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Lipids, Blood Pressure, Kidney-what was New in 2012?

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Abstract: The year 2012 has been extremely interesting concerning new findings on diagnosis, management and therapy of dyslipidaemia, hypertension and kidney disease. Looking at recent lipid disorders studies, two issues have seemed to be especially important-searching for new potent biomarkers of lipid disorders (including studies on dysfunctional High Density Lipoprotein [HDL] cholesterol, as well as subfractions/subpopulations of HDL/Low Density Lipoprotein [LDL] cholesterol) and research on new lipid disorders drugs, especially concerning proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which seem to be very potent in LDL-C lowering. Within the past year, there has been also growing clinical and research progress in hypertension management, especially concerning Resistant Hypertension (RH). In 2012, many important studies on Renal denervation (RDN), as a method of RH therapy have been published, including the ones with patients with different concomitant diseases (e.g., Chronic Kidney Disease (CKD)), as well as with longer follow-up. On the basis of the available data RDN has gained an important role in RH treatment and has recently been introduced to clinical practice. November 2012 has been critical for new nephrology data, as the most important trails were presented during American Society of Nephrology (ASN) Congress in San Diego. They concerned among others, the problems of secondary hyperparathyroidism management in CKD patients, new data on transplantations (e.g., glucocorticoid avoidance strategy), nephrocardiology (stepped pharmacotherapy algorithm vs. ultrafiltration in heart failure patients with CKD), as well as acute kidney injury and diabetic nephropathy (new data on bardoxolone methyl).

Key words: Hypertension, kidney disease, lipid disorders, new data, trials

LIPID UPDATE 2012

The year 2012 has been extremely interesting concerning new findings on diagnosis, management and therapy of lipid disorders and many new trials have been published. It would be very difficult to present them all in this study, so we have decided to focus the current discussion around the role of High Density Lipoprotein Cholesterol (HDL-C) and new, very interesting lipid disorder biomarkers, such as dysfunctional HDL and a new class of very potent Low Density Lipoprotein Cholesterol (LDL-C) lowering drugs-inhibitors of proprotein convertase subtilisin/kexin type 9 (PCSK9).

Novel biomarkers of lipid disorders: According to the 2011 European Society of Cardiology (ESC)/European

Atherosclerosis Society recommendations on management of lipid disorders, low density lipoprotein cholesterol (LDL-C) is the main target of the therapy (Catapano *et al.*, 2011). However, it should be emphasized that LDL-C analysis using Friedewald's equation has many limitations and the results may be inaccurate in different conditions (Rizzo *et al.*, 2012; Katsiki *et al.*, 2010). LDL-C can also underestimate LDL particles (LDL-P), particularly in patients with insulin resistance (Mora *et al.*, 2007) and according to the available trials LDL-P is a much better predictor of cardiovascular events than LDL-C (Manickam *et al.*, 2011). Many recent trials have been dedicated to seeking new, better predictors of cardiac events in patients with lipid disorders (Banach *et al.*, 2012; McQueen *et al.*, 2008; Barylski *et al.*, 2011). Among them, apolipoprotein (apo)A1, apoB

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(and apoB/apoA1 ratio), as well as high-sensitivity C-reactive protein (hsCRP), non-high density lipoprotein cholesterol (HDL-C) (and non-HDL-C/HDL-C ratio) seem to be much better biomarkers than LDL-C with great potential to effectively predict cardiovascular (CV) events (Emerging Risk Factors Collaboration *et al.*, 2009). Sniderman *et al.* (2011) performed a meta-analysis to investigate whether apoB or non-HDL-C adds to the predictive power of LDL-C for CV risk. Apo-B was the most potent marker of CV risk (relative risk ratio [RRR] 1.43), LDL-C was the least (RRR 1.25) and non-HDL-C was intermediate (RRR 1.34) (Sniderman *et al.*, 2011). The authors also calculated the number of clinical events prevented by each of the 3 markers, over a 10-year period: a non-HDL-C strategy would prevent 300 000 more events than an LDL-C strategy, whereas an Apo-B strategy would prevent 500 000 more events than a non-HDL-C strategy (Sniderman *et al.*, 2011). Finally, they observed that each standard deviation increase in HDL-C (15 mg dL^{-1}) was related to a 22% decrease in coronary heart disease risk (for patients with HDL-C of 20-80 mg dL^{-1}). This suggests that the efficacy in reducing the residual risk with HDL-C may be associated with the baseline HDL-C. According to many divergent outcomes concerning the best predictors/biomarkers of CV events in patients with dyslipidemia, as well as limitations of LDL-C measurement, searching for new potent biomarkers seems to be a very important topic (Mark *et al.*, 2011, 2012; Banach *et al.*, 2009; Gotto and Moon, 2012).

HDL-C is an independent protective factor for coronary artery disease (CAD) (Castelli, 1988). This effect was first seen in the Framingham Heart Study (FHS), where an inverse relation between HDL-C and the incidence of CAD was demonstrated. Patients who were in the 80th centile of HDL-C were found to have half the risk of developing CAD when compared with those in the 20th centile. These findings have been supported by other clinical studies (Fumisawa *et al.*, 2012; Gordon *et al.*, 2010; Ali *et al.*, 2012; Kowalski *et al.*, 2006). A meta-analysis of 23 studies performed in the Asia-Pacific region reported that isolated low levels of HDL-C were associated with an increased risk of CAD (for Asians: hazard ratio HR = 1.67). Finally, it was shown that aggressive treatment of LDL-C with statins does not obviate the CV risk associated with low HDL-C (Jafri *et al.*, 2010). The authors noted that each 10 mg dL^{-1} reduction in HDL-C was related to 7.1-8.3 more myocardial infarctions per 1000 patient-years. The same inverse associations were observed for total CV events. However, in the past few years more and more doubts have been raised regarding the role of HDL-C, especially as in many

available randomized clinical trials there was no relation of on-treatment HDL-C and residual risk (Stepien *et al.*, 2009; Ridker *et al.*, 2010). In the additional analysis of the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial it was found that the correlation of HDL-C increase with CV reduction was seen only in the placebo group and was strictly associated with baseline LDL-C. In the placebo group with on-treatment LDL-C 2.80 mmol L^{-1} (110 mg dL^{-1}) HDL-C was inversely related to vascular risk both at baseline (top quartile vs bottom quartile HR 0.54, $p = 0.0039$) and on treatment (HR 0.55, $p = 0.0047$). In the rosuvastatin (20 mg) group (on-treatment LDL-C 1.42 mmol L^{-1} [55 mg dL^{-1}]) no relationships were noted between quartiles of HDL-C and vascular risk either at baseline (1.12, $p = 0.82$) or on treatment (1.03, $p = 0.97$) (Ridker *et al.*, 2010). Additionally, some of these doubts come from studies which showed that a large proportion of CV events may occur in patients with normal or even high levels of HDL-C (referred to as the HDL paradox) (Otocka-Kmiecik *et al.*, 2012). Furthermore, in some conditions, including genetically based diseases, populations with a high HDL-C (e.g., cholesteryl ester transfer protein [CETP] deficiency in Japanese families) still had increased risk of CAD (Otocka-Kmiecik *et al.*, 2012; Van der Steeg *et al.*, 2007). On the other hand, in patients with low HDL-C levels (e.g., Apo-At1 Milano in octogenarians) no increased risk of CAD was observed (Bruckert and Hansel, 2007). Finally, the available large trials (including Atherothrombosis Intervention in Metabolic Syndrome with Low HDL Cholesterol/High Triglyceride and Impact on Global Health Outcomes [AIM-HIGH], JUPITER, Long-term Intervention with Pravastatin in Ischemic Disease [LIPID] and Treating to New Targets [TNT] studies) that evaluated the residual risk reduction (by raising HDL-C levels) have not confirmed the benefits in terms of further reduced risk of CV events (Athysos *et al.*, 2011a). Due to all these doubts, current European and US lipid guidelines do not recommend HDL-C as a target for lipid disorder therapy (Catapano *et al.*, 2011; Mark *et al.*, 2010).

This phenomenon could be in part explained on one hand by unsuitable study design and study processing (e.g., in AIM-HIGH-unexpected almost 10% increase of HDL-C in monotherapy group, baseline low levels of LDL-C [below 75 mg dL^{-1}], wrong termination of the study on the basis of a slight increase in occurrence of ischemic strokes [$p = 0.11$]) and on the other hand by differences in the qualitative properties among the various HDL molecules (Otocka-Kmiecik *et al.*, 2012; Nicholls, 2012). Indeed, it has been found that HDL particles vary according to size, shape, antigenicity and charge. This

heterogeneity results from differences in quantitative and qualitative content of lipids, apolipoproteins (apos), lipid transfer proteins and enzymes which directly affect their biological activity and metabolism (Otocka-Kmiecik *et al.*, 2012; Yamamoto *et al.*, 2012). Therefore, it seems that we should focus on both the quality and quantity of HDL-C (probably first of all on the quality), or potentially on the quantity of the selected subfractions/subpopulations of HDL particles (Otocka-Kmiecik *et al.*, 2012). Additionally, in some pathological conditions associated with oxidative stress and inflammation, HDL may undergo post-transitional changes that affect their antiatherogenic properties, leading to creation of HDL particles with impaired anti-inflammatory functions (so-called dysfunctional HDL). The investigations on that issue might have a breakthrough impact for the diagnostics, therapy and prevention of CVD and dysfunctional HDL might be an important novel biomarker of CV events in lipid disorder patients, which might allow optimal stratification of the cardiac risk (Athysos *et al.*, 2011b). The study on HDL functionality may also allow confirmation of antiatherogenic, as well as proatherogenic properties of specific HDL subfractions/subpopulations in the groups of patients with selected conditions. This could be a starting point for the development of new targeted drugs and better control and more effective treatment of lipid disorders. It might also completely change the current dyslipidemia management and finally answer all the questions on the residual risk therapy, as well as allowing the selection of patients for whom residual therapy should not be considered (or even forbidden) and those who might benefit from such treatment (Barylski *et al.*, 2011; Otocka-Kmiecik *et al.*, 2012).

We have already had some reports confirming that we should avoid looking for HDL-C as a whole particle, and we should rather focus on each subfraction/subpopulation of it. Several available studies have shown that an increase in HDL-C and decrease in LDL-C levels do not always affect the progression of atherosclerosis (Mackey *et al.*, 2012; Bielecka-Dabrowa *et al.*, 2009; Simeunovic *et al.*, 2010; Skora *et al.*, 2012; Stojanovic *et al.*, 2011; Rosenson *et al.*, 2011). Differences in the quality of HDL particles may be responsible for this observation (Otocka-Kmiecik *et al.*, 2012; Mackey *et al.*, 2012; Rosenson *et al.*, 2011). What is probably more important, HDL anti-inflammatory activity may also be influenced by systemic conditions (inflammation, oxidative stress, glycation and carbamylation) and results in conversion of HDL function to pro-inflammatory (Otocka-Kmiecik *et al.*, 2012; Mackey *et al.*, 2012). Under normal conditions,

anti-inflammatory HDL inhibits LDL oxidation and reduces the migration of monocytes within the arterial wall (Rosenson *et al.*, 2011). However, pro-inflammatory HDL does not exhibit such properties and can even exacerbate the inflammatory response and is often referred to as dysfunctional HDL (Otocka-Kmiecik *et al.*, 2012). It was observed that subjects at high cardiovascular risk (e.g., with CAD and type 2 diabetes), possessed small dense HDL particles, which have diminished antioxidant activity and impaired antiatherogenic properties (Otocka-Kmiecik *et al.*, 2012; Lagos *et al.*, 2009; Nobecourt *et al.*, 2005; Kedziora-Kornatowska *et al.*, 2010). It was therefore suggested that dysfunctional HDLs may be a novel very potent biomarker of CV risk (Stepien *et al.*, 2011, 2012; Soran *et al.*, 2012; Younis *et al.*, 2012). However, we are currently only beginning research on this issue, which is also connected to the fact that there is no single approved method of dysfunctional HDL measurement, we still do not know which HDL fractions might be considered as dysfunctional and in what conditions and finally there are no large well-designed studies with dysfunctional HDL as the main analyzed biomarker. We do hope that the Investigating DYSfunctional-HDL in selected groups of patients at high risk of cardiovascular events (DYS-HDL study) which we have designed and for which we plan to start recruiting patients in 2013, will be able to answer all important questions.

New drugs in lipid disorder therapy: Despite the fact that statins were introduced over 20 years ago and we have very potent drugs in the treatment of lipid disorders, the control and effectiveness of therapy is still very low (usually no more than 25-30%) (Banach *et al.*, 2012; Shekhar Pandey *et al.*, 2011; Bandosz *et al.*, 2012; Vulic *et al.*, 2010). What is more, according to the fact that the follow-up of statin therapy for many patients is currently 15-20 years, we have been observing more and more new cases of adverse events. It is not surprising and it should not disrupt the main aim of lipid disorder therapy with statins, i.e., significant reduction of CV risk but we should be aware of it (Paraskevas *et al.*, 2011; Macaulay, 2012; Katsiki and Banach, 2012; Seneff *et al.*, 2011). That is also a reason that we have been still looking for new drugs in lipid disorder therapy, especially focusing on LDL-C lowering (Al-Bazi *et al.*, 2011; Joy, 2012; Cicero and Ertek, 2010).

Recently, great hope has been invested in proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, which seem to be very potent in LDL-C lowering in different groups of dyslipidemia patients, including those with statin intolerance, lack of effectiveness of statin

therapy and in high-risk patients, including subjects with familial hypercholesterolemia (FH) (Banach *et al.*, 2013). PCSK9 is a member of the mammalian serine Proprotein Convertase (PC) family that is responsible for the proteolytic maturation of secretory proteins including neuropeptides, prohormones, cytokines, growth factors, receptors and serum and cell surface proteins (Banach *et al.*, 2013; Farnier, 2011). The major function of PCSK9 is the degradation of the LDL receptor. The mechanisms through which this occurs are complex and have not been fully determined. It is suggested that mainly extracellular (Banach *et al.*, 2013; Zhang *et al.*, 2007) but also possibly intracellular pathways are involved (Banach *et al.*, 2013). The addition of a PCSK9 inhibitor to statin therapy may result in additional beneficial LDL-C lowering (Banach *et al.*, 2013; Wierzbicki *et al.*, 2012). The function of liver PCSK9 may reside in its ability to slow down the catabolism of lipoproteins and to maintain proper circulating levels of total cholesterol and triglycerides. Because human PCSK9 targets ex-vivo human very low density lipoprotein receptor (VLDLR) and binds in vitro mouse VLDLR, it was suggested that PCSK9 may also target VLDLR in humans and interact with apolipoprotein E (apoE) receptor 2 (apoER2) and annexin A2 (Banach *et al.*, 2013; Wierzbicki *et al.*, 2012; Roubtsova *et al.*, 2011).

Several PCSK9-targeted therapies are in development, including 2 fully human monoclonal antibodies against PCSK9, REGN-727 and AMG-145 (Banach *et al.*, 2013). The year 2012 has been crucial for PCSK9 inhibitors, as many large trials have been published. In one of the first important papers, Stein *et al.* (2012a) reported the data from 3 different phase I studies: 2 were single-dose studies while the third one was a multiple-dose study. They performed 2 randomized, single ascending-dose studies of REGN-727 in healthy volunteers, administered either intravenously (40 subjects) or subcutaneously (32 subjects), compared with placebo and LDL-C concentrations were reduced by 28-65 and 32-46%, respectively for the 2 methods of administration (Stein *et al.*, 2012a). The third study reported in this study (Stein *et al.*, 2012a) was a randomized, placebo-controlled, multiple-dose trial in 21 patients with heterozygous FH (HeFH) on atorvastatin 10-40 mg, 30 patients with polygenic hypercholesterolemia on atorvastatin (mostly 10 mg) and 10 patients on diet alone. REGN-727 doses of 50-150 mg were given monthly for a total of 3 injections and the efficacy in reducing LDL-C was 41-56% in patients with HeFH, 38-65% in those with polygenic hypercholesterolemia and 57% for the 150 mg dose used in diet-treated subjects. REGN-727 also significantly reduced apoB levels, and in subjects receiving both

REGN-727 and atorvastatin, there was a significant increase in HDL-C levels, as well as a reduction in lipoprotein (a). In another paper the authors analyzed the efficacy and safety of REGN-727 in patients with primary hypercholesterolemia, receiving ongoing stable atorvastatin therapy (McKenney *et al.*, 2012). One hundred and eighty three patients with LDL-C = 100 mg dL⁻¹ on a stable dose of atorvastatin 10-40 mg for = 6 weeks were randomized to REGN-727 (50-300 mg) s.c. or placebo for a total treatment period of 12 weeks. REGN-727 reduced LDL-C levels by 40-72%. There was a trend towards HDL-C increases vs. placebo as well as 13-29% lipoprotein (a) reduction. In the next study from the group of Stein and colleagues, the authors in a phase 2 trial assessed the efficacy and safety of various doses and dosing intervals of REGN-727 added to statins, to further lower LDL-C in 77 patients with HeFH with LDL-C concentrations of 2.6 mmol L⁻¹ or higher (Stein *et al.*, 2012b). Patients were randomly assigned to receive REGN-727 150 mg, 200 mg, or 300 mg every 4 weeks, or 150 mg every 2 weeks, or placebo every 2 weeks. Mean LDL-C reduction from baseline to week 12 was 28.9% for 150 mg every 4 weeks, 31.54% for 200 mg every 4 weeks, 42.53% for 300 mg every 4 weeks and 67.90% for 150 mg every 2 weeks, compared to 10.65% with placebo. On the basis of results of these 3 presented studies, the authors suggested that REGN-727 had a great potential to provide optimum control of LDL-C in dyslipidemia patients (Banach *et al.*, 2013; Stein *et al.*, 2012a; McKenney *et al.*, 2012; Stein *et al.*, 2012b).

AMG 145 is another fully human monoclonal antibody against PCSK9 and the first full-text articles have been published in November 2012. Sullivan *et al.* (2012) assessed the efficacy and tolerability of AMG 145 in patients with statin intolerance due to muscle-related side effects. 160 patients (mean baseline LDL-C: 193 mg dL⁻¹) were randomized equally to 1 of 5 groups: AMG 145 alone at doses of 280, 350, or 420 mg; AMG 145 at 420 mg plus 10 mg of ezetimibe; or 10 mg of ezetimibe plus placebo. At week 12, mean changes in LDL-C were -67 mg dL⁻¹ (-41%) for the AMG 145 280 mg group; -70 mg dL⁻¹ (-43%) for the 350 mg group; -91 mg dL⁻¹ (-51%) for the 420-mg group; and -110 mg dL⁻¹ (-63%) for the 420-mg/ezetimibe group compared with -14 mg dL⁻¹ (-15%) for the placebo/ezetimibe group. Myalgia was the most common treatment-emergent adverse event during the study. In the efficacy, safety and tolerability of a monoclonal antibody to proprotein convertase subtilisin/kexin type 9 in combination with a statin in patients with hypercholesterolemia (LAPLACE-TIMI 57) trial (Giugliano *et al.*, 2012) the authors assessed, in a phase 2 dose-ranging study, the efficacy, safety and tolerability of

AMG 145 in 631 stable patients with hypercholesterolemia (LDL-C greater than 2.2 mmol L⁻¹) on a statin. They were randomized to subcutaneous injections of AMG 145 70, 105, or 140 mg, or matching placebo every 2 weeks; or subcutaneous injections of AMG 145 280, 350, or 420 mg, or matching placebo every 4 weeks. At the end of the dosing interval at week 12, the mean LDL-C concentrations were reduced generally dose dependently by AMG 145 every 2 weeks (ranging from 41.8 to 66.1%) and AMG 145 every 4 weeks (ranging from 41.8% to 50.3%). The frequencies of treatment-related adverse events were similar in the AMG 145 and placebo groups (39 [8%] of 474 vs. 11 [7%] of 155) (Giugliano *et al.*, 2012). The efficacy of PCSK9 inhibitors in monotherapy was analyzed by Koren *et al.* (2012). In a phase 2 trial 406 patients aged 18-75 years with serum LDL-C concentrations of 2.6 mmol L⁻¹ or greater but less than 4.9 mmol L⁻¹ were randomly assigned to subcutaneous injections of AMG 145 70, 105, or 140 mg, or placebo every 2 weeks; subcutaneous AMG 145 280, 350, or 420 mg or placebo every 4 weeks; or oral ezetimibe 10 mg day⁻¹. AMG 145 significantly reduced LDL-C concentrations in all dose groups. Changes from baseline were: for every 2 weeks AMG 145 70 mg -41.0%, 105 mg -43.9%, 140 mg -50.9%; for every 4 weeks AMG 145 280 mg -39.0%, 350 mg -43.2%, 420 mg -48.0%; placebo every 2 weeks -3.7%; placebo every 4 weeks 4.5% and ezetimibe -14.7% (p<0.0001 for all doses vs placebo or ezetimibe). Treatment-emergent adverse events occurred in 136 (50%) of 271 patients in the AMG 145 groups, 41 (46%) of 90 patients in the placebo groups and 26 (58%) of 45 patients in the ezetimibe group; no deaths or serious treatment-related adverse events were reported. In the Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder (RUTHERFORD) trial (Raal *et al.*, 2012), the authors evaluated the efficacy and safety of AMG 145 in 168 HeFH patients diagnosed by Simon Broome criteria with LDL-C = 2.6 mmol L⁻¹ (100 mg dL⁻¹) despite statin therapy with or without ezetimibe. They were randomized to AMG 145 350 mg, AMG 145 420 mg, or placebo administered subcutaneously every 4 weeks. At week 12, LDL-C reduction was 43 and 55% with AMG 145 350 mg and 420 mg, respectively, compared with 1% increase with placebo (p<0.001 for both dose groups). Serious adverse events (not considered treatment-related) occurred only in 2 patients on AMG 145.

Despite these very promising results, showing high effectiveness of PCSK9 inhibitors, we have to wait for the final results (phase 3) of the above presented studies concerning not only their efficacy, but first of all the effect of cardiovascular risk reduction and safety and tolerance.

It seems that especially the latter aspect should be analyzed very carefully because in some of the available trials the number of adverse events with PCSK9 inhibitors was relatively high. The next ongoing studies, including, among others, the Open Label Study of Long Term Evaluation Against LDL-C (OSLER) trial and the Durable Effect of PCSK9 Antibody CompARed wiTh placEbo Study (DESCARTES) (Banach *et al.*, 2013; Athyros *et al.*, 2011c; Gluba *et al.*, 2010a; Amgen, 2012a, 2012b), will probably answer all these questions.

HYPERTENSION UPDATE 2012

Renal denervation: Uncontrolled hypertension is a major contributor to global CV morbidity and mortality. Despite the wide availability of a number of potent antihypertensive drugs, the prevalence and incidence of high Blood Pressure (BP) are increasingly problematic (Grassi *et al.*, 2011; Bielecka-Dabrowa *et al.*, 2011). Very recently, data from the cross-sectional analysis of the US National Health and Nutrition Examination Survey (NHANES) indicated that despite increased hypertension awareness and the use of antihypertensive treatment, patients with a higher CV risk have lower rates of controlled BP when compared to the average patient risk (Bertoia *et al.*, 2012).

Within the past year, there has been growing clinical and research progress in hypertension management. Indeed, the majority of studies have been primarily focused on apparent treatment Resistant Hypertension (RH). While determining the exact prevalence of patients with RH remains complex, a very recent meta-analysis indicated that one in fifty newly diagnosed patients with hypertension becomes resistant to drug therapy following a median of 1.5 years (Daugherty *et al.*, 2012a). In this comprehensive retrospective study, a total of 205 750 patients with incident hypertension were included and monitored over a 4-year period. Indeed, 3960 patients from this cohort developed RH within 18 months of initial treatment. RH more often occurred in males, older subjects and those with higher rates of diabetes at baseline compared to patients with hypertension responsive to treatment. Additionally, in contrast to patients with controlled BP, patients with RH had twofold increased risk for adverse CV events that was mainly attributable to Chronic Kidney Disease (CKD). The same authors further investigated the relationship between medical adherence, treatment intensification and BP control among patients with RH (Daugherty *et al.*, 2012b). This retrospective study showed that only appropriate therapy intensification, but not therapy adherence, was associated with 1-year BP control in RH. It is noteworthy that the use

of several antihypertensive drug classes declined after 12 months, with the diuretic being discontinued in the majority of patients (>90% of patients at baseline versus 78% of patients at 1-year follow-up). Whilst treatment intensification is an exciting concept providing a beneficial approach for patients with RH, further research is warranted to better define the long-term effects of therapy intensification with subsequent BP control and all-cause CV morbidity and mortality in this patient cohort. Accordingly, these findings appear to be of significant importance given the alarming increase in the prevalence of obesity, diabetes and CKD (Mohamed *et al.*, 2010; Gilbertson *et al.*, 2005; WHO, 2009; Whiting *et al.*, 2011; Gluba *et al.*, 2012) commonly associated with RH.

In this context the antihypertensive strategies that may attenuate the progress of these co-morbidities is apparent. Recent advances in the field of hypertension have been directed toward catheter-based renal sympathetic nerve ablation for the treatment of resistant hypertension (Oparil *et al.*, 2011). Renal denervation (RDN) has gained an important role in treatment-resistant hypertension and has recently been introduced to clinical practice. Based on the existing evidence, the current European Society of Hypertension (ESH) position statement recommends the procedure for patients who are resistant to drug therapy with office systolic blood pressure (SBP) ≥ 160 mmHg (≥ 150 mmHg in the presence of type 2 diabetes) and estimated glomerular filtration rate (eGFR) ≥ 45 ml/min/1.73 m² despite use of at least 3 antihypertensive drugs in adequate doses including a diuretic (Schmieder *et al.*, 2012). Of significant interest are recent clinical experiences with RDN effects on hypertension-related end organ damage and other conditions beyond a safe and effective BP decrease. Indeed, very recent results from a study of a total of 46 patients with RH who underwent bilateral RDN indicated that in addition to the BP fall observed in the treatment group (-27.8/-8.8 mmHg, $p < 0.001$) after 6 months, the procedure resulted in a rapid significant reduction in intraventricular septum thickness (14.1 \pm 1.9 versus 12.5 \pm 1.4 mm, $p = 0.007$) with corresponding improvement of LV mass index (112.4 \pm 33.9 vs. 94.9 \pm 29.8 g m⁻², $p < 0.001$), mitral valve lateral E/E', isovolumic relaxation time and ejection fraction (Brandt *et al.*, 2012). Not unexpectedly, no changes in 18 patients with RH who underwent repeated measurements without having undergone the procedure were observed.

Further indicative evidence for a beneficial effect of RDN has been demonstrated in 21 patients with RH (Mortensen *et al.*, 2012). Specifically, peripheral SBP was reduced by 6.1% ($p < 0.05$) with parallel reduction in central SBP by 7.0% ($p < 0.05$), aortic augmentation index (AIx) by

9.5% ($p < 0.05$) and pulse wave velocity (PWV) by 10.4% ($p < 0.05$). In this study, subgroup analysis revealed that in responders peripheral SBP decreased by 16.1% ($p < 0.01$), central SBP by 18.3% ($p < 0.01$), aortic AIx improved by 19.2% ($p < 0.02$) and PWV by 13.7% ($p < 0.05$). Given the abundant evidence for a causal link between hypertension-induced organ damage and CV morbidity and mortality, the above-mentioned findings appear reassuring as left ventricular hypertrophy, central hemodynamics and arterial stiffness were substantially attenuated 6 months following the RDN procedure. Whether this improvement may have prognostic implications in this patient cohort remains to be determined.

While all patients treated with RDN in the initial clinical trials had an estimated eGFR = 45 mL/min/1.73 m², further support for such a beneficial role comes from investigations of another group of patients characterized by increased sympathetic activation and high CV morbidity and mortality (Banach and Rysz, 2010; Witkowski *et al.*, 2011). Very recently, results from the first pilot study including a total of 15 high CV risk patients with moderate to severe CKD demonstrated that RDN is a safe and effective approach in this patient cohort (Hering *et al.*, 2012). Office systolic and diastolic BP were significantly reduced by -34 \pm 13/-14 \pm 13, -25 \pm 20/-11 \pm 10, -32 \pm 18/-15 \pm 12, -33 \pm 20/-19 \pm 20 mmHg at 1, 3, 6, 12 months following RDN, respectively ($p < 0.001$). RDN decreased night-time ambulatory BP ($p = 0.01$) at 3 month follow-up, resulting in an improved dipping pattern. Notably, no deterioration of renal function, reduction in eGFR or electrolyte disturbances were noted following the procedure. Moreover, improvement in AIx associated with RDN may be relevant to patients with CKD (Hering *et al.*, 2012), given that not only the presence but also the extent of arterial calcifications were strong predictors of CV and total mortality in end stage renal disease (ESRD) (London *et al.*, 2001). Importantly, a significant reduction in maximum SBP associated with RDN in high-risk patients with CKD (Hering *et al.*, 2012) and also reduced BP variability following the procedure in patients with RH (Zuern *et al.*, 2012) appear to be of particular clinical significance given its effect in reducing the risk of stroke (Rothwell *et al.*, 2010).

Available evidence indicates that catheter-based RDN has a favorable safety profile and results in substantial and sustained BP reduction in patients with drug-resistant hypertension up to three years. Very recently, expanded results from the SYMPPLICITY HTN-1 trial including a total of 153 patients were presented at the American College of Cardiology Annual Meeting 2012, indicating an average BP reduction of -33/-19 mmHg at 36

months (n = 24) from baseline (p<0.001). In terms of safety, no deterioration of renal function was encountered at follow-up. The currently ongoing randomized double-blinded SYMPLICITY HTN-3 clinical trial involving more than 500 patients in the United States will further define the safety and effectiveness of renal nerve ablation in patients whose BP is uncontrolled despite the use of multi-drug regimens (Kalaitzidis *et al.*, 2012).

Hypertension pharmacotherapy: In the past year, evidence has also become available from trials investigating the utility of antihypertensive drugs (Banach and Aronow, 2012a; Narkiewicz, 2012; Chou *et al.*, 2011; Banach and Aronow, 2012b). The inhibition of the renin-angiotensin-aldosterone system has been shown to lower BP, to diminish progression of CV and renal disease and to improve CV outcomes. Indeed, several studies have indicated that renin-angiotensin ACE inhibitors in combination with angiotensin II receptor blocking agents provide nephroprotective and cardioprotective benefits beyond BP lowering (Matos *et al.*, 2005; Kunz *et al.*, 2008). However, in the ONTARGET (Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint) trial, dual therapy reduced office BP to greater degree (1.5-2.4 mmHg for systolic BP and 0.8-1.4 mmHg for diastolic BP) and diminished albuminuria, but increased the risk of acute events of hyperkalemia and renal dysfunction without any benefit in the primary composite outcome (Ontarget Investigators *et al.*, 2008). A very recent sub-study of a cohort of 422 patients included in the ONTARGET trial (Mancia *et al.*, 2012) demonstrated that telmisartan alone produced a comparable or only slightly greater BP reduction compared to ramipril alone, whereas dual blockade caused more pronounced 24 h ambulatory BP reduction. While at baseline ambulatory BP was approximately ~14 mmHg lower than clinic SBP, treatment-induced changes in office BP closely correspond with ambulatory BP target drug treatment. The discrepancy between the information obtained from office and 24 h BP measurements over the course of the trial requires further clinical trials to assess the target ambulatory BP level with treatment.

Initial antihypertensive treatment is another important issue. While fixed-dose combinations have been shown to improve adherence, achieve better BP control and reduce adverse events (Bangalore *et al.*, 2007), the effectiveness of longer term initial treatment with monotherapy, free combinations and single-pill combinations on BP control was unknown until a very recent study using electronic data of 106 621 patients with hypertension from 180 practice sites (Egan *et al.*, 2012). In

this retrospective study, patients with uncontrolled BP and untreated for = 6 months before therapy were evaluated during their first treatment year. Patients on initial single-pill combinations were more likely to have grade 2 hypertension compared to those on free combinations or monotherapy. Patients with initiated single-pill combinations had better BP control in the first year than patients initiated on free combinations (HR, 1.34; [95%CI, 1.31-1.37]) or monotherapy. These data seem to suggest that early fixed-dose combination therapy provides effective hypertension control, may improve CV outcomes and notably may be suitable for use in general practice settings (Egan *et al.*, 2012).

It is well recognized that a conventional therapy of a diuretic and a β -blocker is associated with higher incidence of diabetes; therefore, this combination as recommended by the current hypertension guidelines should be avoided (Banach *et al.*, 2010). More recently, in two double-blind placebo-controlled crossover studies the effects of amiloride and hydrochlorothiazide on glucose metabolism have been tested in patients with essential hypertension (Stears *et al.*, 2012). In the first study of 41 patients, 4-week treatment with bendroflumethiazide (BFZ) 10 mg caused a significant increase in blood glucose during the 2 h oral glucose tolerance test (OGTT) (p<0.006 versus baseline), with a tendency toward glucose increase following 2 weeks treatment with 5 mg. In contrast, there were no detectable changes in glucose concentrations during the 2 h OGTT after 4 weeks treatment with atenolol, either alone or in BFZ/atenolol combination. In the second study of 37 patients, a significant increase in the 2 h OGTT was observed after 4 weeks therapy with hydrochlorothiazide (HTZ) 50 mg, whereas OGTT remained unchanged during amiloride therapy following a similar period. No alterations in glucose metabolism were noted following nebivolol in monotherapy or in combination with HTZ. The potential advantage of amiloride might be lack of a negative impact on glucose tolerance and it thereby may prevent thiazide-induced diabetes mellitus (Egan *et al.*, 2012). Whether treatment with a K⁺-sparing diuretic may improve CV outcomes in patients with hypertension remains to be determined.

Another interesting observation has been drawn from a more recent study on the association between hypertension and increased risk for Alzheimer disease (Shah *et al.*, 2012). While the contribution of high BP to the development of vascular cognitive dementia is well recognized, the mechanism through which elevated BP may modulate β -amyloid (A β) and its risk for Alzheimer disease is intriguing. In the prospective design study of 667 Japanese-American men, midlife BP was not linked to

the development of vascular dementia. Interestingly, a direct relationship between midlife diastolic BP and plasma A β for developing Alzheimer disease was observed. The increased risk for late-life dementia associated with every 1-SD reduction in plasma A β at midlife was higher for individuals with Diastolic Blood Pressure (DBP) ≥ 90 mm Hg irrespective of A β -40 and A β -42 assays. Additionally, lower values of plasma A β were seen at least 15 years before the diagnosis of Alzheimer disease. These data indicate that the benefit associated with optimal BP control is not restricted to reduced CV morbidity and mortality worldwide, but may also prevent the development of Alzheimer's disease (Shah *et al.*, 2012).

NEPHROLOGY UPDATE 2012

Late-breaking clinical trials: This year was expected to be particularly important for the nephrology community. We eagerly awaited the results of landmark clinical trials. However, when the name of the session at the American Society of Nephrology (ASN) meeting appeared as "High-impact clinical trials" instead of "Late-breaking clinical trials", only one thought entered our minds. We were almost sure that for the next time the results of our milestone randomized controlled trials did not meet our expectations and we had to face the new reality.

Patients with kidney disease face a substantially increased risk of CV events and death (Chronic Kidney Disease Prognosis Consortium, 2010; Malyszko *et al.*, 2010; Franczyk-Skora *et al.*, 2012): one in five patients who are undergoing dialysis die each year in the United States (USRDS, 2012). Elevated parathyroid hormone levels have been associated with these CV risks, as reported previously (Palmer *et al.*, 2011). As secondary hyperparathyroidism (SHPT) is one of the major complications in patients with CKD, intact parathyroid hormone (iPTH) control remains an important therapeutic goal. The optimal treatment for SHPT has not been defined. Cinacalcet, a calcimimetic, is approved for the treatment of SHPT in patients with CKD stage 5D. Paricalcitol, a selective vitamin D receptor activator, is approved for the treatment of SHPT in patients with CKD stages 3, 4 and 5 including 5D (dialysis) (Ketteler *et al.*, 2012). The IMPACT SHPT study assessed whether dose-titrated paricalcitol plus supplemental cinacalcet (only for hypercalcemia) is superior to cinacalcet plus low-dose vitamin D in controlling iPTH levels in patients with SHPT on hemodialysis. The primary efficacy end point was the proportion of subjects who achieved a mean iPTH value of 150-300 pg mL⁻¹ during weeks 21-28. The authors found that paricalcitol versus cinacalcet plus low-dose

vitamin D provided superior control of iPTH, with low incidence of hypercalcaemia. In addition, Kovesdy *et al.* (2012) reported that in a randomized open-label trial that included 80 patients with CKD (eGFR 15 to 60 mL/min per 1.73 m²) paricalcitol was more effective than ergocalciferol in reducing parathyroid hormone levels at 16 weeks. The rates of hypercalcemia and hyperphosphatemia were not different between groups. So far there are no head-to-head comparisons between active vitamin derivatives and cinacalcet in either CKD or HD patients.

The next study, EVOLVE (EVALUATION Of Cinacalcet HCl Therapy to Lower CardioVascular Events), tried to answer the most important question of whether treatment with cinacalcet of moderate-to-severe SHPT in patients on hemodialysis reduces the risk of death or major CV events (The EVOLVE Trial Investigators, 2012). The trial was based on the hypothesis that SHPT in patients with CKD may contribute to vascular calcification and that the calcimimetic agent cinacalcet might reduce CV risk. EVOLVE enrolled hemodialysis patients with a serum iPTH of 300 pg mL⁻¹ (the level at which the mortality rate appears to increase) or greater, calcium of 8.4 mg dL⁻¹ or greater and a calcium phosphorus product of 45 mg²/dL² or greater. Patients were randomly assigned in a double-blind manner to placebo plus standard of care (n = 1935) or to cinacalcet plus standard of care (n = 1948) which generally included vitamin D sterols and phosphate binders. As reported by the researchers a Kaplan-Meier analysis on an unadjusted intention-to-treat (ITT) analysis showed only a 7% reduction in the risk for death or major CV events using cinacalcet vs placebo. Generally speaking, the trial showed no significant benefit for the primary composite endpoint (time to all-cause mortality or nonfatal CV events). The median duration of study drug exposure was 21.2 months for cinacalcet and 17.5 months for placebo. There was also no difference in all-cause mortality on an ITT basis. However, when the primary composite endpoint results were adjusted for age, a 12% benefit for cinacalcet emerged (HR = 0.88; 95% CI 0.81-0.97; p = 0.007). So, there was a "nominally significant" reduction in these risks. A multivariable (best fit) model gave similar results as did adjustment for all baseline characteristics. In the lag-censored analysis total mortality was reduced as well as cardiovascular mortality (p = 0.003 and p = 0.009, respectively). It should be stressed that patients on cinacalcet had a 56% prolonged time to first parathyroidectomy compared with the placebo group (HR = 0.44; 95% CI 0.36-0.54; p < 0.001). Similarly, the cinacalcet group had a longer time to a first episode of severe, unremitting hyperparathyroidism (HR = 0.43; 95% CI 0.37-0.50; p < 0.001) as well as lower

incidence of calciphylaxis. On the other hand, there was no advantage to cinacalcet in time to a first clinical fracture. It should also be stressed that there was a high and equivalent rate of study drug discontinuation in both the cinacalcet and placebo groups. Of note, one reason for study drug discontinuation in either group was to go on commercially available cinacalcet. Major adverse effects included a 7-fold increase in hypocalcemia ($p < 0.001$) and a 2-fold increase in nausea and vomiting ($p < 0.001$), compared to the placebo arm (The EVOLVE Trial Investigators, 2012). Why was the primary result of the trial negative? There was an unexpected age difference between the active arm and the placebo group. The difference in the median age was 1 year and SD was 14 – much more than in the other trials. The surprising imbalance in baseline characteristics between the two groups may well have had an effect and probably represents simple bad luck, but illustrates the importance of stratification for key prognostic factors. The second and more important problem was the high rates of treatment crossover during the trial: almost two thirds of patients in the cinacalcet group discontinued active therapy and one fifth of those in the placebo group started taking commercially available cinacalcet before trial completion. The resultant reduction in the between-group separation in parathyroid hormone levels substantially reduced the power of the trial to test its hypotheses (The EVOLVE Trial Investigators, 2012). Dr. Jurgen Floege, one of the investigators, during the Nephrology Educational Winter Symposium in Madrid, 23-24th November, concluded that he was now more confident of not doing harm when treating patients with cinacalcet after EVOLVE (personal communication). As a nephrology community we are less confused and more confident in using cinacalcet in our patients.

As sudden cardiac death remains the most common cause of death in dialyzed patients (Franczyk-Skora *et al.*, 2012), the predictors of sudden cardiac death among hemodialysis patients were evaluated using data from the Hemodialysis (HEMO) study (Shastri *et al.*, 2012). Predictors of sudden cardiac death in this population were age, diabetes, peripheral vascular disease, ischemic heart disease, low serum creatinine (reflecting decreased muscle mass and poor nutrition) and elevated alkaline phosphatase. So far no randomized controlled trials have been designed to study directly the effect of daily hemodialysis on survival. In two large observational studies improved survival was associated with intensive home hemodialysis as compared with in-center three times weekly hemodialysis (Weinhandl *et al.*, 2012; Lubas *et al.*, 2010; Skora *et al.*, 2012; Nesrallah *et al.*, 2012).

Dr. Charles Herzog at the High-impact Clinical Trials at ASN in San Diego 2012 presented data on cardiac revascularization in dialysis patients (Skora *et al.*, 2012; Nelson *et al.*, 2012). He showed that Medicare patients on dialysis who need cardiac revascularization have better 1-year survival if they receive drug-eluting stents (DES), but their long-term survival was better if they received a coronary artery bypass graft (CABG). In addition, the best long-term survival was associated with use of internal mammary artery grafts and with a multivessel CABG. He reported that 2-year survival after CABG was 56% and after percutaneous coronary intervention (PCI) with bare metal stents (BMS) was 48%. Insufficient information existed on survival in the era of DES. He also showed that revascularization procedures for dialysis patients peaked in 2004-2005 at about 4400 per year, then revascularization procedures dropped to just under 3500/year in 2007-2009 (Nelson *et al.*, 2012). PCI using DES peaked at about 62% in the years 2005 and 2006, then the proportion of DES use declined to about 42 to 45% of procedures in 2007-2009. During this latter period, the use of BMS increased to about 30% of procedures. We should bear in mind that DES requires dual antiplatelet therapy for one year, when the patient is either not qualified or withdrawn from the transplant waiting list, while with BMS antiplatelet therapy lasts only for 6 weeks. During the 2004-2009 period, patients receiving DES had the best survival (71%) within the first year after revascularization vs 70% for CABG and 63% for BMS. But at about 18 months, the survival curves crossed and survival was best with CABG from then up to 6 years. The survival curves after 2 years were essentially parallel. At 6 years, survival of patients who had received CABG was 22%, 18% for DES and 15% for BMS. In general patients with internal mammary artery grafts and multivessel CABG did best. In a comorbidity-adjusted Cox model independent predictors of death were age, diabetes as the cause of ESRD, time on dialysis, peritoneal dialysis, congestive heart failure, stroke, or peripheral artery disease. Women were at about the same risk for death as men, but black race appeared to be protective. It should be pointed out that according to the United States Renal Data System (USRDS) the total number of coronary revascularization procedures for dialysis patients decreased from 2004 to 2009 and that a major reduction in DES use occurred in 2007 (Nelson *et al.*, 2012).

According to two large meta-analyses by the Chronic Kidney Disease Prognosis Consortium (CKD-PC), kidney disease is a significant predictor of all-cause mortality and end-stage renal disease (ESRD) in patients with and without hypertension or diabetes (Hallan *et al.*, 2012; Fox *et al.*, 2012). In the first meta-analysis, researchers

analyzed data from 45 cohorts, including 25 cohorts of the general population, seven cohorts of high-risk patients, and 13 CKD trials, with 1 127 656 participants, including 364 344 with hypertension (Hallan *et al.*, 2012). They found that in the general population and high-risk cohorts, all-cause mortality risk was approximately 1.1 to 1.2 times higher in individuals with hypertension than those with normal blood pressure with preserved eGFR. They also reported that the prevalence of hypertension in patients with CKD ranges from 22% for stage 1 disease to more than 80% in patients with stage 4 disease. They concluded that the risk of all-cause and cardiovascular mortality increased with lower eGFR and higher albuminuria categories for normo- and hypertensive subjects. However, in the 13 CKD cohorts neither the associations with mortality nor with ESRD differed according to hypertensive status. In the second meta-analysis diabetic patients had a higher risk of all-cause and cardiovascular mortality than those without diabetes across a range of eGFRs and albumin-to-creatinine ratios (ACRs) (Fox *et al.*, 2012). Despite higher risks for mortality and ESRD in diabetes, the relative risks of these outcomes by eGFR and ACR are much the same irrespective of the presence or absence of diabetes. This emphasizes the importance of kidney disease as a predictor of clinical outcomes. In the accompanying editorial by Stevens and Farmer (2012), controversy in the management, diagnosis, and treatment of patients with an isolated finding of eGFR between 45 and 60 mL/min/1.73 m² or >60 mL/min/1.73 m² and a urine ACR between 30 and 300 mg g⁻¹ was pointed out.

So far the search for the appropriate assessment of kidney function remains an open issue (Malyszko *et al.*, 2011, 2012; Nair *et al.*, 2011; Matsushita *et al.*, 2012). In CKD patients with eGFR of 45-60 mL/min/1.73 m², even without hypertension and diabetes, the risks of CV mortality were significantly elevated (Cirillo *et al.*, 2012). Taking into consideration these two large meta-analyses, the ASN has released new kidney disease recommendations as part of the "Choosing Wisely" campaign to avoid unnecessary healthcare spending and improve patient outcomes (Williams *et al.*, 2012). According to the ASN Quality and Patient Safety Task Force, estimates suggest that unnecessary testing, procedures, and therapies account for one third of current medical care spending. They selected five recommendations based on relevance and importance to individuals with kidney disease (Williams *et al.*, 2012). Recommendations selected were as follows: do not perform routine cancer screening for dialysis patients with limited life expectancies without signs or symptoms; do not administer erythropoiesis-stimulating agents to CKD

patients with hemoglobin levels =10 g dL⁻¹ without symptoms of anemia; avoid nonsteroidal anti-inflammatory drugs in individuals with hypertension, heart failure, or CKD of all causes, including diabetes; do not place peripherally inserted central catheters in stage 3-5 CKD patients without consulting nephrology; do not initiate chronic dialysis without ensuring a shared decision-making process between patients, their families, and their physicians. Their aim was to "give providers information to facilitate prudent care decisions and empower patients to actively participate in critical, honest conversations about their care, potentially reducing unnecessary health care spending and preventing harm". They also discouraged the measurement of urine microalbumin in patients with a positive urine dipstick. In addition, they wrote that determination of serum erythropoietin concentration was often used needlessly in patients with CKD and ESRD (Williams *et al.*, 2012). Generally speaking, these recommendations are further proof of the emphasis on evidence-based medicine.

Peritoneal dialysis: This year, there was a light at the end of the tunnel for patients on Peritoneal Dialysis (PD). A multicenter, multi-country randomized controlled trial (the balANZ study) found that the administration of a neutral pH, lactate-buffered, low Glucose Degradation Products (GDP) fluid (Balance[®]) to incident PD patients was associated with an appreciable reduction in peritonitis rates and a significant delay in the onset of anuria compared with conventional, standard, lactate-buffered PD solutions (stay.safe[®]) (Johnson *et al.*, 2012a). In two other papers analyzing the secondary endpoints, focused on peritonitis microbiology, treatment, and outcomes as well as peritoneal membrane permeability, small solute clearance and Ultra-Filtration (UF) over a 2-year period were compared with conventional dialysate (Johnson *et al.*, 2012b, c). Biocompatible PD fluid use was associated with a broad reduction in gram-positive, gram-negative and culture-negative peritonitis that reached statistical significance for non-pseudomonal gram-negative organisms (Johnson *et al.*, 2012b). Hospitalizations due to peritonitis were shorter and peritonitis severity was more commonly rated as mild in patients receiving biocompatible PD fluids, although other peritonitis outcomes were comparable between the groups. In the second study, biocompatible and conventional PD solutions exerted differential effects on peritoneal small solute transport rate and UF over time (Johnson *et al.*, 2012c). Over the 2-year study period, peritoneal UF increased significantly in the Balance group but remained stable in controls (difference 24 mL/day/month, p = 0.002), whereas peritoneal small solute

clearances, prescribed dialysate fill volumes and peritoneal glucose exposure were similar between the two groups.

Patency of arteriovenous fistula (AV) is one of the major issues in the hemodialysis population (Gaudino *et al.*, 2011). Lok *et al.* (2012) in a randomized multicenter study investigated the effect of fish oil (4 g day⁻¹) on AV graft failure. At 12 months of follow-up, compared with placebo, fish oil capsules taken four times daily, starting seven days after graft creation, was associated with a lower rate of graft failure, fewer thromboses and fewer interventions (Lok *et al.*, 2012).

Diabetic nephropathy: As we wrote last year (Barylski *et al.*, 2011), bardoxolone methyl appeared on the horizon as a new therapeutic approach for diabetic kidney disease. This year unfortunately, just before the ASN meeting in San Diego, we were informed by Abbott Laboratories Inc. that its partner, Reata Pharmaceuticals, was discontinuing a late-stage trial of bardoxolone, their hoped-for blockbuster treatment for CKD and diabetes, based on safety concerns raised by an independent safety committee. They also confirmed this information during the ASN Congress. Bardoxolone Methyl Evaluation in Patients With Chronic Kidney Disease and Type 2 Diabetes (BEACON) and other trials with bardoxolone were terminated by an independent data-monitoring committee (IDMS) due to safety concerns (Barylski *et al.*, 2011). They found excess serious adverse events and mortality in patients taking the oral anti-inflammatory drug.

Zoja *et al.* (2012) studied the effect of three-month treatment with RTA 405, a synthetic triterpenoid analog of bardoxolone methyl, in Zucker diabetic fatty (ZDF) rats with overt type 2 diabetes. They found that RTA 405 caused severe changes in food intake and diuresis with a decline in body weight, worsening of dyslipidemia and increase in blood pressure together with elevation in serum transaminase followed by liver injury. This compound worsened proteinuria, glomerulosclerosis and tubular damage and in combination with ramipril attenuated its renoprotective effect. Then they studied a variant of RTA 450, dh404, in ZDF rats. This substance did not display beneficial effects on proteinuria, glomerulosclerosis and interstitial inflammation. On the other hand, the presence of a granulomatous and inflammatory process reminiscent of a pseudotumor was observed in some kidneys. Taken together, these data are not in favor of use of bardoxolone analogues in type 2 diabetic nephropathy and they might explain at least in part the necessity to terminate the whole trial due to safety concerns (Zoja *et al.* 2012).

ALTITUDE (The Aliskiren Trial in Type 2 Diabetes Using Cardiorenal Endpoints) study was undertaken to determine whether use of the direct renin inhibitor aliskiren would reduce CV and renal events in patients with type 2 diabetes and CKD, cardiovascular disease, or both (Parving *et al.*, 2012). However, the trial was stopped prematurely after the second interim efficacy analysis. As presented during the ASN meeting in San Diego in November 2012 by Dr. Parving, after a median follow-up of 32.9 months, the primary end point (a composite of the time to cardiovascular death or a first occurrence of cardiac arrest with resuscitation; nonfatal myocardial infarction; nonfatal stroke; unplanned hospitalization for heart failure; end-stage renal disease, death attributable to kidney failure, or the need for renal-replacement therapy with no dialysis or transplantation available or initiated; or doubling of the baseline serum creatinine level) had occurred more frequently in the aliskiren group as compared with the placebo group. However, statistical significance was not reached (HR, 1.08; $p = 0.12$) (Parving *et al.*, 2012). Effects on secondary renal end points (a composite of the renal components of the primary composite end point) were similar. Systolic and diastolic blood pressures were lower with aliskiren and the mean reduction in the urinary albumin-to-creatinine ratio was greater. As could be expected, the proportion of patients with hyperkalemia (serum potassium level = 6 mmol L⁻¹) was significantly higher in the aliskiren group than in the placebo group, as was the proportion with reported hypotension ($p < 0.001$ for both comparisons). The authors of this trial concluded that the addition of aliskiren to standard therapy with renin-angiotensin system blockade in patients with type 2 diabetes who are at high risk for CV and renal events was not supported by these data and may even be harmful (Parving *et al.*, 2012).

Diabetic nephropathy is also the leading cause of ESRD in the developed countries (Jesic *et al.*, 2011; Rysz *et al.*, 2007; Glowinska *et al.*, 2008). Simultaneous pancreas-kidney (SPK) transplantation provides better long-term patient survival compared with single kidney transplantation alone for patients with type 1 diabetes and ESRD (Dinckan *et al.*, 2012). Dr. Trond Jenssen speaking at the European Association for the Study of Diabetes (EASD) 48th Annual Meeting said that the advantage of SPK transplantation over live kidney donation statistically depends on donor age. According to him, patient survival is best in type 1 diabetes mellitus with ESRD when simultaneous kidney-pancreas transplantation is performed.

Cystic disease: During the ASN meeting a definitely positive trial on that issue was also presented

(Torres *et al.*, 2012). In the Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease (ADPKD) and Its Outcomes (TEMPO) 3:4 trial, a large, phase 3 study of the efficacy and safety of tolvaptan in 1445 patients with ADPKD was performed. The study met its primary and secondary end points, when tolvaptan was given at an average dose of 95 mg per day over a 3-year period, slowed the usual increase in kidney volume by 50% and reduced the decline in the glomerular filtration rate (GFR). The effect of tolvaptan on kidney volume was most pronounced during the first year of the study, probably owing to the early reduction in the secretion of cyst fluid (Irazabal *et al.*, 2011). A considerable number of patients discontinued tolvaptan owing to its aquaretic side effects (thirst, polydipsia, polyuria and nocturia) and tolvaptan treatment was also associated with elevated liver enzyme levels, hyponatremia, an increased level of uric acid and gout (Torres *et al.*, 2012; Irazabal *et al.*, 2011). Despite these criticisms, the TEMPO 3:4 study represents a major advance in the quest for a cure for ADPKD (Torres *et al.*, 2012). How might the information from this trial change the future care of patients with ADPKD? Would tolvaptan be a useful drug for the majority of such patients, or should it be prescribed only for those patients at greatest risk for progression to end-stage kidney disease? These questions still need to be answered.

Simple renal cysts are observed frequently in normal kidneys and most nephrologists consider them of little clinical significance. However, Rule *et al.* (2012) in a large study of healthy potential kidney donors, after adjusting for age and sex, found that presence of cysts ≥ 5 mm was associated with higher albumin excretion, hypertension and hyperfiltration.

General clinical nephrology: Chawla *et al.* (2012) in a nonrandomized cohort study on a large population of 742 909 non-emergent isolated CABG cases with CKD compared off-pump coronary artery bypass graft (CABG) surgery with on-pump surgery in regard to in-hospital death or renal replacement therapy. They found that patients with CKD experienced less death or incident renal replacement therapy (RRT) when treated with off-pump compared with on-pump CABG. They suggested that the reduction in incident RRT, not death, was responsible for this effect on the composite endpoint among patients with low eGFR.

Last year we reported about the new indication for eculizumab as a treatment for atypical hemolytic-uremic syndrome (McCaughan *et al.*, 2012; Bomback *et al.*, 2012; Daina *et al.*, 2012; Vivarelli *et al.*, 2012; Herlitz *et al.*, 2012). This is a humanized monoclonal antibody that binds with

high affinity to C5. It prevents cleavage of C5, thereby precluding formation of C5a and the terminal complement complex (C5b-9), which have been implicated in the pathogenesis of both dense deposit disease (DDD) and C3 glomerulonephritis. Three case reports as well as one phase I open-label clinical trial have reported experience with eculizumab in a total of nine patients. On the basis of these rather limited data nephrologists might take into account administration of eculizumab in patients with DDD or C3 glomerulonephritis who have deteriorating renal function or severe nephrotic syndrome despite treatment with plasma exchange.

Similarly, rituximab was used as a rescue therapy in an off-label indication, in lupus nephritis (Rovin *et al.*, 2012). In the LUPus Nephritis Assessment with Rituximab (LUNAR) study patients with class III or class IV lupus nephritis were randomly assigned to receive four intravenous infusions of placebo or 1.0 g of rituximab at baseline, 2 weeks, 24 weeks and 26 weeks on top of glucocorticoids and mycophenolate mofetil (MMF) as an induction therapy. Although, rituximab produced greater reductions in anti-DNA titers and larger improvements in complement levels, the incidence of complete or partial remission at one year with rituximab as compared with placebo was not statistically significant. Therefore, on the basis of these data, use of rituximab in addition to MMF and steroids for initial induction of remission in proliferative lupus nephritis is not supported.

In the CYCLOPS (Cyclophosphamide Therapy for ANCA-associated Systemic Vasculitis) study, similar remission rates in patients with granulomatosis with polyangiitis or microscopic polyangiitis were found independent of the form of cyclophosphamide use: oral versus intravenous (De Groot *et al.*, 2009; Harper *et al.*, 2012). Despite the higher relapse rate in the intravenous pulse group, there was no difference between the two groups in the number of deaths, the incidence of end-stage renal disease, or the median serum creatinine). However, the intravenous therapy led to a significantly lower cumulative dose and less leukopenia (De Groot *et al.*, 2009). This year also the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines on glomerulonephritis were published (KDIGO, 2012a). In other KDIGO guidelines on anemia treatment the emphasis was put on the diagnosis and treatment based upon systematic literature searches last conducted in October 2010, supplemented with additional evidence up to March 2012 (KDIGO, 2012b). It was designed to provide information and assist decision making. The treatment was shifted to iron administration instead of escalating the dose of erythropoiesis-stimulating agent (ESA). On the other hand, the problem of blood transfusion was also addressed (KDIGO, 2012b).

Acute kidney injury: Acute kidney injury (AKI) is an increasingly common clinical problem faced by nephrologists and intensive care specialists, as well as general physicians and surgeons (Alan *et al.*, 2011; Gluba *et al.*, 2010b; Malyszko, 2010). Acute kidney injury (AKI) appears to be associated with a higher risk of CKD even among relatively low-risk patients. Bucaloiu *et al.* (2012) reported that patients with normal renal function prior to AKI who developed AKI but recovered to within 90 percent of pre-AKI eGFR within 90 days were more likely to develop CKD by 3.3 years compared with matched control patients who did not develop AKI. However, it cannot be determined whether AKI caused CKD or AKI and CKD share common risk factors based on this observational study. The recently published Kidney Disease Improving Global Guidelines (KDIGO) Clinical Practice Guidelines for Acute Kidney Injury provide a welcome and timely synthesis of the evidence base to support the management of AKI (KDIGO, 2012c). Unfortunately, only 11% of the recommendation is strong and supported by robust data.

Nephrocardiology: Little is known about the efficacy and safety of ultrafiltration in patients with acute decompensated heart failure complicated by persistent congestion and worsened renal function. Bart *et al.* (2012) randomly assigned a total of 188 patients with acute decompensated heart failure, worsened renal function, and persistent congestion to a strategy of stepped pharmacologic therapy (94 patients) or ultrafiltration (94 patients) and followed them for 60 days. The primary end point was the bivariate change from baseline in the serum creatinine level and body weight, as assessed 96 h after random assignment. In this CARRESS-HF trial (Testani *et al.*, 2010) the use of a stepped pharmacologic-therapy algorithm was superior to a strategy of ultrafiltration for the preservation of renal function at 96 h, with a similar amount of weight loss with the two approaches. Ultrafiltration was associated with a higher rate of adverse events. However, a rise in serum creatinine level during treatment may represent either desired effects of hemoconcentration (when therapy is efficacious) or undesired deterioration of renal function (when therapy is ineffective). In fact, transient changes in serum creatinine levels during therapy for acute decompensated heart failure may not necessarily reflect substantial underlying renal injury or adverse long-term consequences if congestion is adequately relieved (Testani *et al.*, 2010; Dupont *et al.*, 2012). The results of CARRESS-HF may be consistent with the findings of single-center studies of ultrafiltration in patients with the acute cardiorenal syndrome, which have shown a low rate of renal recovery

despite effective volume removal and favorable hemodynamic effects (Malyszko *et al.*, 2010; Patarroyo *et al.*, 2012).

Transplantation: Rizzari *et al.* (2012) reported the 10-year outcomes of a glucocorticoid avoidance strategy following renal transplantation. Among low-risk adult transplant recipients who received allografts between 1999 and 2010 and in whom steroids were discontinued within one week after transplantation, both patient and graft survival were comparable to national data reported by the Scientific Registry of Transplant Recipients in 2009 (Rizzari *et al.*, 2012; Machnicki *et al.*, 2011). Moers *et al.* (2009) reported in 2009 that machine or pulsatile perfusion of the kidney to be transplanted, versus cold storage, appeared to reduce the incidence of delayed allograft function and improve allograft survival at one year. In 2012 the same group found that the three-year graft survival remained superior for machine perfused kidneys compared with cold storage (Moers *et al.*, 2012).

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