

Blood pressure and kidney update 2016/2017

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Submitted: 12 January 2018

Accepted: 10 February 2018

Arch Med Sci

DOI: <https://doi.org/10.5114/aoms.2018.73555>

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Abstract

The most important studies – from randomized controlled trials to perspective studies and meta-analyses, and guidelines in the topics of blood pressure and kidney research published in 2016 (and at the beginning of 2017) were reviewed. In the blood pressure area, the most important were the Systolic Blood Pressure Intervention Trial (SPRINT), which might have a great impact on the clinical practice as well as on the forthcoming guidelines, including the US recommendations recently published. Similarly important was the Heart Outcomes Prevention Evaluation (HOPE)-3 trial, which clearly confirmed that only combination therapy with antihypertensive drugs and statins might be effective in prevention of cardiovascular outcomes in patients at high risk of cardiovascular disease events. The research on kidney diseases was very interesting and extensive in 2016, and we have tried to present the most important data from the following areas: glomerulopathies, diabetic nephropathy, lupus nephritis, acute kidney injury, chronic kidney disease – risk factors, management and complications, and hemodialysis.

Key words: blood pressure, chronic kidney disease, guidelines, hypertension, kidney, studies.

Blood pressure update 2016

The Systolic Blood Pressure Intervention Trial (SPRINT) included 2636 persons aged 75 years and older (mean age: 79.9 years; 37.9% women) who were randomized to a systolic blood pressure (SBP) target of less than 120 mm Hg or to a SBP target of less than 140 mm Hg [1]. Of 1317 persons randomized to a SBP less than 120 mm Hg, 440 (33.4%) were frail. Of 1319 persons randomized to a SBP less than 140 mm Hg, 375 (28.4%) were frail. The primary composite outcome of nonfatal myocardial infarction, acute coronary syndrome not resulting in a myocardial infarction, nonfatal stroke, nonfatal acute decompensated heart failure, and cardiovascular death was reduced 34% ($p = 0.001$) and all-cause mortality 33% ($p = 0.009$) by a SBP less than 120 mm Hg [1]. These outcomes were not different in frail persons. Persons with a SBP less than 120 mm Hg also had a 37% reduction in nonfatal heart failure ($p = 0.03$) and a 32% reduction in the primary outcome plus all-cause mortality ($p < 0.001$) [1]. The absolute rate of serious adverse events was 2.4% in the lower SBP treatment group versus 1.4% in the standard SBP treatment group

(p not significant). Orthostatic hypotension occurred in 21.0% in the lower SBP treatment group versus 21.8% in the standard SBP treatment group (p not significant) [1]. This study did not include patients living in a nursing home or patients with diabetes mellitus, prior stroke, symptomatic heart failure, or a left ventricular ejection fraction (LVEF) below 35% [1]. The SPRINT eligibility criteria are present in the United States adult population in 7.6% (16.8 million adults) and in 16.7% (8.2 million) of adults with treated hypertension [2]. Stricter BP control is associated with a reduced risk of major cardiovascular events [3].

The American College of Cardiology (ACC)/American Heart Association (AHA) 2017 guidelines will have to answer on the basis of expert medical opinion many questions not answered by SPRINT [4]. What should the SBP goal and the diastolic blood pressure (DBP) be in patients with diabetes mellitus, an acute coronary syndrome, prior stroke or transient ischemic attack, heart failure with a preserved or reduced LVEF, a LVEF below 35%, younger than 50 years, at low-risk for cardiovascular events, or those residing in a nursing home? [4]. The 2015 AHA/ACC/American Society of Hypertension scientific statement on treatment of hypertension in patients with coronary artery disease recommends a blood pressure (BP) goal of less than 140/90 mm Hg in patients with stable angina pectoris, an acute coronary syndrome, and heart failure but state that a BP goal of less than 130/80 mm Hg may be appropriate, especially in those patients with a prior myocardial infarction or stroke or at high risk for developing either [5].

The data from the study by Shih *et al.* found a J-shaped association between observed blood pressure and all-cause mortality in older adults [6]. The blood pressure J curve is extensively discussed elsewhere [7]. The DBP should not be reduced below 60 mm Hg in any person with coronary artery disease with myocardial ischemia, diabetes mellitus, or older than 60 years of age [8, 9]. The SBP should not be reduced below 110 mm Hg in these persons [8]. Cardiovascular risk should be assessed to guide hypertension diagnosis and treatment [10]. Although numerous investigators favor treating patients with cardiovascular risk factors with hypertension to a BP goal of less than 120/80 mm Hg [11], not all do [12]. Hypertension in high-risk patients could be defined as a BP \geq 130/80 mm Hg with a threshold of treatment of 130/80 mm Hg with a goal SBP of less than 120 mm Hg [13].

The Orthostatic Hypotension in Diabetics in the Action to Control Cardiovascular Risk in Diabetes Blood Pressure (ACCORD BP) trial investigated the prevalence, incidence, and prognostic significance of orthostatic hypotension in the ACCORD BP tri-

al [14, 15]. The persons in this trial had a mean age of 62.1 years and were at high risk for having orthostatic hypotension because all of the participants had type 2 diabetes mellitus, had systemic hypertension, and were treated with antihypertensive drugs. The participants were also randomized to treatment with antihypertensive drugs to reduce the SBP to less than 120 mm Hg or to less than 140 mm Hg. After 1 year, the SBP was 119.3 mm Hg with intensive blood pressure control versus 133.5 mm Hg with standard antihypertensive drug therapy [14].

At 48 months, the prevalence of orthostatic hypotension was 12.2% in hypertensive diabetics treated to a SBP below 120 mm Hg versus 13.5% in hypertensive diabetics treated to a SBP below 140 mm Hg (p not significant) [14]. At 48 months, the incidence of orthostatic hypotension was 9.9% in hypertensive diabetics treated to a SBP below 120 mm Hg versus 11.0% in hypertensive diabetics treated to a SBP below 140 mm Hg (p not significant) [14]. Orthostatic hypotension was associated with a 62% increase in all-cause mortality ($p = 0.02$) and with a 85% increase in heart failure death or hospitalization ($p = 0.01$) [14].

A randomized clinical trial using a similar number of participants and design used in SPRINT needs to be performed in older hypertensive diabetics to investigate whether the SBP goal should be less than 120 mm Hg or less than 140 mm Hg in these persons [15]. The Orthostatic Hypotension in ACCORD BP study reassures us that hypertensive diabetics treated to a SBP goal of less than 120 mm Hg will not have a higher prevalence or incidence of orthostatic hypotension than hypertensive diabetics treated to a SBP goal of less than 140 mm Hg [14, 15].

A meta-analysis of 19 randomized antihypertensive drug trials including 44,989 patients showed that patients treated with more intensive BP lowering treatment had a mean BP of 133/76 mm Hg compared to 140/81 mm Hg in the less intensive BP treatment group [16]. At 3.8-year mean follow-up, compared with less intensive BP treatment, more intensive BP treatment reduced major cardiovascular events 14%, myocardial infarction 13%, stroke 22%, albuminuria 10%, and retinopathy progression 19% [16]. Compared with less intensive BP treatment, more intensive BP treatment insignificantly reduced heart failure 15%, end-stage kidney disease 10%, cardiovascular death 9%, non-cardiovascular death 2%, and all-cause mortality 9% [16].

A meta-analysis of 123 antihypertensive drug trials including 613,815 patients showed that every 10 mm Hg reduction in SBP significantly reduced major cardiovascular disease events 20%, coronary heart disease 17%, stroke 27%, heart

failure 28%, and all-cause mortality 13% [17]. The effect on renal failure was a 5% insignificant reduction [17].

The Heart Outcomes Prevention Evaluation (HOPE)-3 trial randomized 12,705 persons, mean age 65.7 years (20.2% white, 29.0% Chinese, 14.7% South Asian, 5.4% other Asian, 27.4% Hispanic 1.8% black, 1.6% other; 46% women) at intermediate risk who did not have cardiovascular disease with a mean BP of 138.1/81.9 mm Hg to receive candesartan 16 mg daily plus hydrochlorothiazide 12.5 mg daily or placebo [18]. The reduction in BP was 6.0/3.0 mm Hg greater in the BP treatment group than in the placebo group. Median follow-up was 5.6 years. The first co-primary endpoint of a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was insignificantly reduced 7% by active treatment [18]. The second co-primary endpoint additionally included resuscitated cardiac arrest, heart failure, and revascularization and was insignificantly reduced 5% by active treatment. Persons in the upper third of SBP (> 143.5 mm Hg) had a significant reduction in the first co-primary endpoint of 23% ($p = 0.02$) and in the second co-primary endpoint of 28% ($p = 0.009$) if they were treated with candesartan plus hydrochlorothiazide [18]. Reasons for the difference in results between the SPRINT trial and the HOPE-3 trial are discussed by their investigators [19, 20].

Treatment of hypertension in high-risk persons to a SBP treatment goal of less than 120 mm Hg yields 10.5 quality-adjusted life-years and accrues \$176, 584 in lifetime costs [21]. Treatment of these high-risk persons to a SBP treatment goal of less than 140 mm Hg yields 9.6 quality-adjusted life-years and accrues \$155, 261 in lifetime costs [21].

The National Heart Foundation of Australia has updated their 2016 guideline for management of hypertension [22]. Their guideline now recommends ambulatory and/or home BP monitoring if the clinic BP is $\geq 140/90$ mm Hg as out-of-clinic BP is a stronger predictor of outcome. Their guideline also recommends in selected high cardiovascular risk populations a SBP goal of less than 120 mm Hg to improve cardiovascular outcomes. Close follow-up is recommended in these patients to identify treatment-related adverse effects including hypotension, syncope, electrolyte abnormalities, and acute kidney injury [22].

The 2016 Canadian hypertension guideline recommends for high-risk patients aged 50 years and older with SBP levels of 130 mm Hg and higher intensive BP management to target a SBP goal of 120 mm Hg and lower [23]. Intensive BP management should be guided by automated office BP measurements. Clinical indications defining high-risk patients for consideration for intensive BP

management are clinical or subclinical cardiovascular disease or chronic kidney disease (nondiabetic nephropathy, proteinuria < 1 g/day, estimated glomerular filtration rate 20–59 ml/min/1.73 m²) or estimated 10-year global cardiovascular risk $\geq 15\%$ or age ≥ 75 years [23]. Patients with 1 or more of these clinical indications should consent to intensive BP management [23].

At 24-year median follow-up of the Trials of Hypertension Prevention, in which 744 phase I and 2,382 phase II participants randomized to sodium reduction or control, there was an increased risk of all-cause mortality for high sodium intake and a direct relationship with all-cause mortality, even at the lowest levels of sodium intake [24]. The hazard ratio per unit increase in sodium/potassium ratio was 1.13 ($p = 0.04$) [24].

A pooled analysis of 4 studies including 63,559 persons with hypertension and 69,559 persons without hypertension, median age 55 years, showed that increased sodium intake was associated with a greater increase in SBP in persons with hypertension (2.08 mm Hg increase per 1 g sodium increase) than in persons without hypertension (1.22 mm Hg increase per 1 g sodium increase), $p < 0.0001$ [25]. Compared with a moderate sodium intake, high sodium intake was associated with a 23% increase in cardiovascular events and death ($p < 0.0001$) in persons with hypertension but not in persons without hypertension [25]. A low sodium intake was associated with an increased risk of cardiovascular events and death in persons with and without hypertension [25].

Recently there have been also many studies, in which the authors evaluate the role of nutraceuticals/natural products on the atherosclerosis, including their effectiveness on lipid disorders, blood pressure (and its complications) as well as inflammation or oxidative stress [26–33]. A meta-analysis of 7 randomized trials comprising 9 treatment arms in 587 patients showed that compared to placebo, the dietary flavonol quercetin reduced BP 3.04 mm Hg ($p = 0.028$)/2.63 mm Hg ($p < 0.001$) [26]. Further studies are indicated to investigate the clinical relevance of these results and the possibility of using quercetin with dosages greater than 500 mg/day as an add-on to antihypertensive drug therapy [34]. A meta-analysis of 15 randomized trials with 16 treatment arms in 739 persons showed that pentoxifylline (a methylxanthine derivative and a nonselective phosphodiesterase inhibitor with hemorheological activity) had no effect on SBP or DBP or plasma IL-6 concentration [27]. However, pentoxifylline reduced plasma concentrations of TNF- α ($p < 0.001$) and C-reactive protein ($p = 0.034$) [35].

Using data from a population-based 11-cohort International Database on Ambulatory Blood

Pressure Monitoring in Relation to Cardiovascular Outcomes, a study compared daytime ambulatory blood pressure monitoring with conventional blood pressure measurements in 653 untreated persons with white coat hypertension and 653 normotensive control persons [28]. Median follow-up was 10.6 years. This study demonstrated that after accounting for age, the size of the white coat effect was not influenced by the severity of risk for cardiovascular disease or the presence of past cardiovascular disease events [28]. The risk of cardiovascular disease in most persons with white coat hypertension was comparable to age- and risk-adjusted normotensive control persons [36].

It is obvious that the described studies present only in the limited form the most important issues from the area of blood pressure, including the above-mentioned, just being published, new ACC/AHA 2017 guidelines [37], which will be reviewed and presented in details separately. Thus, it is worth to mention at least about the other important studies, including the ones on the role of antihypertensive therapy on arterial stiffness [38], on the role of fixed combination/polypill therapy on complicated hypertension in patients with many other risk factors [39–47], as well as on the relation on relation of supine BP to sitting BP and ambulatory BP with regard to identification of diagnostic cut-offs for hypertension [48].

Kidney update 2016

Year 2016 (as well as in the beginning of 2017) has been really interesting in the field of kidney research; several important findings were reported in the field of glomerulopathies, diabetic nephropathy, and lupus nephritis but also in hemodialysis and renal transplantation [49–62]. It is obvious that for the current review we have selected only the most important ones in the authors' opinion.

Glomerulopathies

The optimal role of immunosuppressive therapy in the treatment of IgA nephropathy remains controversial in 2016. Results of a recently completed randomized controlled trial (RCT) and a retrospective analysis of the VALIGA study provided different results [63, 64]. The STOP IgA study strongly support conservative care rather than immunosuppressive therapy in patients at high risk for progression [63]. STOP IgA trial included 379 IgAN patients from 32 nephrology centers in Germany. During a run-in phase of 6 months, patients received supportive care therapy including RAS blockers, dietary counseling, advice to stop smoking and avoid nephrotoxic drugs, and statins if required. After 6 months, 177 patients with proteinuria > 0.75 g/day (non-responder patients)

were randomized to continued supportive care or supportive care plus immunosuppression (monotherapy with CS or combined therapy with three immunosuppressant's). After 36 months, there was no significant difference in the annual decline in estimated glomerular filtration rate (eGFR) between the two groups. More patients in the immunosuppression group than in the supportive-care group had severe infections, impaired glucose tolerance, and weight gain of more than 5 kg in the first year of treatment [63]. In an interesting pro/con debate, Pozzi considered that the conclusions are questionable for several reasons: (1) studies on time-average proteinuria have shown that beneficial effects on renal survival are not evident after 36 months, and only emerge over the course of longer observation periods; (2) supportive care in the STOP-IgAN study resulted in a small loss of renal function during the 36 months of observation (annual decrease in the eGFR of 1.6 ml/min/1.73 m²), but was unable to reduce proteinuria below 1 g/day; in contrast, 6 months of steroid therapy lowered proteinuria below 1 g/day; and (3) the lack of any assessment of histological data does not allow to assess the importance of morphological lesions on renal survival and therapy [65].

The VALIGA study retrospectively analyzed long-term benefits of corticosteroids (CS) in 1147 patients with IgA nephropathy possible including patients with an initial eGFR < 50 ml/min/1.73 m² [64]. Most patients received RAS blockers (86%), 46% had corticosteroids (associated in a minority of patients with other immunosuppressive drugs). Corticosteroids treatment reduced proteinuria and the rate of renal function decline and increased renal survival [64]. Recently presented preliminary data (ERA/EDTA 2016) from the TESTING (Therapeutic Evaluation of Steroids in IgA Nephropathy) study also showed a benefit of corticosteroids [4]. The TESTING Study included 262 patients with IgAN, proteinuria > 1 g/day, and eGFR = 20–120 ml/min/1.73 m² randomized to 0.8 mg/kg/day oral methylprednisolone for 2 months, with weaning over 6–8 months. At the interim analysis time point, a significant benefit of corticosteroids was found compared to supportive therapy with optimized RASBs; time-averaged proteinuria was significantly reduced in the corticosteroid arm ($p < 0.001$). However, The RCT was stopped prematurely after a median follow-up of 1.5 years because of excessive serious AEs, mostly infections, two of which were fatal [66].

Some new preliminary data are also available in focal segmental glomerulosclerosis (FSGS). In the late-breaking High-Impact Clinical Trials oral session at the American Society of Nephrology (ASN) Kidney Week new available data from the DUET study was presented: an international,

randomized, double-blind, phase 2 clinical trial assessing the safety and efficacy of sparsentan (a selective dual-acting receptor antagonist with affinity for endothelin – A type) in 109 patients with primary FSGS [67]. The primary endpoint was change in proteinuria. The mean reduction of proteinuria from baseline after eight weeks of treatment for all patients treated with 200, 400, and 800 mg/day of sparsentan ($n = 64$) was 44.8%, compared to a mean reduction of proteinuria for all patients receiving 300 mg/day of irbesartan ($n = 32$) of 18.5% ($p = 0.006$). Furtherer more, the mean reduction of proteinuria from baseline after 8 weeks of treatment for all patients treated with 400 mg and 800 mg doses of sparsentan ($n = 51$) was 47.4%, compared to a mean proteinuria reduction of 19.0% for patients receiving 300 mg of irbesartan ($n = 25$) [68].

Diabetic nephropathy

Important new data regarding nephroprotection in type 2 diabetes were recently published. In the EMPA-REG OUTCOME trial, empagliflozin, a sodium-glucose co-transporter 2 inhibitors, reduced clinically relevant renal events when added to standard of care in patients with type 2 diabetes [69]. Incident or worsening nephropathy occurred in 525 of 4124 patients (12.7%) in the empagliflozin group and in 388 of 2061 (18.8%) in the placebo group (hazard ratio (HR) = 0.61; 95% confidence interval (CI) = 0.53 to 0.70; $p < 0.001$). Doubling of the serum creatinine level occurred in 70 of 4645 patients (1.5%) in the empagliflozin group and in 60 of 2323 (2.6%) in the placebo group, a significant relative risk reduction of 44%. Renal-replacement therapy was initiated in 13 of 4687 patients (0.3%) in the empagliflozin group and in 14 of 2333 patients (0.6%) in the placebo group, representing a 55% lower relative risk in the empagliflozin group [69]. Additionally, canagliflozin may also confer renoprotective effects independently of its glycaemic effects; a secondary analysis of 2 years of follow-up data from a randomized controlled trial comparing treatment with the SGLT2 inhibitor canagliflozin to glimepiride showed that canagliflozin slows the progression of kidney function decline in patients with type 2 diabetes who are already receiving metformin [70]. In the subgroup of patients with baseline urinary albumin-to-creatinine ratio ≥ 30 mg/g, urinary albumin-to-creatinine ratio decreased more with canagliflozin 100 mg (31.7%; 95% CI: 8.6–48.9%; $p = 0.01$) or canagliflozin 300 mg (49.3%; 95% CI: 31.9–62.2%; $p < 0.001$) than with glimepiride [70].

The glucagon-like-peptide 2 (GLP-1) agonist liraglutide also delays progression of renal events – in particular, new-onset persistent macro albuminuria – in patients with type 2 diabetes, accord-

ing to the latest data from the Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results – A Long Term Evaluation (LEADER) trial [71]. Time to persistent doubling of creatinine, ESRD, and death due to renal disease was similar in both groups. There was a statistically but not clinically significant rate of decline in eGFR, which was driven by the subgroup of patients with CKD 3 at baseline [71].

Several mechanisms might explain the renoprotection seen in both trials: 1) better control of well-known renal risk factors (glycaemic control, blood pressure, dyslipidaemia, uric acid concentration) and a modest improvement in body weight; 2) these drugs could affect directly renal physiology. SGLT2 inhibitors decrease sodium and glucose reabsorption [72]. As a result, the delivery of glucose and sodium is increased in the distal tubule and the juxtaglomerular apparatus, which is sensed as an increase in glomerular perfusion. This leads to a feedback signal that causes afferent arteriolar vasoconstriction, an acute fall in glomerular perfusion and pressure, as well as a diminished extracellular plasma volume and BP [73].

Two new studies reported a significant reduction in proteinuria in patients with type 2 diabetes. Preliminary data from the ETUDE (Effect of Topiroxostat on Urinary Albumin in Hyperuricemic Patients with Diabetic Nephropathy) study showed a significant reduction in UACR in patients who received 40 mg/day or 160 mg topiroxostat/day compared with placebo [74]. The important role of the nitric oxide pathway in the progression of diabetic nephropathy is well described [75]. Two weeks of daily oral treatment with 20 mg of PF-00489791 (the first long-acting PDE5i – phosphodiesterase type 5 inhibitor), reduces UACR by 16% (95% CI: 2–27%) compared with placebo in diabetic subjects with stage 3 or 4 CKD and overt albuminuria, with values returning to baseline 4 weeks after treatment cessation [76].

Lupus nephritis

Almost 60% of patients with systemic lupus erythematosus (SLE) develop lupus nephritis (LN). Lupus nephritis is a major risk factor for overall morbidity and mortality in SLE, and despite potent anti-inflammatory and immunosuppressive therapies 30% of the patients still develop end stage renal disease (ESRD) [77]. This year calcineurin inhibitors have been tested extensively in LN, especially in Asia, with very encouraging result. In the first study, tacrolimus (TAC) was non-inferior to mycophenolate mofetil (MMF), when combined with prednisolone, for induction therapy of active LN. One hundred and fifty patients (81% class III/IV) were randomized to 76 MMF or 74 TAC [78]. At month 6, the rate of complete renal response was

59% in the MMF and 62% in the TAC group (treatment difference: 3.0% (-12%, 18%); $p = 0.71$). Maintenance therapy with azathioprine was given to 79% patients. After 60.8 ±26 months, proteinuric and nephritic renal flares developed in 24% and 18% of patients in the MMF group and 35% ($p = 0.12$) and 27% ($p = 0.21$) in the TAC group, respectively. The cumulative incidence of a composite outcome of decline of creatinine clearance by ≥ 30%, development of chronic kidney disease stage 4/5 or death was 21% in the MMF and 22% in the TAC group of patients ($p = 0.35$) [78].

For patients with acute lupus nephritis, an induction regimen of voclosporin, a novel calcineurin inhibitor, plus mycophenolate mofetil and oral corticosteroids seems to be effective, according with the preliminary data from LUNA-LV (Aurinia Urinary Protein Reduction Active–Lupus with Voclosporin) study [67]. Two hundred and sixty-five patients received mycophenolate mofetil 2 g plus low-dose oral corticosteroids (≤ 10 mg/day). In addition, patients in the low-dose group received voclosporin 23.7 mg twice daily, and patients in the high-dose group received voclosporin 39.5 mg twice daily. The primary outcome of the trial was complete remission at 24 weeks, but the trial will continue out to 48 weeks, when the same end points will be reanalyzed. At week 24, complete remission was achieved by 32.6% in the low dose group, 27.3% in the high dose group, and 19.3% in the placebo group with no difference in renal function over time in any of the groups [67].

Acute kidney injury

It is well established that acute kidney injury (AKI) is associated with an increased risk of death prolonged hospital stay, increased longer-term risks of chronic kidney disease [79]. Recently, in a large prospective study including more than 40,000 patients, AKI development was an independent risk factor for hypertension [80]; in multivariable models, AKI was independently associated with a 22% (95% CI: 12–33%) increase in the odds of developing elevated BP during follow-up [80].

In the last years several important trials to prevent or to ameliorate the course of AKI have been published, mostly with disappointed results. Recently, a number of new data were presented. Fluid management remains the cornerstone of prevention and treatment of AKI. Fluid overload was associated with increased risk of acute kidney injury and increased mortality risk in patients admitted in intensive unit care in two recent studies [81, 82]. In a prospective study including all consecutive patients admitted to 21 intensive care units, both the severity and rapidity for fluid accumulation development represented indepen-

dent risk factors for mortality [81]. This prospective study included 1734 patients; 560 (32%) had AKI but did not have renal replacement therapy (RRT) and 183 (11%) had AKI-RRT. The odds ratio (OR) for hospital mortality increased by 1.075 (95% CI: 1.055–1.095) with every 1 % increase of fluid overload (FO). When adjusting for severity of illness and AKI status, the OR changed to 1.044. Multivariate analysis confirmed that the speed of fluid accumulation was independently associated with ICU mortality. Moreover, fluid accumulation increased significantly in the 3-day period prior to the diagnosis of AKI and peaked 3 days later [81]. Similarly, The BAKIT study followed 2526 ICU patients that stratified according to the KDIGO AKI guideline [82]. For all patient fluid balance was recorded at 24, 48 and 72 h. 1172 developed AKI during the first 3 days. The mortality and the FO were significantly higher in the AKI group ($p < 0.001$) and the FO was an independent risk factor for the incidence of AKI ($p < 0.001$). Non-surviving patients with AKI also had higher fluid balance ($p < 0.001$) than survivors did [82].

Fluid choices are being gradually examined and studied, with recent attention to the chloride content of crystalloid fluids and their relation to kidney injury. In this context, Young *et al.* have conducted the first large multicenter prospective RCT to investigate the risks associated with normal saline vs. a balanced solution (plasmalyte 148) administration in the ‘SPLIT study [83]. Two thousand two hundred and seventy-eight intensive care unit (ICU) patients were randomized to receive either N saline or plasmalyte. The primary outcome was development of AKI (doubling of the serum creatinine level or a serum creatinine level > 3.96 mg/dl owing to an increase of > 0.5 mg/dl). In the buffered crystalloid group, 9.6% developed AKI compared with 9.2% in the saline group (absolute difference = 0.4%, $p = 0.77$). There was also no difference in the need for renal replacement therapy (3.3% vs. 3.4%, $p = 0.91$) or in-hospital mortality (7.6% vs. 8.6%, $p = 0.40$). However, these findings were followed by several editorials analyzing the limitation of the study: 1) the volume of fluid administered was modest, with a median of 2 l administered. It remains unknown if such a modest amount of fluid would result in any hyperchloraemia. 2) The included patients could not be representative for patients admitted to the ICU given their relatively low severity of disease at baseline (mean APACHE II score = 14), low in-hospital mortality (~8%) and low RRT rates (~3%) during hospital stay [83]. In this context the authors have concluded, “further large randomized clinical trials are needed to assess efficacy in higher-risk populations and to measure clinical outcomes such as mortality” [84].

It was hypothesized that more dialysis or earlier initiation of dialysis could potentially improve patient outcomes [85]. Recently, two randomized trials that focused on timing strategies for initiation of RRT in critically ill patients with AKI have reported conflicting findings [86, 87]. In Early Versus Late Initiation of Renal Replacement Therapy In Critically Ill Patients With Acute Kidney Injury (ELAIN) trial 231 mostly post-surgical critically ill adults with KDIGO stage 2 AKI were randomized into 2 treatment groups: a group that initiated early kidney replacement therapy (early group; within 8 hours of reaching stage 2 AKI) and a group that delayed initiation of kidney replacement (delayed group; 12 h after having reached stage 3 AKI per KDIGO criteria) [86]. Mortality after 90 days was 39.3% in the early group compared with 54.7% in the delayed group ($p = 0.03$), for an absolute risk reduction of -15.4% (95% CI: -28.1% to -2.6%). The secondary end points were also significantly different between the groups, including shorter duration of kidney replacement therapy (median, 9 days for the early group vs. 25 days for the delayed group), mechanical ventilation (125.5 h for the early group vs. 181 h for the delayed group), and overall hospital length of stay (51 days for the early group vs. 82 days for the delayed group). Recovery of kidney function without the need for dialysis was also more common in the early treatment group (53.6% for the early group vs 38.7% for the delayed group) [86]. In the Artificial Kidney Initiation in Kidney Injury (AKIKI) trial 620 critically ill adults with stage 3 AKI (according to the KDIGO classification) who were receiving mechanical ventilation and/or vasopressor support were randomized to two strategies of RRT initiation [87]. The early treatment strategy involved starting RRT within 6 h of fulfilling KDIGO stage 3 AKI. The delayed treatment strategy mandated the initiation of RRT if one or more of the following predefined items were present: BUN > 36 mmol/l, potassium > 6 mmol/l, magnesium > 4 mmol/l, severe oliguria or edema. The results showed that early RRT reduced mortality at 90 days by 15.4% compared to delay RRT (39.3% vs. 54.7%, respectively, HR = 0.66, 95% CI: 0.45–0.97). The rate of catheter-related bloodstream infections was higher in the early-strategy group than in the delayed-strategy group (10% vs. 5%, $p = 0.03$) [87]. The interpretation and comparison of the two studies is limited due to considerable differences in study designs [88]. The crucial difference is the time at which renal replacement therapy was initiated [88]. Two large multi-center trials are under way (STARRT-AKI and IDEAL-ICU) and hopefully will provide new insights for the initiation of RRT in critically ill patients with AKI [89].

Chronic kidney disease (CKD)

Risk factors for developing or for CKD progression

Until this year, it was unclear whether sodium and potassium intake is relevant for the development of CKD in the general population; in a recently published, large prospective population-based cohort study, low urinary potassium was associated with a higher risk of developing CKD [90]. This study included 5315 individuals free of CKD at baseline from the Prevention of Renal and Vascular End-Stage Disease (PREVEND) study, a prospective, population-based cohort of Dutch men and women aged 28 to 75 years. Urinary sodium (UNaV) and potassium excretion (UKV) were measured in two 24-hour urine specimens at baseline (1997–1998) and midway during follow-up (2001–2003). During a median follow-up of 10.3 years, 872 patients developed CKD. Each 21-mmol/24 h (1 SD) decrement in UKV was significantly associated with a 16% higher risk of developing CKD (multivariable-adjusted HR = 1.16; 95% CI: 1.06–1.28). The inverse association of UKV with the risk of developing CKD remained after adjustment for confounders, CKD risk factors, and potential mediators of the association – such as systolic BP, antihypertensive medication, and plasma potassium [90]. Surprisingly, the authors did not observe an association for UNaV, as an estimate of sodium intake, with the risk of developing CKD [90].

In another prospective study published in April, He *et al.* studied the association of urinary sodium and potassium excretion with CKD progression and all-cause mortality among 3939 patients with CKD from the Chronic Renal Insufficiency Cohort (CRIC) Study [91]. Urinary sodium and potassium excretion were measured using three 24-hour urine specimens and CKD progression was defined as incident ESRD or halving of eGFR. Compared with the lowest quartile of urinary sodium excretion (< 116.8 mmol/day), hazard ratios (95% confidence intervals) for the highest quartile of urinary sodium excretion (≥ 194.6 mmol/day) were 1.54 (1.23 to 1.92) for CKD progression, 1.45 (1.08 to 1.95) for all-cause mortality, and 1.43 (1.18 to 1.73) for the composite outcome of CKD progression and all-cause mortality after adjusting for multiple covariates, including baseline eGFR. Additionally, compared with the lowest quartile of urinary potassium excretion (< 39.4 mmol/day), hazard ratios for the highest quartile of urinary potassium excretion (≥ 67.1 mmol/day) were 1.59 (1.25 to 2.03) for CKD progression, 0.98 (0.71 to 1.35) for all-cause mortality, and 1.42 (1.15 to 1.74) for the composite outcome. These data indicate that high urinary sodium and potas-

sium excretion are associated with increased risk of CKD progression [91].

Recently, the association of proton pumps inhibitors (PPI) with incident CKD and CKD progression was demonstrated. Lazarus *et al.* analyzed longitudinal data from two large patient cohorts in the United States, the Atherosclerosis Risk in Communities study ($n = 10,482$) and the Geisinger Health System ($n = 248,751$), in order to evaluate the relationship between PPI use and the development of CKD [92]. In the ARIC cohort, PPI use was associated with incident CKD in analysis adjusted for demographic, socioeconomic, and clinical variables (HR = 1.50; 95% CI: 1.14–1.96). The association persisted when baseline PPI users were compared directly with H₂ receptor antagonist users (adjusted HR = 1.39; 95% CI: 1.01–1.91) and with propensity score-matched nonusers (HR = 1.76; 95% CI: 1.13–2.74). In the Geisinger Health System replication cohort, PPI use was associated with CKD in all analyses, including a time-varying new-user design (adjusted HR = 1.24; 95% CI: 1.20–1.28). Twice-daily PPI dosing (adjusted HR = 1.46; 95% CI: 1.28–1.67) was associated with a higher risk than once-daily dosing (adjusted HR = 1.15; 95% CI: 1.09–1.21). The author underlines the major limitation – an observational study that does not provide evidence of causality [92]. A second study was performed using Department of Veterans Affairs national databases to build a primary cohort of new users of PPI ($n = 173,321$) and new users of histamine H₂-receptor antagonists (H₂ blockers; $n = 20,270$) [93]. Over 5 years, 15% of PPI users were diagnosed with CKD, versus 11% of those on H₂-blockers. Patients treated with PPI also had a significantly elevated risk of doubling of serum creatinine level (HR = 1.53; 95% CI: 1.42–1.65), of eGFR decline > 30% (HR = 1.32; 95% CI: 1.28–1.37), and of ESRD (HR = 1.96; 95% CI: 1.21–3.18). Furthermore, the authors detected a graded association between duration of PPI exposure and risk of renal outcomes among those exposed to PPI for 31–90, 91–180, 181–360, and 361–720 days compared with those exposed for ≤ 30 days [93].

CKD complications – anemia

Erythropoiesis stimulating agents and iron therapy now form the cornerstone of anaemia management in CKD [94]; however, the type of iron therapy and route of administration have been topics of much controversy. Oral iron therapies offer safe and efficient options to treat iron deficiency anemia but are associated with increased gastrointestinal AEs, lack of patient adherence, and very often, lack of efficacy in patients with stage 5 CKD. Treatment with *i.v.* iron may be associated with more serious safety concerns, such

as or oxidative stress [95]. FIND-CKD was a 1-year, open-label, multicenter, prospective study recruiting patients with non-dialysis-dependent CKD, anemia and iron deficiency randomized (1 : 1 : 2) to *i.v.* ferric carboxymaltose (FCM), targeting higher (400–600 $\mu\text{g/l}$) or lower (100–200 $\mu\text{g/l}$) ferritin oral iron [96]. The incidence of one or more adverse events, cardiac disorders and infections were similar between groups. At least one ferritin level $\geq 800 \mu\text{g/l}$ occurred in 26.6% of the high ferritin FCM subgroup, but with no associated increase in adverse events. Estimated glomerular filtration rate remained the stable in all groups. Hepcidin is the key regulator of iron homeostasis but data are limited regarding its temporal response to iron therapy, and response to intravenous versus oral iron. Recently, significant data were published [97]. Serum hepcidin levels were measured centrally in a subset of 61 patients from FIND-CKD study. Hepcidin levels rise in response to iron therapy regardless of when the iron is administered periodically via *i.v.* administration or continuously via daily oral dosing. However, the speed and extent of the rise was greatest with *i.v.* iron targeting a higher ferritin level than with oral iron or when *i.v.* iron was used to target a lower ferritin level, reflecting differences in the rate of delivery of iron with each type of treatment [97].

The most promising molecules studied for anemia treatment in CKD patients are HIF prolyl-4-hydroxylase (PH) inhibitors. Vadadustat, also known as AKB-6548, is a novel, oral HIF-PH inhibitor in development for the treatment of anemia in both non-dialysis-dependent (NDD) and dialysis-dependent CKD patients [98]. In a 20-week, double-blind, randomized, placebo controlled, phase 2b study, Pergola *et al.* evaluated the efficacy and safety of once-daily vadadustat in patients with stages 3a to 5 non-dialysis-dependent CKD [98]. The primary endpoint was the percentage of patients who, during the last 2 weeks of treatment, achieved or maintained either a mean hemoglobin level of 11.0 g/dl or more or a mean increase in hemoglobin of 1.2 g/dl or more over the pre-dose average. Significantly, the primary endpoint was met in 54.9% of patients on vadadustat and 10.3% of patients on placebo. Significant increases in both reticulocytes and total iron binding capacity and significant decreases in both serum hepcidin and ferritin levels were observed in patients on vadadustat compared with placebo. The overall incidence of adverse events was comparable between the 2 groups [98].

In February 2016 a systematic review and meta-analysis regarding ESA treatment and quality of life in CKD patients was published in *Annals of Internal Medicine*; this meta-analysis included 17 studies; 10,049 patients with CKD who were re-

ceiving ESA treatment for anemia [99]. Thirteen of these studies reported 36-Item Short Form Survey (SF-36) outcomes, and four reported Kidney Disease Questionnaire outcomes, both of which are validated instruments that measure patient-reported HRQoL. Pooled analyses of the data from these studies showed that compared with lower hemoglobin target levels, higher targets resulted in no statistically or clinically significant improvement in SF-36 or Kidney Disease Questionnaire HRQoL domains [99].

CKD management

The CKD is a heterogeneous condition, characterized by a decrease in GFR or markers of kidney damage and is common in the elderly. This year a clinical Practice Guideline on management of older patients with chronic kidney disease stage 3b or higher was developed by ERBP and was published in NDT [100]. The authors tried to cover the following areas:

- What parameter should be used in older patients (a) to estimate kidney function and (b) for dose adaptation purposes?

The authors recommend using estimating equations that correct for differences in creatinine generation rather than plain serum creatinine measurements to assess kidney function in older patients (1A); they also recommend that there is insufficient evidence to prefer one estimating equation over another since all perform equally and substantial misclassification can occur with any of these equations when used in older patients with differing body composition (1B); moreover, they recommend formal measurement of kidney function if more accurate and precise estimation of GFR is required (1B). We suggest the use of CKD-EPI_{Cr-Cyst} may be an acceptable alternative (2C).

The authors recommend taking account of kidney function when prescribing drugs whose active forms or metabolites are renally cleared (1A). they suggest that for drugs with a narrow toxic/therapeutic range, regular measurement of serum concentrations can provide useful information. Differences in protein binding in relation to uremia may necessitate use of different target levels of total drug concentration (2C).

- For the most reliable risk model score to predict progression of CKD in older patients with advanced CKD (eGFR < 45 ml/min/1.73 m²).
The authors recommend that the 4-variable KFRE performs sufficiently well for use in older patients with advanced CKD and eGFR < 45 ml/min/1.73 m² (1B).
- Regarding the prediction of the individual risk of death the authors:

- recommend not using currently available risk prediction models to predict individual risk of death in frail older patients with or without CKD (1B);
- suggest using the Bansal score to predict individual 5 year risk of death before ESKD in non-frail older patients with CKD stage 3–5 (2B);
- suggest that in patients at low risk in the Bansal score, a score including the assessment of frailty as stated in question 4a be performed (2B);
- suggest also that the REIN score be used to predict the risk for mortality in older patients with CKD stage 5 (2B).
- For the best alternative method to assess functional decline in older and/or frail patients with advanced CKD; the recommendations are:
 - recommend a simple score be used on a regular basis to assess functional status in older patients with CKD stage 3b–5d with the intention to identify those who would benefit from a more in-depth geriatric assessment and rehabilitation (1C);
 - recommend most simple scores, including self-report scales and field tests (sit-to-stand – STS, gait speed or 6-min walk test) have comparable and sufficient discriminating power to identify patients with decreased functional status (1C).
- For increasing functional status in older patients with renal failure (eGFR < 45 ml/min/1.73 m² or on dialysis) the authors:
 - recommend that exercise has a positive impact on the functional status of older patients with CKD stage 3b or higher (1C),
 - suggest that exercise training be offered in a structured and individualized manner to avoid adverse events (2C).
- For the best alternative to evaluate nutritional status in older patients with advanced CKD 3b or higher (eGFR < 45 ml/min/1.73 m²) or on dialysis the authors:
 - recommend the SGA as the gold standard to assess nutritional status of older patients with CKD stage 3b or higher (eGFR < 45 ml/min/1.73 m²) (1C),
 - suggest that in older patients on HD, a score including serum albumin, BMI, serum creatinine/BSA and normalized protein nitrogen appearance nPNA) may be used to assess nutritional status (2D),
 - suggest a trial of structured dietary advice and support with the aim of improving nutritional status (2C).
- Regarding the possible benefit of dialysis in frail and older patients the authors recommend the use of validated tools (KRF score, BANSAL

score, frailty) to project likely outcomes and help decide the appropriateness of discussing options for renal replacement therapy [100].

Renal transplantation

2016 was a plentiful year also for renal transplantation. New significant data from several important trials were presented. In January 2016 Vincenti *et al.* demonstrated that belatacept improves long-term outcomes in kidney transplant recipients [101]. Belatacept is the first new immunosuppressive compound that has been shown to improve patient and graft survival in a phase III trial since cyclosporin was approved for the prevention of kidney transplant rejection in 1983 [102]. The BENEFIT study included 666 adult transplant patients. They were randomized 1 : 1 : 1 to receive either a more-intensive belatacept regimen, a less-intensive belatacept regimen, or cyclosporine. All patients received additional drugs to inhibit graft rejection – basiliximab (Simulect), mycophenolate mofetil, and corticosteroids. A 43% reduction in the risk of death or graft loss was observed for both the more-intensive and the less-intensive belatacept regimens as compared with the cyclosporine regimen (HR with the more-intensive regimen = 0.57; 95% CI: 0.35–0.95; $p = 0.02$; HR with the less-intensive regimen = 0.57; 95% CI: 0.35–0.94; $p = 0.02$), with equal contributions from the lower rates of death and graft loss. The mean GFR increased over the 7-year period with both belatacept regimens but declined with the cyclosporine regimen. The cumulative frequencies of serious adverse events at month 84 were similar across treatment groups [101].

In November 2016, another two important trials were presented at the ASN kidney week; in the first one, 615 low immunological risk renal transplant recipients were randomized to low-dose tacrolimus, mycophenolate mofetil, and either 1) basiliximab induction and steroid maintenance therapy, 2) basiliximab induction with rapid corticosteroid withdrawal on day 8, or 3) rabbit ATG induction therapy and rapid corticosteroid withdrawal on day 8 [67, 103]. The primary endpoint was the incidence of biopsy proven acute rejection at 12 months. There was no difference in biopsy proven acute rejection in the three arms of the study. BPAR rates were not reduced by rabbit ATG (9.9%) compared with both basiliximab induction strategies: A (11.2%) or B (10.6%); A versus C: $p = 0.75$, B vs. C, $p = 0.87$). Moreover, rapid steroid withdrawal was safe, with unchanged excellent survival. Most dramatically, rapid steroid withdrawal led to a marked reduction in post-transplant diabetes mellitus development within the first year (diabetes was reduced in arm B to 24% and in arm C to 23% compared with 39% in control arm A (A vs.

B and C: $p = 0.0004$) [103]. The second one, was the 5-year follow-up REPAIR trial, which assessed remote ischemic preconditioning (RIPC) in living kidney transplantation; Veighey *et al.* randomized 406 patients in a 2 × 2 factorial design study to one of 4 arms: 1) sham procedure, 2) early RIPC, 3) late RIPC, or 4) early and late RIPC [68]. Early RIPC occurred immediately before surgery (also notably before anesthetics were started). Late RIPC was performed 24 h before surgery. Early RIPC resulted in sustained improvement in kidney function after transplantation, reaching 13% by 5 years. There was a similar trend in late RIPC but it was not statistically significant. Trends for graft loss and mortality over the 5 years appeared worse in the group randomized to the sham procedure but did not reach statistical significance [68].

Hemodialysis

Preliminary data from an important hemodialysis study was presented in November 2016 at ASN [68]. The SOLID trial randomized 99 individuals on home hemodialysis to dialysate sodium of 135 mM versus 140 mM. Primary outcome was left ventricular mass index by cardiac MRI at 12 months. There was no treatment effect seen on the primary outcome of left ventricular mass. Most secondary outcomes are still being evaluated; however, they did see a significant decrease in intradialytic weight gain in the 135 mM dialysate group. Full safety and tolerability results are still pending [68].

Conflict of interest

The authors declare no conflict of interest.

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