What’s new in hypertension 2010?

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Introduction

This editorial comment intends to inform readers of Nephrology Dialysis Transplantation about some new data in the field of hypertension published from mid-October 2008 to November 2010 but ‘not’ in nephrological journals. As in our previous exercises, we have chosen about 10 papers.

Interventional strategies to lower blood pressure

In last year’s review, we discussed radiofrequency ablation of the renal nerves as a potential new tool to treat resistant hypertension. In a controlled trial [1], that technique was now examined in 106 patients with a systolic blood pressure >160 mmHg despite three or more antihypertensive agents, which were randomized to either continuation of previous antihypertensive medication alone or continuation of previous antihypertensive medication plus ablation. There was no sham ablation and no attempt of blinding investigators or adjudicators, and it was required not to change antihypertensive medications for the 6 months of the study. During a 2-week run-in period, participants had to measure their home blood pressure and register their medication. At randomization, participants received a mean of 5.2 antihypertensive drugs with angiotensin-converting enzyme (ACE) inhibitors and diuretics in ~90%, calcium antagonists in 80%, but direct vasodilators surprisingly in only 16%. They exhibited an office blood pressure of 178/98 mmHg. The intervention was easy to perform, taking ~40 min, and was not associated with substantial adverse events, notably no hint of target artery stenosis. The main outcome measure, office blood pressure, was reduced by a stunning 32/12 mmHg after 6 months, with essentially no change in the control group. Curiously, 24-h ambulatory blood pressure monitoring (ABPM) performed in about half of the population showed a reduction...
of only 11/7 mmHg; with home self-recordings of blood pressure with an automated device, a reduction of 20/12 mmHg was observed.

The data of the SIMPLICITY HTN2 trial provide some hope for the numerous patients with resistant hypertension who we encounter in our clinics. However, it appears not appropriate that ‘all-comers’ patients be referred for ablation by physicians not specialized in hypertension. Renal nerve ablation is still an experimental technique. Obvious limitations of the SIMPLICITY are the very short observation period of 6 months in a population with a mean age of only 58 years, the lack of appropriate controls (no sham ablation), and no blinding of the investigators who recorded the outcomes. In the end, less than half of the intervention group reached target blood pressure of <140 mmHg systolic, and the huge difference between office blood pressure and ABPM is disconcerting. The latter raises the question whether the renal nerves are involved in the ‘white coat’ phenomenon. Reassuring is the increasing antihypertensive effect of ablation during the 6-month trial period and the lack of serious adverse events of the intervention; the latter may change when hundreds of inexperienced interventionists use this new technique. We definitely need long-term data that tell whether the potential reduction in cardiovascular and renal risk that is hoped for is rather related to the impressive change of office blood pressure or the quite moderate change of 24-h blood pressure. In addition, physicians using ablation in other diseases question whether the catheter used in the SIMPLICITY HTN2, a non-flushed type, is ideal for conveying energy to the nerves and not to the endothelium. Finally, the SIMPLICITY HTN2 excluded participants with an estimated glomerular filtration rate (eGFR) <45 mL/min, so there are lots of controlled trials to be done especially in people with CKD; however, with the current schemes of technique-driven reimbursement, ablation will be done anyway. In addition, the requirements for approval of devices by agencies such as the EMA are remarkably small compared with drug approval.

Another interventional technique for resistant hypertension is baroreceptor reflex stimulation (BRS). Here, thin leads are surgically attached to the carotid sinus nerve and connected to a subcutaneously placed pacemaker that stimulates afferent nerves. Scheffers et al. [2] implanted such a device in 45 subjects very similar to the above study but with somewhat higher blood pressure (mean 179/105 mmHg at enrollment). At 2 years, office blood pressure was reduced by 33/22 mmHg. There was no control group, and in remarkable agreement with the SIMPLICITY HTN2, the effect of the intervention on ABPM was >50% smaller than on office blood pressure. While the technique worked in most participants of this pilot study, there were some adverse events that needed surgical intervention, due to infection in three patients and pacemaker malpositioning in one patient. A fatal angio-neurotic oedema a few days after device insertion was potentially related to medication. The results of the BRS trial are interesting, but if we need an interventional technique, we will certainly first turn to renal nerve ablation for obvious advantages of the latter and may reserve BRS to those not responding to ablation. If BRS is considered, patients should be enrolled in trials because that technique is still highly experimental.

**Inhibiting endothelin in resistant hypertension**

Endothelin is a very strong vasoconstrictor, stronger than angiotensin II on a molar basis. For several years, clinical trials in primary hypertension were conducted to test endothelin antagonists, successful agents in pulmonary hypertension, as antihypertensive agents. This development is important to nephrologists because several endothelin antagonists have been shown to exhibit impressive antiproteinuric properties even when added to ACE inhibitors [3]. So far, no endothelin antagonist has been approved for therapy of arterial hypertension. Weber et al. [4] randomized people with hypertension, despite adequate treatment with at least three antihypertensive drugs, including a diuretic, to the endothelin antagonist darusentan at three different doses. Approximately 80 participants per dosing group, or to placebo, (n = 132) were included with a double-blinded follow-up of 14 weeks. Independent of the chosen doses, darusentan lowered blood pressure by 18/11 mmHg, and placebo by 9/5 mmHg. On 24-h ABPM, blood pressure did not essentially change with placebo but decreased by 9/7 mmHg with active drug. While these antihypertensive properties are substantial, darusentan, as other vaso-dilatory agents, was associated with signs of fluid retention in 27% of the participants compared with 14% in the placebo group. Signs of fluid retention are a known complication of endothelin antagonists [5]. In future studies, it will be essential to control meticulously fluid status and treat swiftly any fluid retention. The authors point out that all participants received diuretics, but in doses not specified by the protocol and the doses may not have been high enough. With the concomitant use of relatively high doses of diuretics, endothelin antagonists may be a valuable addition to our antihypertensive and particularly to our antiproteinuric armamentarium. Especially for the latter, there is a huge unmet need. Until we know how to best use endothelin antagonists, there is a lot of work ahead. The work of Weber et al. touches on some of this work that starts with the appropriate dosing. Darusentan was given at 50, 100 and 300 mg/day with no difference between those doses. Lower doses should be studied that may preserve the antihypertensive properties but elicit less fluid retention.

In the ASCEND trial [5], we noted that an endothelin antagonist, avosentan, had an outstanding antiproteinuric effect in >1300 participants with overt diabetic nephropathy, on full-dose ACE inhibitors or angiotensin receptor blockers and diuretics. Residual proteinuria was reduced by >40%. However, the trial had to be ended prematurely because of complications due to fluid retention. We also found a moderate reduction in blood pressure. The potential renal benefit of such substantial lowering in proteinuria should be explored with lower doses of available endothelin antagonists. It may also be that the relative selectivity for the endothelin type A and type B receptor is playing a role.

**Target blood pressure in diabetes**

In our last year’s review on antihypertensive therapy, we discussed whether a blood pressure target <130 or even 120 mmHg is useful in people at high risk for vascular
disease. The data of the ACCORD BP trial [6] support our suggestion that the traditional target systolic blood pressure of <140 mmHg is adequate for people with diabetes and hypertension. The ACCORD was a NIH-founded trial with a factorial design that randomized ~5700 people with type 2 diabetes, mean age 62 years and baseline-treated blood pressure of 139/76 mmHg to a target systolic blood pressure of either <120 or <140 mmHg. The investigators were successful in achieving a mean on-treatment systolic blood pressure of 134 vs 119 mmHg, respectively. Despite these substantial differences in blood pressure, the primary outcome was not different between the groups (HR of 0.88). However, of the secondary outcomes, stroke incidence was benefited by the lower target blood pressure, i.e. HR 0.59. That benefit must be weighed against a number of adverse outcomes with the lower target, namely more cases of doubling of serum creatinine (99 vs 52 cases), syncope (12 vs 5) and symptomatic hypotension (17 vs 1 case). There was no difference in the incidence of end-stage renal disease (ESRD) (59 vs 58 cases), but people with a baseline serum creatinine >1.5 mg/dL were excluded.

The ACCORD results contradict most guidelines of anti-hypertensive treatment where a target blood pressure of <130/80 mmHg is stated as a rule. The latter target was mainly based on a subanalysis of the HOT study. Several societies have now altered their guidelines and adopted a target blood pressure in people with diabetes that is not different from primary hypertension without diabetes, namely <140/90 mmHg. One may argue that the ACCORD did not test the <130-mmHg target. However, if targets of a randomized trial are only separated by 10 mmHg, achieved blood pressure is often so close that differences in outcomes related to blood pressure cannot be expected—hence the negative results of the HOT study. Still, in people at high risk of stroke, a lower blood pressure may be beneficial but comes with a significant risk for adverse events and certainly no benefit of mortality.

There is a further study underway, SPRINT, again funded by the NIH, that examines a systolic target blood pressure of <120 vs <140 mmHg in primary hypertension and intentionally randomizes people with CKD and elderly >75 years. The results are expected in 2015.

Which blood pressure?

Head et al. [7] answered the question as to how can we relate office blood pressure to 24-h ABPM based on the results of >8500 recordings of ABPM. Those recordings were related to office blood pressure measured either by trained medical personnel or by physicians. An office blood pressure of 140/90 mmHg corresponded to a daytime ABPM of 136/87 mmHg, and office blood pressures of 130/80 or 125/75 mmHg to ABPM daytime values of 128/78 and 124/74 mmHg, respectively. The lower the blood pressure, the closer the office and ABPM values. The office data, however, were so close to ABPM data only when measured by trained medical personnel; physician measurements were substantially higher, close to a 10-mmHg systolic blood pressure. Results of large trials examining blood pressure often report office blood pressure, but we know that ABPM values more closely reflect risk; thus, we often adjust treatment according to ABPM. Head et al. provided a solid database to which targets of ABPM we should treat our patients.

It is often assumed that in an individual, the mean blood pressure load over time determines blood pressure-dependent risk. In other words, intermittent increases of blood pressure and blood pressure variability by themselves do not affect risk over and above mean blood pressure. That assumption was challenged by Rothwell et al. [8] with a post hoc analysis of several stroke prevention trials and the ASCOT trial. With these large datasets, the authors related systolic blood pressure parameters, namely mean, maximum and parameters of variability including standard deviation, to cardiovascular outcomes. They found that both maximum and variability predicted outcomes, especially stroke, independent of mean with impressive hazard ratios that increased with the number of measurements. No major effect for diastolic blood pressure variability was found. For example, participants of the ASCOT trial with controlled blood pressure and compliant to therapy had a 5-fold increase in risk for stroke if the variability of systolic blood pressure was very high. The prediction of cardiovascular outcomes was striking in younger age groups. The same group [9] reported that variability of blood pressure is reduced by thiazide diuretics and calcium blockers but increased by beta-blockers and inhibitors of the renin system. Indeed, stroke risk in hypertension is less affected by the latter than the former drug classes, but certainly not in all trials [10].

These post hoc analyses are provocative and call for diligent recording of blood pressure variability in hypertension trials and, above all, for trials that target variability of blood pressure. In the end, we want to reduce risk associated with blood pressure, and there is no randomized trial available showing that reducing variability of blood pressure reduces risk over and above lowering of mean blood pressure. The outcome of such trials is open as they may show a reduction in cardiovascular events with lower variability but also an increase in adverse events related to hypotension. Here, the ACCORD teaches a lesson on the balance between stroke and adverse outcomes [6].

Lowering blood pressure to prevent loss of renal function

There is overwhelming observational and experimental data that lowering blood pressure will prevent renal outcomes. Randomized trials, however, examining those outcomes are sparse, and at least two trials, the AASK with a two-digit difference in blood pressure and the REIN-2 trial with a small difference, found not much evidence that in people with CKD with low-grade proteinuria and rather well-controlled blood pressure, a lower target blood pressure will alter renal outcomes. Paediatric nephrologists from a European consortium have to be congratulated for the ESCAPE [11] trial that randomized children and adolescents with CKD, mean age 11 years and urine protein ~1.3 g/g creatinine to two different blood pressure goals. Initial blood pressure was 118/73 mmHg and was reduced to 109/65 mmHg in both groups with a mean blood pressure difference of 3–4 mmHg (ABPM) over the course of the study between the lower and higher target groups. In
the former and latter, 64% and 49% of participants respectively reached the target blood pressure. The primary outcome, ESRD or a decrease in eGFR by ≥50%, was reached in 30% and 42%, a significant benefit for the lower target blood pressure. That benefit was much greater in those with glomerulopathies and smaller in renal dysplasia/hypoplasia, the diseases with more or less proteinuria. Directly after initiation of antihypertensive therapy which included a high dose of ramipril in both groups, eGFR fell by 2.1 mL/min/1.73 m². Over the course of the study, the change of eGFR was much less with a lower target blood pressure (−1.1 vs −2.5 mL/min/1.73 m²).

While the absolute values of blood pressure cannot be translated into adult patients, this trial establishes that lowering blood pressure within normal ranges lowers renal risk over and above ACE inhibition. In agreement with studies in adult CKD, the effect of blood pressure lowering was greater with higher levels of proteinuria. In contrast, however, the ESCAPE also found a significant benefit in diseases with low-grade proteinuria, namely dysplasia/hypoplasia. In comparison with previous trials in adults, the ESCAPE had a longer follow-up of 5 years in all participants and targeted blood pressure with ABPM. Effect sizes were impressive with a reduction in risk for the primary outcome by 68% for glomerulopathies and 42% for dysplasia/hypoplasia. Purists may argue that the results of the ESCAPE apply to children only. However, given the ESCAPE data and the data in subgroups of adults with CKD and proteinuria above the 0.5–1.0-g range, we can state that lowering of blood pressure in CKD within the normotensive range is appropriate in children and adults to prevent major renal outcomes. Whether a systolic target blood pressure of <120 mmHg in CKD in general and <125 mmHg with proteinuria, as recommended in some guidelines, are the optimal targets in adult CKD remains elusive. As a cautionary note, the ESCAPE reported no substantial differences in adverse events but that may however be different in adults treated to a low blood pressure target.

ACE inhibitors with hydrochlorothiazide or with amlosipine to prevent renal outcomes?

In last year’s report, we commented on the ACCOMPLISH trial that randomized ~11 000 participants with hypertension and risk factors for cardiovascular disease to amlosipine or hydrochlorothiazide (HCT), with all participants receiving benazepril at a high dose. The trial ended prematurely because of cardiovascular benefit and reduced mortality in the amlosipine + benazepril arm. Bakris et al. [12] reported the renal outcomes, a pre-specified outcome of that trial that had to be terminated after only 2.9 years of mean follow-up. The primary renal outcome was defined as doubling of serum creatinine or ESRD and happened in 215 participants with HCT and 113 with amlosipine (a significant difference, HR 0.52). The outcome was driven by doubling of serum creatinine. There was no change of blood pressure that could explain the difference in renal outcomes. However, there were 20 cases of dialysis, 7 with the amlosipine and 13 with the HCT combination. Interestingly, the change in albuminuria was not in parallel with the outcome. That parameter was reduced by 63% with HCT and by only 29% with the amlosipine combination in those patients with macroalbuminuria at baseline; in all participants altogether, albuminuria was reduced with HCT by 27% and increased insignificantly by 2% with the amlosipine combination. There were only ~10% of the participants of the ACCOMPLISH with CKD. While CKD was somewhat unusually defined (eGFR <46 mL/min/1.73 m² in women and <55 mL/min/1.73 m² in men), the numbers were too low to provide reliable estimates of renal outcomes in that subgroup. The data of the ACCOMPLISH provide good evidence that an ACE inhibitor + amlosipine prevents renal outcomes better than the combination of ACE inhibitor + HCT, despite similar control of blood pressure in a population of hypertensive people at high cardiovascular but low renal risk. Therefore, the data cannot be applied to people with more advanced and especially proteinuric renal diseases. Here, more specific studies in that population are needed.

Pre-eclampsia and the role of angiotensin II receptor agonistic autoantibodies

Since the work of Wallukat et al. [13], we know that in a substantial number of women with pre-eclampsia, receptor-activating antibodies of the angiotensin II type 1 receptor play a role in this disease affecting ~5% of all pregnancies. Irani et al. [14] reported two mechanisms by which those agonistic autoantibodies induced morbidity alterations that led to intrauterine growth retardation. The investigators found those autoantibodies in cord blood of women with pre-eclampsia. Such autoantibodies when injected into pregnant mice appeared in the fetal circulation and led to small fetuses with intrauterine growth retardation. The autoantibodies also induced apoptosis in the placenta of human trophoblast cells. Treatment either with losartan, an angiotensin receptor blocker, or with a locking peptide for the autoantibody reversed the above changes. Thus, Irani et al. described two pathways of damage by angiotensin II receptor agonistic autoantibodies, namely by direct damage to organ development of the fetus and by placental damage. The findings highlight the fact that those autoantibodies are an important target to prevent pre-eclampsia. However, angiotensin receptor blockers cannot be administered because these drugs have been associated with malformations, impaired renal organogenesis and acute renal failure in the newborn.

Paracetamol (acetaminophen) increases blood pressure

Non-steroidal anti-inflammatory drugs (NSAIDs) increase blood pressure and are associated with an increased incidence of cardiovascular disease. There is little evidence available that an alternative and often used analgesic, paracetamol (acetaminophen in North America), alters blood pressure. Sudano et al. [15] examined the effects of paracetamol 3 g/day vs placebo in a cross-over randomized, double-blind study with 35 people with coronary artery disease who received standard therapy, including ACE inhibitors or angiotensin receptor blockers as well as aspirin and statins in almost everybody. Treatment periods lasted 2 weeks, and 24-h ABPM established an increase in blood pressure that was statistically significant and clinically relevant for both systolic and diastolic blood pressure.
pressure of 3 mmHg with active drug. Interestingly, heart rate also increased significantly by ~2 beats/min, although one may expect a baroreceptor-mediated decrease in heart rate. As blood pressure and heart rate increased in parallel, a central pressor effect of paracetamol is possible. There was no effect on platelet function, renin–angiotensin system or renal parameters, and there was little evidence for altered endothelial function; prostaglandin metabolism was not measurably altered. The changes of blood pressure were subtle indeed, but as the authors point out, given the huge consumption of paracetamol, that subtle change can be considered a concern for public health. The authors went even further and cited evidence of associations between regular paracetamol use and a higher risk for hypertension in observational studies. For example, in the nurses’ health study, this risk increased 2-fold. The study by Sudano et al. was meticulous but indeed very small and short; it raised but did not answer questions regarding guidelines that recommend paracetamol rather than NSAIDs for pain relief for people at high cardiovascular risk. We cannot leave pain untreated in people with cardiovascular disease, and any analgesic drug will have a flip side of adverse events. It is good to know that flip side and, here, the data of this study are helpful.

Another relaxing gas

It has been a surprise many years ago that gases serve as signalling molecules, the best known are nitric oxide and carbon monoxide. Hydrogen sulphide (H$_2$S) is another gaseous signalling molecule, produced by the enzyme cystathionine gamma-lyase (CSE). In an elegant series of experiments, Yang et al. [16] showed that H$_2$S is produced in blood vessels, relaxes those vessels at physiological levels and reduces blood pressure. In mice with targeted deletion of CSE, production of H$_2$S was greatly reduced, and blood pressure increased substantially compared with controls after 10 weeks of age. In the CSE knockout mice, vessels were more sensitive to exogenous H$_2$S, and the blood pressure-decreasing effect was enhanced, as expected. Interestingly, homocysteine levels were higher in the knockout mice, but in several further experiments, the authors established that homocysteine was not involved in the antihypertensive effect of H$_2$S nor was there evidence for an effect on central blood pressure regulation. The authors pointed out that H$_2$S is an important factor in blood pressure regulation, also because it accounts for ~60% of endothelium-derived relaxing factor (EDRF) activity in some vascular beds. Another gaseous signalling molecule, NO, has a similar potency. The production of both gases is regulated by a calcium–calmodulin mechanism. The inhibition of either H$_2$S or NO or deletion of the generating enzymes, CSE and NO synthase, suppresses EDRF activity only partially. It appears reasonable to look forward to experiments with inactivation of both gases. Clinically, the information of different mediators of EDRFs may open avenues to new therapies.

Rock around the sodium clock

Circadian rhythm disturbances play a role in several diseases. There is evidence that altered circadian rhythm is involved in blood pressure regulation and blood pressure-dependent adverse events. There is genetic regulation of circadian rhythm, and clock genes have been mapped. Doi et al. [17] generated mice lacking the core clock components cryptochrome-1 (Cry1) and cryptochrome-2 (Cry2) (Cry-null mice). Cry-null mice developed hypertension when fed a high-sodium diet that was associated with uninhibited formation and secretion of aldosterone by the adrenal gland, in other words a model of primary hyperaldosteronism. An extensive search for the underlying cause identified type VI 3beta-hydroxysteroid dehydrogenase (Hsd3b6) as the culprit. Hsd3b6 is expressed exclusively in aldosterone-producing cells. In the Cry-null mice, Hsd3b6 gene expression and hence 3beta-hydroxysteroid dehydrogenase-isomerase (3beta-HSD) levels are constitutively high, and as a consequence, aldosterone production. The authors concluded that Hsd3b6 plays a pivotal role through which the circadian clock is coupled to the development of some types of hypertension. A substantial percentage of people with hypertension are salt-sensitive. Studies in humans should reveal whether the human HSD3B1 gene is playing the same pivotal role as in mice.

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