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

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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 (fluvasatin, 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 that can help to prevent or delay 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, Newsom 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 130/80 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 possibly also with ventricular...
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].

Marcin Barylski, Jolanta Małyszko, Jacek Rysz, Michał Myśliwiec, Maciej Banach
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 of 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 pre-transplant 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 PL-A2 receptor 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...
specifically targets uncontrolled complement activity in three children with HUS [142]. Eculizumab, the terminal complement cascade inhibitor already approved for paroxysmal nocturnal haemoglobinuria, was able to cure the severe neurological symptoms of three children with HUS [142]. 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].

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/1.73 m² in patients with type 2 diabetes mellitus and impaired kidney function, i.e. eGFR between 20 and 45 ml/min per 1.73 m² (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 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 > 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 D Vascular calcificationN 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 (KDOQI 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].

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