a hair solution and about 4 hours later developed a tachycardia, which failed to settle with intravenous fluids, but resolved by 36–72 hours after ingestion [104A].
- A 48-year-old man drank a whole bottle of hair solution containing minoxidil and developed refractory hypotension, despite intravenous fluids and various vasopressors [105A]. His blood pressure eventually responded to midodrine and he recovered within 48 hours.

References

[1] National Institute of Health and Clinical Excellence. Hypertension: clinical management of primary hypertension in adults (Clinical Guideline 127). 2011 August: London.
[2] Meyers RS, Siu A. Pharmacotherapy review of chronic pediatric hypertension. Clin Ther 2011; 33(10): 1331–56.
[3] Magee LA, Abalos E, von Dadelszen P, Sibai B, Easterling T, Walkinshaw S, CHIPS Study Group. How to manage hypertension in pregnancy effectively. Br J Clin Pharmacol 2011; 72(3): 394–401.
[4] Gribbin J, Hubbard R, Gladman J, Smith C, Lewis S. Risk of falls associated

with antihypertensive medication: self-controlled case series. Pharmacoepidemiol Drug Saf 2011; 20(8): 879–84.
[5] Solomon DH, Mogun H, Garneau K, Fischer MA. Risk of fractures in older adults using antihypertensive medications. J Bone Miner Res 2011; 26(7): 1561–7.
[6] Chan KE, Ikizler TA, Gamboa JL, Yu C, Hakim RM, Brown NJ. Combined angiotensin-converting enzyme inhibition and receptor blockade associate with increased risk of cardiovascular death in hemodialysis patients. Kidney Int 2011; 80(9): 978–85.
[7] Bangalore S, Kumar S, Messerli FH. Angiotensin-converting enzyme inhibitor associated cough: deceptive information from the Physicians' Desk Reference. Am J Med 2010; 123(11): 1016–30.
[8] Moulis G, Sailler L, Sommet A, Lapeyre-Mestre M, Montastruc JL, French Association of Regional Pharmacovigilance Centers. Exposure to inhibitors of the renin-angiotensin system is a major independent risk factor for acute renal failure induced by sucrose-containing intravenous immunoglobulins: a case–control study. Pharmacoepidemiol Drug Saf 2012; 21(3): 314–9.
[9] Beltrami L, Zanichelli A, Zingale L, Vacchini R, Carugo S, Cicardi M. Long-term follow-up of 111 patients with angiotensin-converting enzyme inhibitor-related angioedema. J Hypertens 2011; 29(11): 2273–7.
[10] Aggarwal A, Mehta N, Shah SN. Small bowel angioedema associated with angiotensin converting enzyme inhibitor use. J Gen Intern Med 2011; 26(4): 446–7.
[11] Cuypers S, Van Meerbeeck S, De Pauw M. ACE inhibitor-induced angioedema of the small intestine: a case report. Acta Cardiol 2011; 66(5): 645–8.
[12] Haines EC, Wall GC. Possible angiotensin-converting enzyme inhibitor (ACEI)-induced small bowel angioedema. J Pharm Pract 2011; 24(6): 564–7.
[13] Korniyenko A, Alviar CL, Cordova JP, Messerli FH. Visceral angioedema due to angiotensin-converting enzyme inhibitor therapy. Cleve Clin J Med 2011; 78(5): 297–304.
[14] Janković SM, Stefanović SM. Odloženi angioedem tokom primene inhibitora angiotenzin-konvertujućeg enzima. [Delayed angioedema during therapy with angiotensin-converting enzyme inhibitors.] Vojnosanit Pregl 2011; 68(4): 372–6.
[15] Andrew N, Gabb G, Del Fante M. ACEI associated angioedema—a case study and review. Aust Fam Physician 2011; 40(12): 985–8.
[16] Kloth N, Lane AS. ACE inhibitor-induced angioedema: a case report and review of current management. Crit Care Resusc 2011; 13(1): 33–7.
[17] Bramante RM, Rand M. Images in clinical medicine. Angioedema. N Engl J Med 2011; 365(2): e4.
[18] Hom KA, Hirsch R, Elluru RG. Antihypertensive drug-induced angioedema causing upper airway obstruction in children. Int J Pediatr Otorhinolaryngol 2012; 76 (1): 14–9.
[19] El Koraichi A, Tadili J, Benjelloun MY, Benafitou R, El Kharraz H, Lahlou J, Chkoura M, El Haddoury M, Ech-Chérif El, Kettani SS. Enapranil-induced angioedema in a 2-year-old infant: case report. Cardiovasc Toxicol 2011; 11(4): 382–4.
[20] Duan QL, Nikpoor B, Dube MP, Molinaro G, Meijer IA, Dion P, Rochefort D, Saint-Onge J, Flury L, Brown NJ, Gainer JV, Rouleau JL, Agostoni A, Cugno M, Simon P, Clavel P, Potier J, Wehbe B, Benarbia S, Marc-Aurele J, Chanard J, Foroud T, Adam A, Rouleau GA. A variant in XPNPEP2 is associated with angioedema induced by angiotensin I-converting enzyme inhibitors. Am J Hum Genet 2005; 77(4): 617–26.
[21] Woodard-Grice AV, Lucisano AC, Byrd JB, Stone ER, Simmons WH, Brown NJ. Sex-dependent and race-dependent association of XPNPEP2 C-2399A polymorphism with angiotensin-converting enzyme inhibitor-associated angioedema. Pharmacogenet Genomics 2010; 20(9): 532–6.
[22] Byrd JB, Woodard-Grice A, Stone E, Lucisano A, Schaefer H, Yu C, Eyler AE, Salloum NE, Brown NJ. Association of angiotensin-converting enzyme inhibitor-associated angioedema with

transplant and immunosuppressant use. Allergy 2010; 65(11): 1381–7.
[23] Bas M, Greve J, Stelter K, Bier H, Stark T, Hoffmann TK, Kojda G. Therapeutic efficacy of icatibant in angioedema induced by angiotensin-converting enzyme inhibitors: a case series. Ann Emerg Med 2010; 56(3): 278–82.
[24] Tan LH, Du LZ, Carr MR, Kuzin JK, Moffett BS, Chang AC. Captopril induced reversible acute renal failure in a premature neonate with double outlet right ventricle and congestive heart failure. World J Pediatr 2011; 7(1): 89–91.
[25] Testani JM, Kimmel SE, Dries DL, Coca SG. Prognostic importance of early worsening renal function after initiation of angiotensin-converting enzyme inhibitor therapy in patients with cardiac dysfunction. Circ Heart Fail 2011; 4(6): 685–91.
[26] Sánchez-Borges M, González-Aveledo LA. Photoallergic reactions to angiotensin converting enzyme inhibitors. J Eur Acad Dermatol Venereol 2011; 25 (5): 621–2.
[27] Zalawadiya SK, Sethi S, Loe S, Kumar S, Tchokonte R, Shi D, Adam AK, May EJ. Unique case of presumed lisinopril-induced hepatotoxicity. Am J Health Syst Pharm 2010; 67(16): 1354–6.
[28] MacKintosh M, Tower C, Clarke B, Vause S. Anhydramnios secondary to angiotensin II converting enzyme inhibitors: a reversible condition? J Obstet Gynaecol 2010; 30(8): 865–6.
[29] Fogari R, Zoppi A, Mugellini A, Destro M, Lazzari P, Derosa G. Difference in incidence of cough induced by imidapril and ramipril: role of prostaglandin synthesis inhibition. Biomed Aging Pathol 2011; 1: 73–7.
[30] Oertelt-Prigione S, Crosignani A, Gallieni M, Vassallo E, Podda M, Zuin M. Severe hepatic encephalopathy in a patient with liver cirrhosis after administration of angiotensin-converting enzyme inhibitor/angiotensin II receptor blocker combination therapy: a case report. J Med Case Rep 2010; 4: 141.
[31] Pileri A, Brunasso AM, Tilz H, Wolf P, Massone C. Ramipril-induced drug reaction with eosinophilia and systemic symptoms (DRESS). Eur J Dermatol 2011; 21(4): 624–5.
[32] Jaconelli T, Collinson H. The importance of counselling in patients initiated on potentially nephrotoxic drugs. Prim Care Cardiovasc J 2011; 4: 63.
[33] Orgaz-Molina J, Soriano-Hernández MI, Husein-Elahmed H, Arias-Santiago S. Angioedema por losartán [Angioedema due to losartan.] Med Clin (Barc) 2011; 137(6): 281–2.
[34] Shino M, Takahashi K, Murata T, Iida H, Yasuoka Y, Furuya N. Angiotensin II receptor blocker-induced angioedema in the oral floor and epiglottis. Am J Otolaryngol 2011; 32(6): 624–6.
[35] Beavers CJ, Dunn SP, Macaulay TE. The role of angiotensin receptor blockers in patients with angiotensin-converting enzyme inhibitor-induced angioedema. Ann Pharmacother 2011; 45(4): 520–4.
[36] Hünseler C, Paneitz A, Friedrich D, Lindner U, Oberthuer A, Körber F, Schmitt K, Welzing L, Müller A, Herkenrath P, Hoppe B, Gortner L, Roth B, Kattner E, Schaible T. Angiotensin II receptor blocker induced fetopathy: 7 cases. Klin Padiatr 2011; 223(1): 10–4.
[37] Tullus K. Safety concerns of angiotensin II receptor blockers in preschool children. Arch Dis Child 2011; 96(9): 881–2.
[38] Kurtz TW, Kajiya T. Differential pharmacology and benefit/risk of azilsartan compared to other sartans. Vasc Health Risk Manag 2012; 8: 133–43.
[39] Baker WL, White WB. Azilsartan medoxomil: a new angiotensin II receptor antagonist for treatment of hypertension. Ann Pharmacother 2011; 45 (12): 1506–15.
[40] Zaiken K, Cheng JW. Azilsartan medoxomil: a new angiotensin receptor blocker. Clin Ther 2011; 33(11): 1577–89.
[41] Barrios V, Escobar C. Candesartan in the treatment of hypertension: what have we learnt in the last decade? Expert Opin Drug Saf 2011; 10(6): 957–68.
[42] Porta M, Hainer JW, Jansson SO, Malm A, Bilous R, Chaturvedi N, Fuller JH, Klein R, Orchard T, Parving HH, Sjølie AK, DIRECT Study

Group. Exposure to candesartan during the first trimester of pregnancy in type 1 diabetes: experience from the placebo-controlled Diabetic Retinopathy Candesartan Trials. Diabetologia 2011; 54(6): 1298–303.

[43] Xu FY, Yang B, Shi D, Li H, Zou Z, Shi XY. Antihypertensive effects and safety of eprosartan: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 2012; 68(2): 195–205.

[44] Forni V, Wuerzner G, Pruijm M, Burnier M. Long-term use and tolerability of irbesartan for control of hypertension. Integr Blood Press Control 2011; 4: 17–26.

[45] ACTIVE I Investigators, Yusuf S, Healey JS, Pogue J, Chrolavicius S, Flather M, Hart RG, Hohnloser SH, Joyner CD, Pfeffer MA, Connolly SJ. Irbesartan in patients with atrial fibrillation. N Engl J Med 2011; 10: 928–38.

[46] Miao Y, Dobre D, Heerspink HJ, Brenner BM, Cooper ME, Parving HH, Shahinfar S, Grobbee D, de Zeeuw D. Increased serum potassium affects renal outcomes: a post hoc analysis of the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) trial. Diabetologia 2011; 54 (1): 44–50.

[47] Lamba G, Palaniswamy C, Singh T, Shah D, Lal S, Vinnakota R, Charrow EJ, Forman L. Psoriasis induced by losartan therapy: a case report and review of the literature. Am J Ther 2011; 18(3): e78–80.

[48] Plumb JO, Stewart C, Eddleston M, de Beer T. Prolonged refractory hypotension following combined amlodipine and losartan ingestion responsive to metaraminol. Case Rep Med 2011; 2011: 283672.

[49] Dessì M, Piras A, Madeddu C, Cadeddu C, Deidda M, Massa E, Antoni G, Mantovani G, Mercuro G. Long-term protective effects of the angiotensin receptor blocker telmisartan on epirubicin-induced inflammation, oxidative stress and myocardial dysfunction. Exp Ther Med 2011; 2(5): 1003–9.

[50] Fogari R, Zoppi A. A drug safety evaluation of valsartan. Expert Opin Drug Saf 2011; 10(2): 295–303.

[51] Wells T, Blumer J, Meyers KE, Neto JP, Meneses R, Litwin M, Van de Walle J, Solar-Yohay S, Shi V, Han G, Valsartan Pediatric Hypertension Study Group. Effectiveness and safety of valsartan in children aged 6 to 16 years with hypertension. J Clin Hypertens (Greenwich) 2011; 13(5): 357–65.

[52] Law M, Morris JK, Jordan R, Wald N. Headaches and the treatment of blood pressure: results from a meta-analysis of 94 randomized placebo-controlled trials with 24,000 participants. Circulation 2005; 112(15): 2301–6.

[53] Birkenfeld AL, Adams F, Schroeder C, Engeli S, Jordan J. Metabolic actions could confound advantageous effects of combined angiotensin II receptor and neprilysin inhibition. Hypertension 2011; 57(2): e4–5.

[54] Fogari R, Zoppi A. New class of agents for treatment of hypertension: focus on direct renin inhibition. Vasc Health Risk Manag 2010; 6: 869–82.

[55] Morganti A, Lonati C. Aliskiren: the first direct renin inhibitor available for clinical use. J Nephrol 2011; 24(5): 541–9.

[56] Rashid HU, Mende C. The role of direct renin inhibition in clinical practice: focus on combination therapy. Am J Cardiovasc Drugs 2011; 11(5): 303–15.

[57] Siragy HM. Rationale for combining a direct renin inhibitor with other renin-angiotensin system blockers. Focus on aliskiren and combinations. Cardiovasc Drugs Ther 2011; 25(1): 87–97.

[58] Chrysant SG, Murray AV, Hoppe UC, Dattani D, Patel S, Ritter S, Zhang J. Long-term safety and efficacy of aliskiren and valsartan combination with or without the addition of HCT in patients with hypertension. Curr Med Res Opin 2010; 26(12): 2841–9.

[59] Persson F, Lewis JB, Lewis EJ, Rossing P, Hollenberg NK, Parving HH, AVOID Study Investigators. Impact of baseline renal function on the efficacy and safety of aliskiren added to losartan in patients with type 2 diabetes and nephropathy. Diabetes Care 2010; 33(11): 2304–9.

[60] Pitt B, Latini R, Maggioni AP, Solomon SD, Smith BA, Wright M,

Prescott MF, McMurray JJ. Neurohumoral effects of aliskiren in patients with symptomatic heart failure receiving a mineralocorticoid receptor antagonist: the Aliskiren Observation of Heart Failure Treatment study. Eur J Heart Fail 2011; 13(7): 755–64.

[61] Sica D, Gradman AH, Lederballe O, Kolloch RE, Zhang J, Keefe DL. Long-term safety and tolerability of the oral direct renin inhibitor aliskiren with optional add-on hydrochlorothiazide in patients with hypertension: a randomized, open-label, parallel-group, multicentre, dose-escalation study with an extension phase. Clin Drug Investig 2011; 31(12): 825–37.

[62] Yamauchi J, Shibagaki Y, Uehara K, Yasuda T, Kimura K. Aliskiren-associated acute kidney injury in a patient with pre-existing chronic kidney disease and dilated cardiomyopathy. Clin Exp Nephrol 2012; 16(2): 333–6.

[63] Kelland EE, McAuley LM, Filler G. Are we ready to use aliskiren in children? Pediatr Nephrol 2011; 26(3): 473–7.

[64] Rebello S, Compain S, Feng A, Hariry S, Dieterich HA, Jarugula V. Effect of cyclosporine on the pharmacokinetics of aliskiren in healthy subjects. J Clin Pharmacol 2011; 51(11): 1549–60.

[65] Tapaninen T, Backman JT, Kurkinen KJ, Neuvonen PJ, Niemi M. Itraconazole, a P-glycoprotein and CYP3A4 inhibitor, markedly raises the plasma concentrations and enhances the renin-inhibiting effect of aliskiren. J Clin Pharmacol 2011; 51(3): 359–67.

[66] Rebello S, Leon S, Hariry S, Dahlke M, Jarugula V. Effect of verapamil on the pharmacokinetics of aliskiren in healthy participants. J Clin Pharmacol 2011; 51 (2): 218–28.

[67] Rebello S, Zhao S, Hariry S, Dahlke M, Alexander N, Vapurcuyan A, Hanna I, Jarugula V. Intestinal OATP1A2 inhibition as a potential mechanism for the effect of grapefruit juice on aliskiren pharmacokinetics in healthy subjects. Eur J Clin Pharmacol 2012; 68(5): 697–708.

[68] Cartin-Ceba R, Swanson K, Iyer V, Wiesner RH, Krowka MJ. Safety and efficacy of ambrisentan for the treatment of portopulmonary hypertension. Chest 2011; 139(1): 109–14.

[69] Judson MA, Highland KB, Kwon S, Donohue JF, Aris R, Craft N, Burt S, Ford HJ. Ambrisentan for sarcoidosis associated pulmonary hypertension. Sarcoidosis Vasc Diffuse Dis 2011; 28(2): 139–45.

[70] Yoshida S, Shirato K, Shimamura R, Nakahara N, Iwase T, Nakajima H. Efficacy, safety, and pharmacokinetics of ambrisentan in Japanese adults with pulmonary arterial hypertension. Curr Med Res Opin 2011; 27(9): 1827–34.

[71] Frampton JE. Ambrisentan. Am J Cardiovasc Drugs 2011; 11(4): 215–26.

[72] Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, Martinez FJ, Nathan SD, Wells AU, Collard HR, Costabel U, Richeldi L, de Andrade J, Khalil N, Morrison LD, Lederer DJ, Shao L, Li X, Pedersen PS, Montgomery AB, Chien JW, O'Riordan TG, ARTEMIS-IPF Investigators. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med 2013; 158 (9): 641–9.

[73] GlaxoSmithKline. Volibris (ambrisentan) must not be used in patients with idiopathic pulmonary fibrosis (IPF). July 9th 2012.

[74] Valerio CJ, Handler CE, Kabunga P, Smith CJ, Denton CP, Coghlan JG. Clinical experience with bosentan and sitaxentan in connective tissue disease-associated pulmonary arterial hypertension. Rheumatology (Oxford) 2010; 49(11): 2147–53.

[75] Hislop AA, Moledina S, Foster H, Schulze-Neick I, Haworth SG. Long-term efficacy of bosentan in treatment of pulmonary arterial hypertension in children. Eur Respir J 2011; 38(1): 70–7.

[76] Monfredi O, Griffiths L, Clarke B, Mahadevan VS. Efficacy and safety of bosentan for pulmonary arterial hypertension in adults with congenital heart disease. Am J Cardiol 2011; 108(10): 1483–8.

[77] Avellana P, Segovia J, Sufrate E, Gómez-Bueno M, García-Cosío Carmena MD, García-Pavía P, Gutiérrez Landaluce C,

Pérez Pereira E, Alonso-Pulpón L. Long-term (5 years) effects of bosentan in patients with pulmonary arterial hypertension. Rev Esp Cardiol 2011; 64(8): 667–73.
[78] Kefford RF, Clingan PR, Brady B, Ballmer A, Morganti A, Hersey P. A randomized, double-blind, placebo-controlled study of high-dose bosentan in patients with stage IV metastatic melanoma receiving first-line dacarbazine chemotherapy. Mol Cancer 2010; 9: 69.
[79] Chinello P, Cicalini S, Cortese A, Cicini MP, Petrosillo N. Bosentan and sildenafil in the treatment of HIV-associated pulmonary hypertension. Infectious Dis Rep 2011; 3: e14.
[80] Eriksson C, Gustavsson A, Kronvall T, Tysk C. Hepatotoxicity by bosentan in a patient with portopulmonary hypertension: a case-report and review of the literature. J Gastrointestin Liver Dis 2011; 20 (1): 77–80.
[81] Grassi G. Selective endothelin receptor blockade in resistant hypertension: results of the DORADO trial. Expert Opin Pharmacother 2011; 12(1): 153–5.
[82] Medicines and Healthcare Products Regulatory Agency. Sitaxentan (Thelin): worldwide withdrawal from the market due to hepatotoxicity. Drug Saf Update 2011; 4 (6): A3.
[83] Lee WT, Kirkham N, Johnson MK, Lordan JL, Fisher AJ, Peacock AJ. Sitaxentan-related acute liver failure in a patient with pulmonary arterial hypertension. Eur Respir J 2011; 37(2): 472–4.
[84] Galiè N, Hoeper MM, Gibbs JS, Simonneau G. Liver toxicity of sitaxentan in pulmonary arterial hypertension. Eur Respir J 2011; 37(2): 475–6.
[85] Cilingiroğlu M, Rahman S, Helmy T, Seshiah P. Spontaneous right coronary artery dissection possibly associated with clonidine transdermal patch. Turk Kardiyol Dern Ars 2011; 39(3): 224–7.
[86] Johnson ML, Visser EJ, Goucke CR. Massive clonidine overdose during refill of an implanted drug delivery device for intrathecal analgesia: a review of inadvertent soft-tissue injection during implantable drug delivery device refills and its management. Pain Med 2011; 12(7): 1032–40.
[87] Folic MM, Jankovic SM, Varjacic MR, Folic MD. Effects of methyldopa and nifedipine on uteroplacental and fetal hemodynamics in gestational hypertension. Hypertens Pregnancy 2012; 31(1): 31–9.
[88] Mortenson JA, Robison JA. Tolazoline-induced apnea in mule deer (*Odocoileus hemionus*). J Zoo Wildl Med 2011; 42(1): 105–7.
[89] Horvath K, Vultur F. Correlation between urological alpha1-AR antagonist medication and changed intraoperative iris behavior. Int Ophthalmol 2011; 31(2): 99–104.
[90] Chatziralli IP, Sergentanis TN. Risk factors for intraoperative floppy iris syndrome: a meta-analysis. Ophthalmology 2011; 118(4): 730–5.
[91] Titos-Arcos JC, Hallal H, Andrade RJ, López Martín A. Lesión hepatocelular recurrente por alfuzosina [Recurrent hepatocellular lesion due to alfuzosin.] Gastroenterol Hepatol 2011; 34(2): 125–7.
[92] Sun GH, Tsui KH, Wu TT, Chang CH, Cheng CL, Schou M. Efficacy and safety of the doxazosin gastrointestinal therapeutic system for the treatment of benign prostate hyperplasia. Kaohsiung J Med Sci 2010; 26(10): 532–9.
[93] Yoshida M, Kudoh J, Homma Y, Kawabe K. Safety and efficacy of silodosin for the treatment of benign prostatic hyperplasia. Clin Interv Aging 2011; 6: 161–72.
[94] Chapple CR, Montorsi F, Tammela TL, Wirth M, Koldewijn E, Fernández Fernández E, European Silodosin Study Group. Silodosin therapy for lower urinary tract symptoms in men with suspected benign prostatic hyperplasia: results of an international, randomized, double-blind, placebo- and active-controlled clinical trial performed in Europe. Eur Urol 2011; 59(3): 342–52.
[95] Ku TK, Naseri A, Han Y, Porco TC, Rutar T. Effect of timing and duration of tamsulosin exposure on complications in resident-performed phacoemulsification. Ophthalmic Surg Lasers Imaging 2011; 42 (5): 416–22.
[96] Abdelghaffar W, Elsebaey A. Prospective evaluation of cataract surgery in female

patients taking tamsulosin. Br J Ophthalmol 2011; 95(5): 749–50.
[97] Spagnul SJ, Cabral PH, Verndl DO, Glina S. Adrenergic α-blockers: an infrequent and overlooked cause of priapism. Int J Impot Res 2011; 23(3): 95–8.
[98] Troost J, Tatami S, Tsuda Y, Mattheus M, Mehlburger L, Wein M, Michel MC. Effects of strong CYP2D6 and 3A4 inhibitors, paroxetine and ketoconazole, on the pharmacokinetics and cardiovascular safety of tamsulosin. Br J Clin Pharmacol 2011; 72(2): 247–56.
[99] Gaponova NI, Abdrakhmanov VR, Baratashvili VL, Tereshchenko SN. [Analysis of efficacy and safety of administration of moxonidine in patients with arterial hypertension and hypertensive crises.] Kardiologiia 2011; 51(6): 91–6.
[100] Demirel F, Unal S, Çetin II, Esen I, Arasli A. Pulmonary hypertension and reopening of the ductus arteriosus in an infant treated with diazoxide. J Pediatr Endocrinol Metab 2011; 24 (7–8): 603–5.
[101] Campbell P, Baker WL, Bendel SD, White WB. Intravenous hydralazine for blood pressure management in the hospitalized patient: its use is often unjustified. J Am Soc Hypertens 2011; 5(6): 473–7.
[102] Richmond BW, Cole MB, Dash A, Eyler A, Boomershine CS. A tale of two rashes. Am J Med 2011; 124(5): 414–7.
[103] Nautiyal A, Wong T, Kumar S, Mukherjee JT, Schick EC. Very large incidental pericardial effusion attributable to minoxidil: resolution without drainage. J Cardiovasc Med (Hagerstown) 2011; 12 (3): 186–8.
[104] Aprahamian A, Escoda S, Patteau G, Merckx A, Chéron G. Intoxication par le minoxidil, principe actif d'une lotion capillaire. À propos d'un cas. [Minoxidil intoxication, the pharmacological agent of a hair lotion.] Arch Pediatr 2011; 18(12): 1302–4.
[105] Garrard A, Wood A, Sollee D, Aaronson P. Refractory hypotension due to Rogaine® (minoxidil) ingestion managed with midodrine. Clin Toxicol (Phila) 2011; 49(10): 907–9.