Lipids, blood pressure, kidney – what was new in 2011?

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Submitted: 11 October 2011
Accepted: 10 December 2011

Arch Med Sci 2011; 7, 6: 1055-1066
DOI: 10.5114/AOMS.2011.26620

Abstract

The year 2011 was very interesting regarding new studies, trials and guidelines in the field of lipidology, hypertensiology and nephrology. Suffice it to mention the new European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines on the management of dyslipidaemias, American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines on hypertension in the elderly, and many important trials presented among others during the American Society of Nephrology (ASN) Annual Congress in Philadelphia and the AHA Annual Congress in Orlando. The paper is an attempt to summarize the most important events and reports in the mentioned areas in the passing year.

Key words: anaemia, blood pressure, dyslipidaemia, hypertension, lipids, renal disease, transplantation.

Lipidology update 2011

Cardiovascular disease (CVD) due to atherosclerosis and thrombosis is the foremost cause of premature mortality and drop in disability-adjusted life years in Europe, and is also increasingly common in developing countries [1, 2]. The main clinical entities are coronary artery disease (CAD), ischaemic stroke, and peripheral arterial disease (PAD) [3]. This year, new joint European Society of Cardiology (ESC)/European Atherosclerosis Society (EAS) guidelines on the management of dyslipidaemias have been issued [4]. The most important and somewhat novel aspects identified by the task force were the following: (1) treatment of dyslipidaemia should not be considered as an isolated process, but rather within the context of integrated prevention of CVD in an individual patient. The SCORE scale is recommended as a basic tool for calculating CV risk; (2) therapeutic objectives: strengthening of strict low-density lipoprotein cholesterol (LDL-C) targets for patients with very high, high, and intermediate risk levels (no longer as an optional criterion) [4-7]; (3) non-pharmacological therapies: the relevance of diet and exercise not just in the reduction of total risk, but also in the specific treatment of dyslipidaemias [4, 8]; (4) lipid-lowering drugs: a logical emphasis on statins as an essential treatment for cardiovascular prevention, and scarce details on fibrates, niacin, and absorption inhibitors; (5) dyslipidaemia treatment in special clinical situations:

the detailed description of targets and prescriptions in several situations and subgroups [4, 9, 10].

The ESC/EAS guidelines were highly anticipated, but there are still many questions remaining [4]. The guidelines do not give the answer how to proceed with patients in many clinical situations, e.g. with high-risk patients and a low level of high-density lipoprotein cholesterol (HDL-C), and they only describe very general conditions, such as patients with metabolic syndrome or acute coronary syndrome [4]. They also do not give detailed recommendations on combined therapy in lipid disorder patients, which seems to be a future method of dyslipidaemia treatment, for example in patients with chronic kidney disease (CKD). The recent Study of Heart and Renal Protection (SHARP) trial with simvastatin and ezetimibe showed 17% reduction in major atherosclerotic events and 15.3% in major vascular events in CKD [4, 11, 12].

The new guidelines continue to recognize that elevated levels of total cholesterol and LDL-C are the most important lipid disorders in terms of prognosis as well as the quantity of available epidemiological, pathological, and therapeutic data that exist [4]. Also, much more attention needs to be paid to changing treatment of patients to achieve target levels. In one of the trials Mark *et al.* reported a higher percentage of 12 317 high-risk patients achieving LDL-C targets when treated by specialists compared with those followed up by GPs (43% vs. 32%, respectively; $p < 0.0001$) [13, 14]. The impact of this effect is likely to increase as more statins (and other lipid-lowering drugs) become generic. The authors also specified that the use of combination therapy (e.g. statin plus ezetimibe) contributed to better goal achievement [13, 14]. This interpretation is in agreement with community-based studies that showed a significantly improved outcome in lipid targets following the addition of ezetimibe to a statin [15-17].

Higher doses of statins in monotherapy represent another therapeutic option, although this may be associated with an increased risk of adverse effects [18, 19]. With regard to safety, the primary document mentions that the majority of statins, with the exception of pravastatin, rosuvastatin, and pitavastatin, are significantly metabolized by cytochrome P450, which could provide an advantage in terms of safety [18-20]. The safety of statins is also independent of the treatment duration [20]. Additionally, statins could be used in patients with renal failure, since these compounds are preferentially eliminated through the hepatic pathway (fluvastatin, atorvastatin, and pitavastatin) [18]. It is, however, worth mentioning that recently, according to the results of the Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) trial, the Food and Drug Administration (FDA) released an alert regarding the increased risk of myopathy and rhabdomyolysis with 80 mg doses of simvastatin [21]. However, the recent studies with other statins (atorvastatin, rosuvastatin) have not given similar results [22].

The recent data have also revealed that statin therapy might be associated with an increased risk of developing diabetes. A meta-analysis of the most major placebo and standard care-controlled statin trials with more than 90,000 participants confirmed that statin therapy was associated with a 9% increased risk of developing diabetes [23]. Newly published data have confirmed a dose-dependent effect, with 12% higher risk of developing diabetes on intensive-dose statin therapy compared with moderate-dose therapy [24]. In this meta-analysis, one additional patient developed diabetes for every three patients protected from a major cardiovascular event [24]. The observation of higher diabetes risk remains unexplained at present, although studies in animal models suggest the possibility of impaired peripheral insulin signalling induced by statins [25]. Cardiovascular benefits of statin therapy clearly outweigh the risk of developing diabetes, but the data suggest the need to make patients aware of this possible risk and to monitor patients for development of diabetes, especially on intensive-dose therapy [4, 26-28]. On the other hand, we urgently need well-designed statin clinical trials with new onset diabetes as a main endpoint, in order to finally answer the question on the increased risk of carbohydrate disturbances as an effect of statin therapy [29].

The current guidelines recommend wide prescription of statins, even the highest allowable or tolerable doses, in order to reach LDL-C goals [4]. For patients with statin intolerance, the recommendation is for bile acid chelating agents or niacin, although this was published before the Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) study was prematurely terminated due to lack of effectiveness of this treatment (extended-release niacin – 500-2000 mg per day) and unexplained increase in ischaemic stroke [30, 31]. Absorption inhibitors are not recommended with much zeal, although they are mentioned in possible association with low doses of statins in patients whose poor tolerance impedes prescribing an adequate statin dose, as well as with bile acid chelating agents or niacin [4].

Therapeutic interventions should be aimed not only at lowering ApoB-containing fractions of lipoproteins, but also at increasing HDL-C, especially when there is a trend to decrease the number of patients with HDL-C above 46 mg/dl (1.2 mmol/l) in women and 40 mg (1.0 mmol/l) in men – 56% to

50.1% when comparing the NATPOL 2002 and 2011 registries respectively [32].

Some of the already used pharmacological agents such as niacin, fibrates and statins present various mechanisms of protection from the deleterious effects of chronic inflammation on HDL functionality. However, a need for a novel therapeutic approach has emerged, in order to prevent or restrain the transformation of native HDL into dysfunctional HDL. Testing new agents which attenuate atherosclerosis in dyslipidaemic patients, such as cholesterylester transfer protein (CETP) inhibitors, rHDL, Apo A-I Milano, and Apo-mimetic peptides, is giving promising results [33-37]. It seems that the year 2011 was especially advantageous for CETP inhibitors. The dal-VESSEL study showed that only 4 weeks of dalcetrapib 600 mg daily caused a significant increase (by 31%) in HDL-C (HDL2-C to a greater extent than HDL3-C) and Apo A-I levels, without increasing blood pressure and without impairing endothelial function [38]. The dal-PLAQUE study additionally showed reduction in vascular inflammation and a decrease in adverse structural vascular changes in subjects receiving dalcetrapib [39].

Still there are no clear data dealing with statin use in elderly patients, particularly those with depression, dementia and multiple falls. Myalgia and myopathy following statin use may be particularly troublesome in that population. Most statin-related muscle symptoms occur in people with some predisposition (e.g. low level of blood vitamin D) and are often related to strenuous exercise. Interference with other drugs (calcium channel blockers, azoles or macrolides) may increase myotoxic effects of statins [35, 36]. Additionally, Newson *et al.* [40] found that higher total cholesterol and non-high-density lipoprotein cholesterol in older persons was associated with a lower risk of non-cardiovascular and total mortality. In part, this was attributable to a lower risk of cancer deaths [40].

We are still waiting for new Adult Treatment Panel (ATP) IV guidelines, which may answer some of the above questions. The publication of the recommendations is expected for public review and comment, with an expected release date in 2012 (probably in the second half).

Hypertension update 2011

According to the *cardiovascular continuum* theory, lipid disorders and hypertension lead to atherosclerosis progression and next to CAD and its complications – acute coronary syndrome, heart failure (HF) and sudden cardiac death [32, 41, 42]. Coronary artery disease is also related to endothelial dysfunction [43, 44]. Over the last years, several studies have suggested that some factors, e.g. endothelin-1, C-reactive protein (CRP), dimethylarginine, haptoglobin polymorphism, transforming growth factor β (TGF-β), heat shock protein 70 (HSP70), plasma nitric oxide (NO) and vascular endothelial growth factor (VEGF), could be markers of risk for endothelial dysfunction and have an impact on long-term prognosis in patients with CAD [45-55]. Some studies showed that proton pump inhibitor based therapy may have beneficial effects in patients with CAD. The 14-day therapy with a double dose of rabeprazole (open-label trial) [56] or omeprazole (randomized, placebo-controlled cross-over trial) [57] may lead to a decrease in the number of total chest pain episodes and in some electrocardiographic signs of myocardial ischaemia in patients with stable angina pectoris and CAD. Another trial showed that treatment with a double dose of omeprazole increases endorphin plasma level in patients with coronary artery disease [58].

The goal of antihypertensive therapy is to abolish the risks associated with blood pressure (BP) elevation without adversely affecting quality of life [59]. Drug selection is based on efficacy in lowering BP and in reducing CV endpoints, including stroke, myocardial infarction, and heart failure [60]. Clinical trials document that achieving BP targets is usually not possible with a single agent [60, 61]. In the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), only 26% of patients achieved goal BP with monotherapy [62]. In the Hypertension Optimal Treatment (HOT) trial, 33% of patients achieved their BP target (diastolic only) with monotherapy, 45% required 2 drugs, and 22% needed ≥ 3 agents [63]. It is recommended to routinely use combination therapy to achieve BP targets, to use only preferred or acceptable 2-drug combinations and to initiate combination therapy in patients who require ≥ 20/10 mmHg reduction to achieve target BP [60].

In October 2009, the European Society of Hypertension (ESH) presented its updated recommendations, which were important in many respects [64, 65]. However, after almost 2 years since the publication, there are still many issues to be solved. Despite continuously accumulating data, many decisions on hypertension management are still made without the support of evidence from the available clinical trials. For example, we still do not know the optimal strategy for dealing with patients with stage 1 hypertension, and there is uncertainty about whether subjects with BP in the range 140-149/90-99 mmHg would benefit from antihypertensive treatment [66-68]. Moreover, data from the available clinical trials do not support the view that lowering BP below 130 mmHg in high-risk patients provides an additional benefit, which might be connected with the J-curve phenomenon, observed particularly in patients with hypertension and diabetes and/or CAD (and probably also with ventricular

dysfunction) [69-71]. Since the publication of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines (2003) [72], there has also been much discussion whether we should treat high-risk patients with high normal BP (with prehypertension), although the current ESH guidelines do not recommend such therapy [64, 73-75].

Hypertension therapy in elderly patients is another important issue [76], which had been controversial until the results of the Hypertension in the Very Elderly Trial (HYVET) were published [77]. Hypertension in elderly people is a major risk factor for coronary events, stroke, heart failure, and peripheral arterial disease [78-81]. Compared with younger patients with hypertension, the prevalence of target organ damage and clinical CVD is significantly higher in the elderly, as is the incidence of new CV events [76]. However, despite this increased risk, elderly patients have the lowest rate of BP control [82, 83]. This has been recently confirmed in the PolSenior registry in patients aged > 65 years, which showed that elevated blood pressure exists in 76% of patients (72% of men and 78% of women), and in only 25% of patients is well controlled [83].

In April 2011, new American College of Cardiology Foundation (ACCF)/American Heart Association (AHA) guidelines on hypertension in the elderly were published [84]. According to them the initial antihypertensive drug therapy should be started at the lowest dose and gradually increased, depending on the BP response to the maximum tolerated dose [84]. If the antihypertensive response to the initial drug is inadequate after reaching the full dose, a second drug from another class should be added, provided the initial drug is tolerated [84, 85]. ACCF/AHA guidelines confirm the current ESH [64] and current NICE recommendations [84] that all main antihypertensive drug classes – diuretics, angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs), and β-blockers – have shown significant benefits in reducing CV outcomes in randomized trials among elderly persons [86-91]. Where possible, a combination therapy should be the method of choice [84, 85].

The current ACCF/AHA recommendations still raise some important questions regarding hypertension treatment in the elderly [84]. It is crucial to finally establish BP values for making the diagnosis of hypertension as well as setting targets for treatment. The most practical definition of hypertension in the elderly should describe a BP level above which medical intervention (lifestyle changes or drugs) might be expected to provide significant clinical benefits. It is also important to identify which drugs will be most effective for reducing CV events [84]. However, especially in these patients, we should be very careful to avoid intensive lowering of BP, as this might be poorly tolerated and might increase CV events – the *J-curve phenomenon* [69]. Probably only the forthcoming studies, including the Systolic Blood Pressure Intervention Trial (SPRINT) [91] and ESH-SCHL-SHOT (Stroke in Hypertension Optimal Treatment trial of the European Society of Hypertension) [69], will provide the data to establish clear guidelines on the optimal target BP level for these patients [93].

According to all the current hypertension guidelines, it is recommended to look for the best diagnostic methods in order to effectively prevent subclinical organ damage (SOD) [64, 84, 85]. Genetic variability and/or some biomarkers can be valuable diagnostic and prognostic tools [93-103]. Although there are numerous studies investigating biomarkers in heart failure (HF), there are relatively few that relate them to HF in hypertensive patients. This is vital as hypertension is considered to be one of the main predictors of HF. Prolonged hypertension has been shown to cause left ventricular (LV) structural remodelling, cardiac function alterations and chronic heart failure (CHF) [104-107]. There are often no signs of CAD on an electrocardiographic stress test with no change in epicardial coronary vessels on coronary angiography [64, 108]. Therefore, it is important to establish a panel of diagnostic tests in patients with hypertension to enable the early detection of abnormalities before the occurrence of symptoms and thus allow the implementation of optimal treatment [64, 84]. Elevations in inflammatory markers, not observed in isolated hypertension, become evident in the presence of target organ damage [109-112]. Raised levels of high-sensitivity CRP (hs-CRP) and myeloperoxidase (MPO) have been suggested as markers of HF in hypertensive patients [113]. Although a lack of significant correlation between log-transformed hs-CRP and MPO was observed, combined analysis of these 2 parameters revealed a 6-fold increased risk of HF ($p < 0.01$) when both markers were elevated [114, 115]. According to the authors, concurrent hs-CRP and MPO measurements may be of distinct and complementary prognostic value in patients with chronic systolic HF [113-115].

Biomarkers, such as natriuretic peptides, have been suggested to be useful in determining the severity of disease and prognosis of clinical outcomes in patients with acute HF [116, 117]. Brain natriuretic peptide (BNP), a neurohormone synthesized in ventricular myocardium, is released into the circulation in response to ventricular dilatation and pressure overload [118, 119]. The plasma level of BNP is considered to be a powerful marker for cardiac dysfunction and a useful prognostic indicator in patients with critical CV diseases [120-122].

It seems that some answers may be provided by the Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 8) and the European Society of Hypertension 2012 guidelines, which are to be released by the end of 2012.

Hypertension and kidney diseases update 2011

Concerning hypertension and kidney diseases there is evidence that a low sodium diet (in patients with proteinuric kidney disease treated with lisinopril) (The HOlland NEphrology Study – HONEST trial) reduced mean arterial blood pressure from 134 mmHg at baseline to 123 mmHg, whereas addition of valsartan to either a regular or low salt diet resulted in a decrease in mean blood pressure by only 2-3 mmHg [123]. Moreover, two meta-analyses presented the data from randomized controlled trials on salt restriction and cardiovascular mortality. Taylor *et al*. [124] analyzed the effect of sodium restriction on the blood pressure status at baseline (normotensive vs hypertensive). They found a tendency to better cardiovascular outcomes when patients were salt-restricted [124]. He *et al*. [125] reported that sodium restriction was associated with significant reduction in cardiovascular events but not in mortality. In most patients with hypertensive nephropathy and a low glomerular filtration rate (GFR), the kidney function progressively declines despite adequate control of the hypertension with angiotensin-converting enzyme inhibition [125]. Mahajan *et al*. [126] found in a 5-year, prospective, randomized, placebo-controlled, and blinded interventional study that daily oral sodium bicarbonate slowed GFR decline in patients with hypertensive nephropathy with reduced but relatively preserved estimated GFR (eGFR) (mean 75 ml/min). The authors concluded that in hypertensive nephropathy, daily sodium bicarbonate was an effective nephroprotective adjunct to blood pressure control with angiotensin-converting enzyme inhibition [126].

There are two major challenges in the treatment of resistant hypertension. In the Rheos Pivotal Trial [127], surgical implantation of a device designed to stimulate the carotid baroreceptors resulted, during a 6-month period, in a non-significant decrease in systolic blood pressure and significant achievement of target systolic blood pressure of 140 mmHg or lower [127]. Other potentially effective therapies in the treatment of resistant hypertension include catheter-based radiofrequency ablation of the renal sympathetic nerves. In the Symplicity-HTN-2 trial it was reported that 6 months after the procedure a significant fall in blood pressure was found in patients with resistant hypertension treated so far with an average of five hypotensives including diuretics [128]. During the American Society of Nephrology Congress, held in Philadelphia during 8-13.11.2011, in the Hot Topics Session, Prof. Gerald Frederic Dibona questioned the long-term efficacy and safety of this procedure (personal communication). Medical evaluation was performed only in 64 patients 12 months after and in 18 patients 24 months after the radiofrequency ablation. The number of antihypertensives remained the same as at the baseline [129].

Nephrology 2011 update

Focal and segmental glomerulosclerosis has become an important lesion underlying the nephrotic syndrome. There are several morphological variants found in light microscopy, but all share podocyte pathology ultrastructurally [130]. Primary focal segmental glomerulosclerosis (FSGS) is one the causes of nephrotic syndrome, and injury to glomerular cells, including podocytes, may be due to a circulating toxin [130-132]. However, Wei *et al*. [131] reported that serum soluble urokinase receptor (suPAR) could be a possible cause of primary FSGS. They found that in 78 patients with FSGS suPAR was significantly higher than in patients with other glomerular disease and healthy volunteers. Moreover, the highest suPAR levels were in pretransplant sera of patients who developed recurrent FSGS after transplantation [131]. The probable mechanism of FSGS by suPAR is the activation of β3 integrin in podocytes. In an animal model the selective expression of suPAR was associated with progressive glomerulopathy with histological changes characteristic of FSGS [129]. In the treatment of steroid-resistant primary FSGS multicenter clinical trial (FSGS-CT) there was no difference between patients treated with mycophenolate mofetil and oral dexamethasone vs. cyclosporine in regard to achieving sustained remission [133]. The limitation of the study is the small sample size: of the projected 500 patients only 138 were randomized. Olson *et al*. [134] found that patients with anti-GBM (anti-glomerular basement membrane) disease may develop low titres of anti-neutrophilic cytoplasmic antibodies (ANCA) years before the clinical symptoms and months prior to synthesis of anti-GBM antibodies. In idiopathic membranous nephropathy the phospholipase A2 receptor was recently identified as a major target antigen [135]. Circulating antibodies against PLA2R were found in 70-80% of patients with idiopathic, but not in secondary membranous nephropathy or other kidney diseases. Beck *et al*. [136] reported that a decline in anti-PLA2R antibodies may predict the clinical response to rituximab treatment.

Lysosomal membrane protein 2 (LAMP2) is a target of ANCA antibodies, in addition to more commonly known targets proteinase 3 and myeloperoxidase. Roth *et al*. [137] however found no

correlation between LAMP2 titres and disease activity. Their data do not support a mechanistic relationship between anti-LAMP-2 antibodies and ANCA glomerulonephritis. During the American Society of Nephrology (ASN) Congress in November 2011, Prof. Glassock insisted on more detailed study in membranoproliferative glomerulonephritis (MPGN), as only 10% are really idiopathic (personal communication). Most cases of MPGN are secondary in the course of immune complex diseases (lupus erythematosus [LE], cryoglobulinaemia, chronic HCV infection, paraproteinaemia), disorders of complement regulation, thrombotic microangiopathy, and paraprotein deposition e.g. monoclonal gammopathy. The most common complement related disease with MPGN is atypical haemolytic uraemic syndrome (HUS), which may be caused by inherited (often familial) polymorphism of factor H – a down-regulating component of the complement system – or acquired antibodies against factor H. Finding a primary cause of MPGN may have a paramount effect on its proper therapy [137, 138].

A novel strain of *Escherichia coli* O104:H4 bacteria caused a serious outbreak of food-borne illness focused in northern Germany in May to June 2011. The illness was characterized by bloody diarrhoea, with a high frequency of serious complications, including HUS, a condition that requires urgent treatment. The outbreak was originally thought to have been caused by an enterohaemorrhagic (EHEC) strain of *E. coli*, but it was later shown to have been caused by an enteroaggregative *E. coli* (EAEC) strain that had acquired the genes to produce Shiga toxins [139]. On 30 June 2011 the German Federal Institute for Risk Assessment announced that seeds of fenugreek imported from Egypt were likely the source of the outbreak [140]. While HUS is usually seen in children under the age of 6 years, the recent outbreak affected mostly (87%) individuals above the age of 20 years [141]. Therapeutic plasma exchange was the mainstay of therapy. Almost at the same time, it was reported that eculizumab, a monoclonal antibody inhibiting the terminal complement cascade and already approved for paroxysmal nocturnal haemoglobinuria, was able to cure the severe neurological symptoms of three children with HUS [142]. Eculizumab, a first-in-class terminal complement inhibitor, specifically targets uncontrolled complement activation, and is also indicated for the treatment of patients with atypical HUS (aHUS) to inhibit complement-mediated thrombotic microangiopathy (TMA), although it is off-label use of this drug (it awaits registration for this indication in Europe, while in September 2011, the FDA granted accelerated approval for use in aHUS). We have to bear in mind that this treatment is associated with enhanced risk of viral infections, and meningococcal vaccination is recommended in patients with complement deficiencies [142, 143].

Recently, Roccatello *et al.* [144] reported that intensive administration of rituximab combined with low doses of intravenous cyclophosphamide and methylprednisolone pulses followed by a rapid tapering of prednisone to 5 mg/day as a sole maintenance therapy was able to induce long-term remissions in patients with severe systemic lupus erythematosus (SLE) and major organ involvement. However, we have to be aware that rituximab is an off-label drug in patients with severe SLE (with or without nephritis) who are intolerant of conventional therapy and need alternative therapeutic options, and look carefully for long-term adverse events occurring mainly months after its administration [144].

Diabetic kidney disease

Despite treatment, diabetic kidney disease is the leading cause of end-stage kidney disease in the developed world [145, 146]. There is an urgent need for new approaches to prevent progression of diabetic kidney disease. On the horizon there has appeared bardoxolone methyl, an oral modulator of Nrf2 (nuclear factor erythroid-2-related factor 2), which with its negative regulator KEAP1 (Kelch-like ECH-associated protein 1) triggers cytoprotective responses affecting over 300 genes encoding detoxification, antioxidant and anti-inflammatory molecules [147]. Expression of Nrf2 is increased in the diabetic kidney in parallel to increased levels of reactive oxygen species and activation of nuclear factor κB. Several putative Nrf2 activators are shown to have renoprotective effects in experimental diabetes such as sulforaphane (found in *Brassica* species, e.g. broccoli), diallyl sulfides (found in garlic, chives, and onion), curcumin (turmeric) and caffeic acid phenethyl ester (many plants and honey) due to the attenuation of vascular damage in hyperglycaemia [147]. A selective activator of Nrf2, bardoxolone methyl, was found to increase estimated GFR by 5-10 ml/min/17.73 m^2 in patients with type 2 diabetes mellitus and impaired kidney function, i.e. eGFR between 20 and 45 ml/min per 1.73 m^2 (BEAM trial) [147]. Bardoxolone methyl increased eGFR within 4 weeks of the treatment and the improvements at each dose (75 mg and 150 mg qd) were sustained during the 1 year of active treatment when compared to placebo. Upon withdrawal of bardoxolone methyl, kidney function returned to the baseline [147]. The proposed mechanisms include Nrf2 activation leading to an antioxidant response via regulatory domains of the target genes. It may also increase the expression of haem oxygenase (known to inhibit directly or indirectly tubuloglomerular feedback by reducing superoxide) in renal tubules. Reduction in superoxide

leads to diminished afferent arteriolar vasoconstriction and subsequently to a rise in GFR. Bardoxolone methyl also affects muscle (muscle cramps are a major side effect); therefore we may also presume that it may affect creatinine metabolism [147]. However, 24-h creatinine clearance increased upon bardoxolone methyl treatment and serum urea was diminished. On the other hand, albuminuria significantly increased in bardoxolone methyl-treated patients. Studies on cystatin C or isotope GFR should be performed to further clarify the issue of the fall in serum creatinine and a rise in eGFR in patients treated with bardoxolone methyl [147]. In 2013 the results of the Bardoxolone methyl EvAluation in patients with Chronic kidney disease and type 2 diabetes: the Occurrence of renal eveNts (BEACON) trial on the effects of bardoxolone methyl in a much larger population of type 2 diabetic patients should be available.

Dialysis

Secondary hyperparathyroidism (SHPT) is a major complication in patients with CKD and intact parathyroid hormone (iPTH) control remains an important therapeutic goal. Cinacalcet, a calcimimetic, is approved for the treatment of SHPT in patients with CKD 5D. Paricalcitol, a selective vitamin D receptor activator, is approved for the treatment of SHPT in patients with CKD 3, 4, and 5 including 5D (dialysis) [148, 149]. During both the ASN Congress and the ERA-EDTA Congress in 2011, results of the IMPACT-SHPT study (international randomized phase IV open-label multi-centre study) comparing the safety and efficacy of paricalcitol and cinacalcet to determine the most effective therapy for the treatment of SHPT in 272 subjects undergoing haemodialysis were presented. The study was divided into an Oral and IV (intravenous) Stratum. Patients received either paricalcitol (initial dose of 0.07 µg/kg in the IV Stratum and PTH/80 in the Oral Stratum) and additive cinacalcet for hypercalcaemia or cinacalcet (30 mg initial dose) plus low-dose vitamin D for 28 weeks [150]. Overall, during 21-28 weeks of the treatment, reduction of ≥ 30% and ≥ 50% in baseline iPTH was achieved in 78% and 65% of subjects treated with paricalcitol as compared with 50% and 36% of subjects receiving cinacalcet-based treatment. However, in the IV stratum, paricalcitol was superior to cinacalcet in achieving primary efficacy, with a mean iPTH value of 150-300 pg/ml during the evaluation period (paricalcitol = 57.7% and cinacalcet = 32.7%; $p = 0.016$) [150]. In the oral stratum, paricalcitol and cinacalcet were similarly effective. The proportion of hypercalcaemia (Ca > 10.5 mg/dl) in the paricalcitol group was low (4 out of 69) (only in IV stratum) whereas a higher proportion in the cinacalcet group (27 of 59) experienced hypocalcaemia (Ca < 8.4 mg/dl) [151]. Additionally, total SHPT medication costs were 40% lower in the paricalcitol arm compared with the cinacalcet arm. However, the costs were calculated based on the American wholesale pricing (with various cinacalcet and vitamin D preparations and IV paricalcitol preparations); therefore, this analysis must be regarded as preliminary and should not be extrapolated to the European market [151].

On the other hand, data from the ADVANCE (A randomiseD VAscular calcificatioN study to evaluate the effects of CinacalcEt) study (prospective, randomized, controlled trial comparing the progression of vascular and cardiac valve calcification in 360 prevalent adult haemodialysis patients with secondary hyperparathyroidism treated with either cinacalcet plus low-dose vitamin D sterols or flexible doses of vitamin D sterols alone) were also published in 2011. Raggi *et al.* [152] demonstrated that 91% of the patients studied had calcification of the thoracic aorta, 50% had mitral valve calcification, and 46% had aortic valve calcification at baseline. The estimated rate of progression of calcifications was 14.3% lower in the cinacalcet plus low-dose vitamin D group (95% CI: –23.1%, –4.5%) ($p = 0.006$) [152]. Using Agatston scores, the percent change in these scores for the thoracic aorta, the aortic and mitral valve were nominally less in the cinacalcet plus low-dose vitamin D group than in the flexible vitamin D group; however, using volume scores the differences between groups were significant at the aortic valve. The authors suggested that cinacalcet plus low-dose vitamin D sterols may attenuate vascular and cardiac valve calcification in patients on haemodialysis with moderate to severe SHPT [152]. The results from the ongoing EVOLVE (Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events) study [153], designed to determine whether cinacalcet can reduce the exceptionally high rates of mortality and cardiovascular events among patients on haemodialysis, are eagerly awaited [153].

After the publication of the Trial to Reduce Cardiovascular Events With Aranesp Therapy (TREAT) trial [154] the US Food and Drug Administration (FDA) modified its indications for the treatment of renal anaemia with erythropoietin stimulating agents (ESA) [155]. According to the revised indication, ESA therapy should be considered when the haemoglobin level is less than 10 g/dl in CKD and dialysed patients. Erythropoietin stimulating agents dose should be reduced or ESA should be withdrawn when haemoglobin exceeds 10 g/dl in CKD patients and approaches or exceeds 11 g/dl in dialysed patients [155-158]. During ASN Prof. Parfrey presented new guidelines on anaemia treatment; however, it is anticipated that these guidelines will be published in early 2012 (KDIGO Clinical

Practice Guideline on Anemia in CKD, chaired by Drs. John McMurray and Patrick Parfrey).

According to Foley *et al.* [159], patients haemodialysed thrice weekly are more likely to die on the day following the long interval (over a weekend) relative to other days. These data were based on the retrospective analysis of the End Stage Renal Disease Clinical Performance Measures Project, involving 32,065 haemodialysed patients [159]. In the secondary analysis of the Hemodialysis (HEMO) study (1426 patients) it has been shown that hypotensive episodes during a haemodialysis session were associated with increased risk of arteriovenous fistula thrombosis [160].

Transplantation

Despite use of new immunosuppressive regimens, e.g. with belatacept, no milestone in graft survival or patient survival was reported [161-165]. Montgomery *et al.* [166] reported that a desensitization protocol (for patients with preformed HLA antibodies) with intravenous immunoglobulin (IVIG) combined with plasmapheresis improved survival in long-term follow-up (at 3, 5 and 8 years) when compared with dialysed patients on the waiting list or transplanted with an HLA-compatible kidney [166].

Acknowledgments

Doctors Barylski and Malyszko contributed equally to this review.

References

1. Allender S, Scarborough P, Peto V, et al. European cardiovascular disease statistics, 2008 ed. European Heart Network 2008.
2. Simeunovic S, Milincic Z, Nikolic D, et al. Physical activity evaluation in Yugoslav Study of the Precursors of Atherosclerosis in School Children – YUSAD study. Arch Med Sci 2010; 6: 874-8.
3. Goch A, Banach M, Mikhailidis DP, Rysz J, Goch JH. Endothelial dysfunction in patients with noncomplicated and complicated hypertension. Clin Exp Hypertens 2009; 31: 20-30.
4. The Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). ESC/EAS Guidelines for the managementof dyslipidaemias. Eur Heart J 2011; 32: 1769-818.
5. Kannam H, Aronow WS, Chilappa K, et al. Association of the QRS duration on the resting electrocardiogram with the severity of coronary artery disease in 2,196 patients undergoing coronary angiography for suspected coronary artery disease. Arch Med Sci 2009; 5: 163-5.
6. Goch A, Misiewicz P, Rysz J, Banach M. The clinical manifestation of myocardial infarction in elderly patients. Clin Cardiol 2009; 32: E46-51.
7. Rutter MK, Nesto RW. Blood pressure, lipids and glucose in type 2 diabetes: how low should we go? Re-discovering personalized care. Eur Heart J 2011; 32: 2247-55.
8. Rabiei K, Kelishadi R, Sarrafzadegan N, Sadri G, Amani A. Short-term results of community-based interventions for improving physical activity: Isfahan Healthy Heart Programme. Arch Med Sci 2010; 6: 32-9.
9. Bielecka-Dabrowa A, Mikhailidis DP, Hannam S, Aronow WS, Rysz J, Banach M. Statins and dilated cardiomyopathy: do we have enough data? Expert Opin Investig Drugs 2011; 20: 315-23.
10. Xu M, Yuan G, Wei F. Effect of atorvastatin in patients with chronic heart failure – insights from randomized clinical trials. Arch Med Sci 2010; 6: 866-73.
11. Rysz J, Aronow WS, Stolarek RS, Hannam S, Mikhailidis DP, Banach M. Nephroprotective and clinical potential of statins in dialyzed patients. Expert Opin Ther Targets 2009; 13: 541-50.
12. Baigent C, Landray MJ, Reith C, et al. SHARP Investigators. The effects of lowering LDL cholesterol with simvastatin plus ezetimibe in patients with chronic kidney disease (Study of Heart and Renal Protection): a randomised placebo-controlled trial. Lancet 2011; 377: 2181-92.
13. Mark L, Paragh G, Karadi I, et al. Changes in attaining lipid goals by general practitioners and specialists in patients at high cardiovascular risk in Hungary between 2004-2008. Arch Med Sci 2010; 6: 695-700.
14. Katsiki N, Mikhailidis DP, Athyros VG, Hatzitolios AI, Karagiannis A, Banach M. Are we getting to lipid targets in real life? Arch Med Sci 2010; 6: 639-41.
15. Fras Z, Mikhailidis DP. Statin plus ezetimibe treatment in clinical practice: the SI-SPECT (Slovenia (SI) Statin Plus Ezetimibe in Cholesterol Treatment) monitoring of clinical practice study. Curr Med Res Opin 2008; 24: 2467-76.
16. Migdalis I, Efthimiadis A, Pappas S, et al. Clinical experience with ezetimibe/simvastatin in a Mediterranean population. Curr Med Res Opin 2009; 25: 2571-6.
17. Angelopoulos J, Krassakopoulos N, Nathanson R, Boukas S, Sampalis JS. Co-administration of ezetimibe and a statin in management of dyslipidemias: a meta-analysis of clinical trials. Arch Med Sci 2009; 5: 347-63.
18. Kiortsis DN, Filippatos TD, Mikhailidis DP, et al. Statin-associated adverse effects beyond muscle and liver toxicity. Atherosclerosis 2007; 195: 7-16.
19. Woźniak B, Woźniak A, Drewa G, Mila-Kierzenkowska C, Ślusarz R. The effect of treatment on lipid peroxidation in patients with subarachnoid haemorrhage. Arch Med Sci 2009; 5: 394-400.
20. Heart Protection Study Collaborative Group. Bulbulia R, Bowman L, Wallendszus, et al. Effects on 11-year mortality and morbidity of lowering LDL cholesterol with simvastatin for about 5 years in 20?536 high-risk individuals: a randomised controlled trial. Lancet 2011; 378: 2013-20.
21. The SEARCH Collaborative Group. SLCO1B1 variants and statin-induced myopathy a genomewide study. N Engl J Med 2008; 359: 789-99.
22. Nicholls SJ, Ballantyne CM, Barter PJ, et al. Effect of two intensive statin regimens on progression of coronary disease. N Engl J Med 2011; 365: 2078-87.
23. Sattar N, Preiss D, Murray HM, et al. Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 2010; 375: 735-42.
24. Preiss D, Seshasai SR, Welsh P, et al. Risk of incident diabetes with intensive-dose compared with moderate-dose statin therapy: a meta-analysis. JAMA 2011; 305: 2556-64.
25. Ravipati G, Aronow WS, Kumbar S, et al. Patients with diabetes mellitus with ischemic stroke have a higher hemoglobin A1c level and a higher serum low-density lipoprotein cholesterol level than diabetics without ischemic stroke. Arch Med Sci 2009; 5: 391-3.

26. Preiss D, Sattar N. Statins and the risk of new-onset diabetes: a review of recent evidence. Curr Opin Lipidol 2011; 22: 460-6.
27. Grycewicz J, Scibor Z, Cwikla JB, Lewinski A, Cypryk K. Recurrent hypoglycaemia in a type 2 diabetes patient – diagnostic difficulties. Arch Med Sci 2010; 6: 126-9.
28. Fawaz L, Elwan AE, Kamel YH, et al. Value of C-reactive protein and IL-6 measurements in type 1 diabetes mellitus. Arch Med Sci 2009; 5: 383-90.
29. McEvoy JW. Statin therapy dose and risk of new-onset diabetes. JAMA 2011; 306: 1325-6.
30. AIM-HIGH Investigators. The role of niacin in raising high-density lipoprotein cholesterol to reduce cardiovascular events in patients with atherosclerotic cardiovascular disease and optimally treated low-density lipoprotein cholesterol: baseline characteristics of study participants. The Atherothrombosis Intervention in Metabolic syndrome with low HDL/high triglycerides: impact on Global Health outcomes (AIM-HIGH) trial. Am Heart J 2011; 16: 538-43.
31. Wise J. Trial of niacin alongside statin is stopped early. BMJ 2011; 342: d3400.
32. Banach M, Davidson M, Toth PO. Polish Lipid Association – a strong response to the problem of lipid disorders in Poland, Central and Eastern Europe. J Clin Lipidol 2011 (in press).
33. Delavari A, Kelishadi R, Forouzanfar MH, Safaei A, Birjandi F, Alikhani S. The first cut-off points for generalized and abdominal obesity in predicting lipid disorders in a nationally representative population in the Middle East: The National Survey of Risk Factors for Non-Communicable Diseases of Iran. Arch Med Sci 2009; 5: 542-9.
34. Sadeghi-Hashjin G, Abuhosseini M, Asri-Rezaei S. Role of nitric oxide in the plasma lipid profile in the rabbits. Arch Med Sci 2009; 5: 308-12.
35. Bielecka-Dąbrowa A, Hannam S, Rysz J, Banach M. Malignancy-associated dyslipidemia. Open Cardiovasc Med J 2011; 5: 35-40.
36. Gordon L, Ragoobirsingh D, Morrison E, McGrowder D, Choo-Kang E, Martorell E. Dyslipidaemia in hypertensive obese type 2 diabetic patients in Jamaica. Arch Med Sci 2010; 6: 701-8.
37. Haleagrahara N, Yee TM, Chakravarthi S, Lee N. Protective effect of N-acetylcysteine on cyclosporine A-induced changes in lipid hydroperoxide levels and renal dysfunction in rats. Arch Med Sci 2009; 5: 16-22.
38. Lusher TF, et al. Presented at the European Society of Cardiology Congress 2011, August 28, 2011, Paris, France.
39. Fayad ZA, Mani V, Woodward M, et al. Safety and efficacy of dalcetrapib on atherosclerotic disease using novel non-invasive multimodality imaging (dal-PLAQUE): a randomised clinical trial. Lancet 2011; 378: 1547-59.
40. Newson RS, Felix JF, Herringa J, et al. Association between serum cholesterol and non-cardiovascular mortality in older age. J Am Geriatr Soc 2011; 59: 1779-85.
41. Dzau V, Braunwald E. Resolved and unresolved issues in the prevention and treatment of coronary artery disease: a workshop consensus statement. Am Heart J 1991; 121: 1244-63.
42. Banach M, Mikhailidis DP, Kjeldsen SE, Rysz J. Time for new indications for statins? Med Sci Monit 2009; 15: MS1-5.
43. Barylski M, Mikhailidis DP, Ciebiada M, Rysz J, Banach M. Gender differences in the treatment of ischemic heart disease. Curr Pharm Des 2011; 17: 1059-69.
44. Luzak B, Golanski J, Rozalski M, Krajewska U, Olas B, Watala C. Extract from Aronia melanocarpa fruits potentiates the inhibition of platelet aggregation in the presence of endothelial cells. Arch Med Sci 2010; 6: 141-4.
45. Catakoglu AB, Aytekin V, Demiroglu C, Aytekin S. The interaction between endothelin-1 and C-reactive protein and their impact on long-term prognosis after percutaneous coronary interventions. Arch Med Sci 2009; 5: 38-44.
46. Khosravi A, Kelishadi R, Poormoghadas M, et al. Preprocedural C-reactive protein predictive value in angiographic in-stent restenosis after coronary stent placement in patients with stable angina. Arch Med Sci 2009; 5: 166-71.
47. Kulach A, Dabek J, Wilczok T, Gasior Z. Changes in transforming growth factor beta; and its receptors' mRNA expression in monocytes from patients with acute coronary syndromes. Arch Med Sci 2010; 6: 526-32.
48. Bielecka-Dabrowa A, Barylski M, Mikhailidis DP, Rysz J, Banach M. HSP 70 and atherosclerosis-protector or activator? Expert Opin Ther Targets 2009; 13: 307-17.
49. Aktoz M, Aktoz T, Tatli E, et al. Asymmetrical dimethylarginine and severity of erectile dysfunction and their impact on cardiovascular events in patients with acute coronary syndrome. Arch Med Sci 2010; 6: 168-75.
50. Alegranci P, de Mattos LC, de Godoy MF, Moreira HW. Haptoglobin polymorphism correlated with coronary artery disease. Arch Med Sci 2009; 5: 32-7.
51. Barylski M, Kowalczyk E, Banach M, et al. Plasma total antioxidant activity in comparison with plasma NO and VEGF levels in patients with metabolic syndrome. Angiology 2009; 60: 87-92.
52. Vulic D, Loncar S, Krneta M, et al. Risk factor control and adherence to treatment in patients with coronary heart disease in the Republic of Srpska, Bosnia and Herzegovina in 2005-2006. Arch Med Sci 2010; 6: 270-5.
53. Diakou M, Miltiadous G, Xenophontos S, et al. Characterization of low density lipoprotein receptor (LDLR) gene mutations in Albania. Arch Med Sci 2010; 6: 198-200.
54. Pavlidis AN, Kolovou GD, Anagnostopoulou KK, Petrou PC, Cokkinos DV. Postprandial metabolic heterogeneity in men with primary dyslipidaemia. Arch Med Sci 2010; 6: 879-86.
55. Wainwright G, Mascitelli L, Goldstein MR. Cholesterol-lowering therapy and cell membranes. Stable plaque at the expense of unstable membranes? Arch Med Sci 2009; 5: 289-95.
56. Świątkowski M, Budzyński J, Kłopocka M, et al. Suppression of gastric acid production may improve the course of angina pectoris and the results of treadmill stress test in patients with coronary artery disease. Med Sci Monit 2004; 10: CR524-9.
57. Budzyński J, Kłopocka M, Pulkowski G, et al. The effect of double dose of omeprazole on the course of angina pectoris and treadmill stress test in patients with coronary artery disease – a randomised, double-blind, placebo controlled, crossover trial. Int J Cardiol 2008; 127: 233-9.
58. Budzyński J, Pulkowski G, Kłopocka M, et al. Treatment with double dose of omeprazole increases -endorphin plasma level in patients with coronary artery disease. Arch Med Sci 2010; 6: 201-7.
59. Ramezani MA, Dastanpour M, Eshaghi SR, et al. Determinants of awareness, treatment and control of hypertension in Isfahan, Central Iran. Arch Med Sci 2009; 5: 523-30.
60. Gradman AH, Basile JN, Carter BL, Bakris GL; American Society of Hypertension Writing Group. Combination therapy in hypertension. J Clin Hypertens (Greenwich) 2011; 13: 146-54.
61. Bielecka-Dabrowa A, Aronow WS, Rysz J, Banach M. The rise and fall of hypertension: lessons learned from Eastern Europe. Curr Cardiovasc Risk Rep 2011; 5: 174-9.

62. Collaborative Research Group. Major outcomes in high risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: the Antihypertensive and Lipid-lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA 2002; 288: 2981-97.
63. Hansson L, Zanchetti A, Carruthers SG, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet 1998; 351: 1755-62.
64. Mancia G, Laurent S, Agabiti-Rosei E, et al.; European Society of Hypertension. Reappraisal of European guidelines on hypertension management: a European Society of Hypertension Task Force document. J Hypertens 2009; 27: 2121-58.
65. Banach M, Aronow WS. Should we have any doubts about hypertension therapy in elderly patients? Pol Arch Med Wewn 2011; 121: 253-8.
66. Banach M, Rysz J. Current problems in hypertension and nephrology. Expert Opin Pharmacother 2010; 11: 2575-8.
67. Banach M, Kjeldsen SE, Narkiewicz K. Controversies in hypertension treatment. Curr Vasc Pharmacol 2010; 8: 731-2.
68. Symonides B, Jedrusik P, Artyszuk L, Grybos A, Dzilinski P, Gaciong Z. Different diagnostic criteria significantly affect the rates of hypertension in 18-year-old high school students. Arch Med Sci 2010; 6: 689-94.
69. Banach M, Michalska M, Kjeldsen SE, et al. What should be the optimal levels of blood pressure: does the J?curve phenomenon really exist? Expert Opin Pharmacother 2011; 12: 1835-44.
70. Banach M, Bhatia V, Feller MA, et al. Relation of baseline systolic blood pressure and long-term outcomes in ambulatory patients with chronic mild to moderate heart failure. Am J Cardiol 2011; 107: 1208-14.
71. Aronow WS. Commentary on implications of new hypertension guidelines in the United States. Hypertension 2011; 58: 347-8.
72. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure. The JNC 7 Report. JAMA 2003; 289: 2560-72.
73. Sethi A, Arora RR. Ambulatory blood pressure as a predictor of cardiovascular risk. Arch Med Sci 2009; 5: 3-9.
74. Shah T, Aronow WS, Peterson SJ, Goldwag D. Diagnosis, treatment, and referral of hypertension or prehypertension in an emergency department after an educational program: preliminary results. J Clin Hypertens (Greenwich) 2011; 13: 413-5.
75. Selassie A, Wagner CS, Laken ML, Ferguson ML, Ferdinand KC, Egan BM. Progression is accelerated from prehypertension to hypertension in blacks. Hypertension 2011; 58: 579-87.
76. Aronow WS. Why and how we should treat elderly patients with hypertension? Curr Vasc Pharmacol 2010; 8: 780-7.
77. Beckett NS, Peters R, Fletcher AE, et al. Treatment of hypertension in patients 80 years of age or older. N Eng J Med 2008; 358: 1887-98.
78. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics – 2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009; 119: e21-181.
79. Amin H, Aronow WS, Lleva P, et al. Prevalence of transthoracic echocardiographic abnormalities in patients with ischemic stroke, intracerebral hemorrhage, and subarachnoid hemorrhage. Arch Med Sci 2010; 6: 40-2.
80. Aronow WS, Ahmed MI, Ekundayo OJ, et al. A propensity-matched study of the association of peripheral arterial disease with cardiovascular outcomesin community-dwelling older adults. Am J Cardiol 2009; 103: 130-5.
81. Catakoglu AB, Aytekin S, Celebi H, et al. The influence of aspirin resistance on non-fatal coronary events following percutaneous coronary interventions. Arch Med Sci 2009; 5: 531-8.
82. Baghaei A, Sarrafzadegan N, Rabiei K, et al. How effective are strategies for non-communicable disease prevention and control in a high risk population in a developing country? Isfahan Healthy Heart Programme. Arch Med Sci 2010; 6: 24-31.
83. Bledowski P, Mossakowska M, Chudek J, et al. Medical, psychological and socioeconomic aspects of aging in Poland Assumptions and objectives of the PolSenior project. Exp Gerontol 2011; 46: 1003-9.
84. Aronow WS, Fleg JL, Pepine CJ, et al.; ACCF Task Force. ACCF/AHA 2011 expert consensus document on hypertension in the elderly: a report of the American College of Cardiology Foundation Task Force on Clinical Expert Consensus Documents. Circulation 2011; 123: 2434-506.
85. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; Guideline Development Group. Management of hypertension: summary of NICE guidance. BMJ 2011; 343: d4891.
86. Lubas A, Zelichowski G, Prochnicka A, et al. Renal vascular response to angiotensin II inhibition in intensive antihypertensive treatment of essential hypertension. Arch Med Sci 2010; 6: 533-8.
87. Bielecka-Dabrowa A, Aronow WS, Rysz J, Banach M. Current place of beta-blockers in the treatment of hypertension. Curr Vasc Pharmacol 2010; 8: 733-41.
88. Piotrowski G, Szymański P, Banach M, et al. Left atrial and left atrial appendage systolic function in patients with post-myocardial distal blocks. Arch Med Sci 2010; 6: 892-9.
89. Stepień M, Banach M, Jankowski P, Rysz J. Clinical implications of non-invasive measurement of central aortic blood pressure. Curr Vasc Pharmacol 2010; 8: 747-52.
90. Fleg JL, Aronow WS, Frishman WH. Cardiovascular drug therapy in the elderly: benefits and challenges. Nat Rev Cardiol 2011; 8: 13-28.
91. Bartnicki P, Majewska E, Wilk R, Baj Z, Rysz J. Captopril and losartan modify mitogen-induced proliferative response and expression of some differentiation antigents on peripheral blood mononuclear cells in chronic uraemic patients. Arch Med Sci 2009; 5: 401-7.
92. SPRINT trial. Clinicaltrials.gov: http://www.clinicaltrials.gov/ct2/show/NCT01 206 062. Accessed June 17, 2011.
93. Ogihara T, Saruta T, Rakugi H, et al.; Valsartan in Elderly Isolated Systolic Hypertension Study Group. Target blood pressure for treatment of isolated systolic hypertension in the elderly: valsartan in elderly isolated systolic hypertension study. Hypertension 2010; 56: 196-202.
94. Sakowicz A, Fendler W, Lelonek M, Pietrucha T. Genetic variability and the risk of myocardial infarction in Poles under 45 years of age. Arch Med Sci 2010; 6: 160-7.
95. Dabek J, Wilczok J, Kulach A, Gasior Z. Altered transcriptional activity of gene encoding GAPDH in peripheral blood mononuclear cells from patients with cardiac syndrome X – an important part in pathology of microvascular angina? Arch Med Sci 2010; 6: 709-12.
96. Shanker J, Kakkar VV. Role of periodontal infection in cardiovascular disease: a current perspective. Arch Med Sci 2009; 5: 125-34.

97. Olsen MH, Wachtell K, Ibsen H, et al. Changes in subclinical organ damage vs. in Framingham risk score for assessing cardiovascular risk reduction during continued antihypertensive treatment: a LIFE substudy. J Hypertens 2011; 29: 997-1004.
98. Kędziora-Kornatowska K, Czuczejko J, Motyl J, et al. Effects of coenzyme Q10 supplementation on activities of selected antioxidative enzymes and lipid peroxidation in hypertensive patients treated with indapamide. A pilot study. Arch Med Sci 2010; 6: 513-8.
99. Mantione KJ, Kream RM, Stefano GB. Catechol-O-methyltransferase: potential relationship to idiopathic hypertension. Arch Med Sci 2010; 6: 291-5.
100. Piotrowski G, Banach M, Gerdts, et al. Left atrial size in hypertension and stroke. J Hypertens 2011; 29: 1988-93.
101. Cicero AF, Ertek S. Preclinical and clinical evidence of nephro- and cardiovascular protective effects of glycosaminoglycans. Arch Med Sci 2010; 6: 469-77.
102. Matusik E, Wajgt A, Janowska J, et al. Cell adhesion molecular markers in ischaemic stroke patients: correlation with clinical outcome and comparison with primary autoimmune disease. Arch Med Sci 2009; 5: 182-9.
103. Natale F, Aronne L, Russo MG, Calabrí R. Ambulatory arterial stiffness index: a marker of subclinical organ damage in treated and untreated dipper hypertensive patients. Hypertens Res 2011; 34: 161.
104. Levy D, Larson MG, Vasan RS, Kannel WB, Ho KKL. The progression from hypertension to congestive heart failure. JAMA 1996; 275: 1557-62.
105. Kenchaiah S, Pfeffer MA. Cardiac remodeling in systemic hypertension. Med Clin North Am 2004; 88: 115-30.
106. Ahmed SH, Clark LL, Pennington WR, et al. Matrix metalloproteinases/tissue inhibitors of metalloproteinases: relationship between changes in proteolytic determinants of matrix composition and structural, functional, and clinical manifestations of hypertensive heart disease. Circulation 2006; 113: 2089-96.
107. Bielecka-Dabrowa A, Rysz J, Mikhailidis DP, Banach M. What is the risk of hyperkalaemia in heart failure? Expert Opin Pharmacother 2011; 12: 2329-38.
108. Karasek D, Sinkiewicz W, Blazejewski J. Relationship between B-type natriuretic peptide serum level, echocardiographic TEI index and the degree of diastolic dysfunction in patients with heart failure with preserved systolic function. Arch Med Sci 2011; 7: 449-56.
109. Navarro-Gonzalez JF, Mora C, Muros M, Jarque A, Herrera H, Garcia J. Association of tumor necrosis factor-alpha with early target organ damage in newly diagnosed patients with essential hypertension. J Hypertens 2008; 26: 2168-75.
110. Mujib M, Desai R, Levitan EB, et al. Prospective population studies of incident heart failure without data on baseline left ventricular ejection fraction. Arch Med Sci 2010; 6: 686-8.
111. Collier P, Watson CJ, Voon V, et al. Can emerging biomarkers of myocardial remodelling identify asymptomatic hypertensive patients at risk for diastolic dysfunction and diastolic heart failure? Eur J Heart Fail 2011; 13: 1087-95.
112. Tang WH, Shrestha K, Troughton RW, Borowski AG, Klein AL. Integrating plasma high-sensitivity C-reactive protein and myeloperoxidase for risk prediction in chronic systolic heart failure. Congest Heart Fail 2011; 17: 105-9.
113. Tatli E, Aktoz M, Altun A. Do plasma leptin levels predict diastolic dysfunction in patients with hypertension? Arch Med Sci 2009; 5: 342-6.
114. Malyszko J, Zbroch E, Malyszko J, Mysliwiec M, Iaina A. The cardio-renal-anaemia syndrome predicts survival in peritoneally dialyzed patients. Arch Med Sci 2010; 6: 539-544.
115. Chatterjee M, Saluja R, Tewari S, Barthwal MK, Goel SK, Dikshit M. Augmented nitric oxide generation in neutrophils: oxidative and pro-inflammatory implications in hypertension. Free Radic Res 2009; 43: 1195-204.
116. Núñez J, Núñez E, Robles R, et al. Prognostic value of brain natriuretic peptide in acute heart failure: mortality and hospital readmission. Rev Esp Cardiol 2008; 61: 1332-7.
117. Fonarow GC, Peacock WF, Phillips CO, Givertz MM, Lopatin M; ADHERE Scientific Advisory Committee, Investigators. Admission B-type natriuretic peptide levels and in-hospital mortality in acute decompensated heart failure. J Am Coll Cardiol 2007; 49: 1943-50.
118. Levin ER, Gardner DG, Samson WK. Natriuretic peptides. N Engl J Med 1998; 339: 321-8.
119. Trojnarska O, Gwizdala A, Katarzynski S, et al. Evaluation of exercise capacity with cardiopulmonary exercise testing and BNP levels in adult patients with single or systemic right ventricles. Arch Med Sci 2010; 6: 192-7.
120. Suzuki M, Hamada M, Yamamoto K, Kazatani Y, Hiwada K. Brain natriuretic peptide as a risk marker for incident hypertensive cardiovascular events. Hypertens Res 2002; 25: 669-76.
121. Baghdady Y, Kamel Y, Elwan A. N-Terminal pro-Brain Natriuretic Peptide in decompansated ventricular septal defect. Arch Med Sci 2009; 5: 376-82.
122. Irzmański R, Banach M, Piechota M, et al. Atrial and brain natriuretic peptide and endothelin-1 concentration in patients with idiopathic arterial hypertension: the dependence on the selected morphological parameters. Clin Exp Hypertens 2007; 29: 149-64.
123. Slagman MC, Waanders F, Hemmelder MH, et al. Moderate dietary sodium restriction added to angiotensin converting enzyme inhibition compared with dual blockade in lowering proteinuria and blood pressure: randomised controlled trial. BMJ 2011; 343: d4366.
124. Taylor RS, Ashton KE, Moxham T, et al. Reduced dietary salt for the prevention of cardiovascular disease: a meta-analysis of randomized controlled trials (Cochrane review). Am J Hypertens 2011; 24: 843.
125. He FJ, MacGregor GA. Salt reduction lowers cardiovascular risk: meta-analysis of outcome trials. Lancet 2011; 378: 380.
126. Mahajan A, Simoni J, Sheather SJ, et al. Daily oral sodium bicarbonate preserves glomerular filtration rate by slowing its decline in early hypertensive nephropathy. Kidney Int 2010; 78: 303-9.
127. Bisognano JD, Bakris G, Nadim MK, et al. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. J Am Coll Cardiol 2011; 58: 765.
128. Esler MD, Krum H, Sobotka PA, Schlaich MP, Schmieder RE, Böhm M. Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial. Symplicity HTN-2 Investigators. Lancet 2010; 376: 1903-9.
129. Symplicity HTN-1 Investigators. Catheter-based renal sympathetic denervation for resistant hypertension: durability of blood pressure reduction out to 24 months. Hypertension 2011; 57: 911-7.
130. Shouman M, Abdallah N, El Tablawy N, Rashed L. Biochemical markers of endothelial dysfunction in pediatric nephrotic syndrome. Arch Med Sci 2009; 5: 415-21.

131. Wei C, El Hindi S, Li J, et al. Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. Nat Med 2011; 17: 952.
132. El-Ters M, Muthyala U, Philipneri MD, Hussein FA, Lentine KL. Immune-complex deposits in "pauci-immune" glomerulonephritis: a case report and brief review of recent literature. Arch Med Sci 2010; 6: 633-7.
133. Gipson DS, Trachtman H, Kaskel FJ, et al. Clinical trial of focal segmental glomerulosclerosis in children and young adults. Kidney Int 2011; 80: 868.
134. Olson SW, Arbogast CB, Baker TP, et al. Asymptomatic autoantibodies associate with future anti-glomerular basement membrane disease. J Am Soc Nephrol 2011; 22: 1946.
135. Beck LH Jr, Salant DJ. Membranous nephropathy: recent travels and new roads ahead. Kidney Int 2010; 77: 765-70.
136. Beck LH Jr, Fervenza FC, Beck DM, et al. Rituximab-induced depletion of anti-PLA2R autoantibodies predicts response in membranous nephropathy. J Am Soc Nephrol 2011; 22: 1543.
137. Roth AJ, Brown MC, Smith RN, et al. Anti-LAMP-2 Antibodies Are Not Prevalent in Patients With Antineutrophil Cytoplasmic Autoantibody Glomerulonephritis. J Am Soc Nephrol 2011 Oct 21 [Epub ahead of print].
138. Gil RJ, Gimeno FM. Abdominal aortic aneurysmectomy in renal transplant recipients. Arch Med Sci 2009; 5: 111-4.
139. Mora A, Herrrera A, López C, et al. Characteristics of the Shiga-toxin-producing enteroaggregative Escherichia coli O104:H4 German outbreak strain and of STEC strains isolated in Spain. Int Microbiol 2011; 14: 121-41.
140. Jansen A, Kielstein JT. The new face of enterohaemorrhagic Escherichia coli infections. Euro Surveill 2011 Jun 23; 16 (25).
141. The German 2011 epidemic of Shiga toxin-producing E. coli-the nephrological view The German EHEC-HUS Registry. Nephrol Dial Transplant 2011; 26: 2723-6.
142. Lapeyraque AL, Malina M, Fremeaux-Bacchi V, et al. Complement blockade in severe Shiga-toxin-associated HUS. N Engl J Med 2011; 364: 2561-3.
143. Greinacher A, Friesecke S, Abel P, et al. Treatment of severe neurological deficits with IgG depletion through immunoadsorption in patients with Escherichia coli O104:H4-associated haemolytic uraemic syndrome: a prospective trial. Lancet 2011; 378: 1166-73.
144. Roccatello D, Sciascia S, Rossi D, et al. Intensive short-term treatment with rituximab, cyclophosphamide and methylprednisolone pulses induces remission in severe cases of SLE with nephritis and avoids further immunosuppressive maintenance therapy. Nephrol Dial Transplant 2011; 26: 3987-92.
145. Mohamed MH, Gad GI, Ibrahim HY, et al. Cord blood resistin and adiponectin in term newborns of diabetic mothers. Arch Med Sci 2010; 6: 558-66.
146. Rysz J, Banach M, Stolarek RA, et al. Serum matrix metalloproteinases MMP-2 and MMP-9 and metalloproteinase tissue inhibitors TIMP-1 and TIMP-2 in diabetic nephropathy. J Nephrol 2007; 20: 444-52.
147. Pergola PE, Raskin P, Toto RD, et al. Bardoxolone methyl and kidney function in CKD with type 2 diabetes. N Engl J Med 2011; 365: 327.
148. Wojciechowska-Durczyńska K, Lewiński A. Phosphoinositide 3-kinase alterations in the thyroid gland – a review study. Arch Med Sci 2009; 5: 10-5.
149. Hansen D, Rasmussen K, Pedersen SM, Rasmussen LM, Brandi L. Changes in fibroblast growth factor 23 during treatment of secondary hyperparathyroidism with alfacalcidol or paricalcitol. Nephrol Dial Transplant 2011 Dec 1 [Epub ahead of print].
150. Ketteler M, Martin KJ, Cozzolino M, et al. Paricalcitol versus cinacalcet plus low-dose vitamin D for the treatment of secondary hyperparathyroidism in patients receiving haemodialysis: study design and baseline characteristics of the IMPACT SHPT study. Nephrol Dial Transplant 2011 Sep 19 [Epub ahead of print].
151. Ketteler M, Martin KJ, Cozzolino M, et al. Results from IMPACT-SHPT: a comparator trial of paricalcitol and cinacalcet centered therapies in the treatment of secondary hyperparathyroidism in subjects on hemodialysis, ERA-EDTA Congress, Prague, 23-26.06.2011.
152. Raggi P, Chertow GM, Torres PU, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. ADVANCE Study Group. Nephrol Dial Transplant 2011; 26: 1327-39.
153. Chertow GM, Pupim LB, Block GA, et al Evaluation of Cinacalcet Therapy to Lower Cardiovascular Events (EVOLVE): rationale and design overview. Clin J Am Soc Nephrol 2007; 2: 898-905.
154. Pfeffer MA, Burdmann EA, Chen CY, et al.; TREAT Investigators. A trial of darbepoetin alfa in type 2 diabetes and chronic kidney disease. N Engl J Med 2009; 361: 2019-32.
155. http://www.fda.gov/Drugs/DrugSafety/ucm259639.htm (Accessed on November 28, 2011).
156. Malyszko J, Suchowierska E, Malyszko JS, Mysliwiec M. A comprehensive study on hemostasis in CAPD patients treated with erythropoietin. Perit Dial Int 2002; 22: 582-92.
157. Kowalczyk M, Banach M, Mikhailidis DP, Rysz J. Erythropoietin update 2011. Med Sci Monit 2011; 17: RA240-7.
158. Malyszko J, Drozdz M, Zolkiewicz A, Rutkowski B. Renal anemia treatment with ESA in hemodialysis patients in relation to early versus late referral in everyday clinical practice in Central and Eastern European countries: baseline data. Kidney Blood Press Res 2011; 35: 58-67.
159. Foley RN, Gilbertson DT, Murray T, Collins AJ. Long interdialytic interval and mortality among patients receiving hemodialysis. N Engl J Med 2011; 365: 1099.
160. Chang TI, Paik J, Greene T, et al. Intradialytic hypotension and vascular access thrombosis. J Am Soc Nephrol 2011; 22: 1526.
161. Pascual J. Steroid avoidance or withdrawal in kidney transplantation. Curr Opin Organ Transplant 2011; 16: 600-5.
162. Gil RJ, Gimeno FM. Abdominal aortic aneurysmectomy in renal transplant recipients. Arch Med Sci 2009; 5: 111-4.
163. Przybylowski P, Malyszko J, Malyszko J. Immunosuppressive regimen and prevalence of chronic kidney disease in orthotopic heart transplant recipients. Med Sci Monit 2010; 16: CR563-6.
164. Tkocz M, Kupajski M, Duda D, Witosińska-Walica A. Spontaneous subcapsular kidney haemorrhage – the first symptom of renal cell carcinoma. Arch Med Sci 2009; 5: 107-10.
165. Vincenti F, Dritselis A, Kirkpatrick P. Belatacept. Nat Rev Drug Discov 2011; 10: 655-6.
166. Montgomery RA, Lonze BE, King KE, et al. Desensitization in HLA-incompatible kidney recipients and survival. N Engl J Med 2011; 365: 318.