Kidney Diseases Beyond Nephrology

What’s new in hypertension 2009?

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Keywords: blood pressure; cardiovascular; death; pre-eclampsia; renal insufficiency

Introduction

This contribution to the section ‘kidney diseases beyond nephrology’ intends to inform our readers about new information in the field of hypertension from mid October 2008 to October 2009 that has not been published in nephrological journals. Pubmed lists 2906 citations in the last 12 months with ‘hypertension’ as major topic including 468 reviews. We have chosen about 10 of those papers.

Stenting of renal artery stenosis is not the solution (STAR and ASTRAL trials)

Treatment of renovascular hypertension remains a topic of much dispute. The simplistic approach says that if a renal artery stenosis (RAS) causes hypertension, invasive therapy will cure the patient. That approach overlooks that patients with atherosclerotic RAS as a rule exhibit widespread vascular disease of other organs leading to premature death that is barely influenced by the blood pressure. In addition, long-standing hypertension tends to perpetuate itself independent of the initiating mechanism. Previous randomized trials, showing that percutaneous transluminal angioplasty (PTA) in addition to antihypertensive drug therapy does not result in additional benefits, were criticized because no stents were used. Bax et al. [1] report a randomized controlled trial comparing optimal medical therapy with or without PTA and stent placement in 140 people with hypertension with an eGFR < 80 ml/min (mean 45 ml/min at inclusion) and ostial RAS of > 50% of luminal diameter, unilateral or bilateral (bilateral in about half). The primary outcome was a decrease in eGFR by > 20% after a follow-up of 2 years that was not different between the groups; however, the confidence interval was wide (HR 0.73, CI 0.33–1.63). There were three deaths in the PTA group and one cholesterol embolism resulting in permanent dialysis among 140 people with hypertension with an eGFR < 80 ml/min (mean 45 ml/min at inclusion) and ostial RAS of > 50% of luminal diameter, unilateral or bilateral (bilateral in about half). The primary outcome was a decrease in eGFR by > 20% after a follow-up of 2 years that was not different between the groups; however, the confidence interval was wide (HR 0.73, CI 0.33–1.63). There were three deaths in the PTA group and one cholesterol embolism resulting in permanent dialysis although the PTA was performed in only 10 institutions, requiring radiologists with at least 10 years of PTA experience. While this review is written, a further paper from the ASTRAL investigators (N Engl J Med 2009; November 12 issue) on 806 patients with atherosclerotic renovascular disease randomized to medical therapy with or without additional percutaneous revascularization was published. No worthwhile clinical benefit but substantial risks with PTA were found. Revascularization was associated with a slightly slower decline in GFR and no difference in death or major renal and cardiovascular outcomes. However, serious complications in 23 of 806 patients, including 2 deaths and 3 amputations of toes or limbs, were observed. In conjunction with previous reports, these new studies provide no support whatsoever for PTA and stent treatment of atherosclerotic stenosis, including ostial stenosis, to preserve renal function or to lower blood pressure apart from very special circumstances, e.g. tight stenosis of a single kidney. Needless to say that many will continue to offer PTA and stent to patients with RAS because every trial has its limitations, performing a PTA is challenging and its vascular ‘cosmetic’ effects can be impressive to the patient. We can only hope that high revenues of PTA for caregivers and hospitals, as they are compared to conservative treatment in many health care systems, are not driving the continued and ill-indicated use of PTA.

Induction of labour for gestational hypertension or mild pre eclampsia at term (HYPITAT trial)

About 5–10% of all pregnancies are complicated by gestational hypertension and preeclampsia. These complications may have serious consequences such as a HELLP (haemolysis, elevated liver enzymes, low platelets) syndrome, eclampsia, placental abruption, pulmonary oedema and even maternal death. No trial has investigated whether induction of labour would be beneficial to avoid those consequences. Koopmans et al. [2] randomly allocated 756 women after 36 weeks of gestation and hypertension or mild preeclampsia to expectant monitoring or induction of labour; both strategies are prevalent in various countries. A combined measure of poor maternal outcome was the primary endpoint of the trial and was more often observed with expectant monitoring than with induced labour. No women died and no single measure of poor maternal outcome was driving the primary endpoint but effects on subsequent development of severe hypertension and of HELLP syndrome...
were impressive. In many hospitals, nephrologists are involved as consultants in the care of gestational hypertension. HYPITAT supports the invasive management of these women beyond the gestational week 36 when blood pressure is above 95 mmHg diastolic or when other signs of mild preeclampsia are present. The authors conclude that their findings may be of special relevance in developing countries where poor maternal outcome is more prevalent.

Catheter-based, percutaneous renal denervation for resistant hypertension

Various animal models of hypertension have established that denervation of renal nerves has profound antihypertensive effects. The renal nerves are anatomically closely associated with the renal arteries, close to or within its wall. Krum et al. [3] now report a radiofrequency ablation technique, developed in experimental studies in pigs, that successfully reduces renal sympathetic nerve activity in humans. In an uncontrolled, open, proof-of-concept study, they submitted 50 people to radiofrequency ablation of the renal nerves. All participants exhibited resistant hypertension despite a mean of 4.6 antihypertensive drugs, including diuretics and blockers of the renin system in almost everybody. The procedure itself was fast, less than 40 min on average from the beginning to the end of angiography and did not entail substantial complications, namely no RAS when follow-up angiography was done at 1 and 6 months. There were major effects of renal denervation on office blood pressure with an initial decrease in systolic blood pressure by about −10 mmHg that became greater with longer follow-up, about −27 mmHg, and −17 mmHg diastolic. However, drug treatment could not be alleviated and 24 h ambulatory blood pressure monitoring (ABPM), done in a subset of patients, revealed much less of an effect, a decrease in systolic blood pressure of −11 mmHg. In 10 patients renal venous noradrenaline spillover was measured before and found to be reduced by 47% after denervation. Unpublished studies in pigs had shown that intrarenal catecholamines were reduced by 85% with the catheter-based ablation, but no details of those experiments are reported. Further studies in patients should show whether more profound effects on noradrenaline spillover, as a sign of more complete renal denervation, can be achieved and whether the changes in office blood pressure or the less impressive changes in 24 h ABPM represent the real efficacy of this new technique. Finally, randomized studies will be needed to show whether the new technique is clinically useful. Most patients with resistant hypertension can be managed with appropriate doses of diuretics and minoxidil on top of previous antihypertensive medication. Adverse events are often the limiting factor for reaching target pressure. The intriguing question for future studies will be whether renal denervation leads to blood pressure control with fewer adverse events, namely hypotensive symptoms including orthostatic hypotension, than multiple drug treatments at the extremes of the dose–response curves.

Target blood pressure, an endless tale

Two articles cover the question of target blood pressure in different populations and with different techniques. Verdecchia et al. [4] examined relatively healthy hypertensive people and the development of left ventricular hypertrophy (LVH) in groups randomized to a target blood pressure below 140 mmHg versus below 130 mmHg. Sleight et al. [5] examine high-risk individuals with vascular disease in an observational analysis of achieved blood pressure in the ONTARGET study. The two studies come to quite different conclusions. The strength of Verdecchia et al. is the randomized design; the limitations include a relatively small sample size of 1100 participants and a short follow-up of 2 years. The strength of Sleight et al. is the large sample size of 26 000 participants and a follow-up of 5 years, the major limitation is that achieved blood pressure was analysed but participants were not randomized to different target blood pressures. Verdecchia et al. report that the lower target of below 130 mmHg in a population with a baseline blood pressure of 163/90 mmHg led to a substantial reduction in the risk for LVH. In addition a composite cardiovascular outcome measure that included rather soft and hard outcomes (all-cause mortality, myocardial infarction, stroke, hospitalization for heart failure or for unstable angina, cardiac revascularizations, new atrial fibrillation, transient ischaemic attack, aortic dissection, occlusive peripheral vascular disease and dialysis) was also reduced in the lower target group. Achieved systolic pressure was different by 4 mmHg, a decrease by −23.5 versus −27.4 mmHg, and those with the lower target received more diuretics and more angiotensin receptor blockers (ARB) than the higher target group. In the analysis of Sleight et al., stroke risk decreased with lowering of blood pressure at any given baseline blood pressure. However, myocardial infarction was not affected and cardiovascular mortality increased with further blood pressure lowering in people with a baseline systolic pressure below 130 mmHg. The valid conclusion is that we need trials in high-risk vascular patients, the usual patients in our hospitals and offices that evaluate lowering of blood pressure in those with baseline systolic pressure in the 130–150 mmHg range. Similar trials on hard outcomes are needed in lower risk people with mild hypertension that is highly prevalent in the general population. The major current evidence on hard outcomes from the HOT study is restricted to people with diabetes in whom a target diastolic blood pressure of <80 mmHg was beneficial compared with <90 mmHg; in that trial a target systolic blood pressure was not defined. In other words, recommendations of guidelines to lower systolic blood pressure to 130 mmHg or below in people with diabetes and with renal disease are not based on studies examining such target systolic pressure but from observational analyses. Sleight et al. question the wisdom of such guidelines and support the conduct of controlled trials to support or refute those guidelines. The ADVANCE study [6] is no help here despite lowering of blood pressure within the normotensive range because its main outcome was driven by soft microvascular outcomes while macrovascular outcomes were not affected.

Lowering blood pressure in dialysis patients

Current guidelines recommend the same target blood pressure in dialysis patients as in all other patients with hypertension, namely <140/90 mmHg. There is no evidence from
trials with randomized assignment of dialysis patients to different target blood pressure levels, say <140 mmHg versus <160 mmHg, to support the above recommendation. Observational data relating blood pressure to mortality or to cardiovascular outcomes in dialysis patients in various countries usually demonstrate a U-shaped relationship with an almost flat line from about 120 mmHg to values as high as 170 mmHg systolic, and increasing mortality below and above those limits. Heerspink et al. [7] now report a meta-analysis of eight randomized controlled trials that tested antihypertensive drugs in dialysis patients. Unfortunately, the title of that paper inappropriately implies that lowering blood pressure is beneficial in hypertensive dialysis patients. The appropriate conclusion of that paper is that blood pressure lowering drugs (by whatever mechanism that may or may not include lowering of blood pressure) may prevent 2 out of 10 deaths in 100 patient-years of dialysis patients, an effect size that dwarf's most other strategies to reduce mortality in the dialysis population.

Why is the title of the paper misleading? Only three of the eight included studies randomized patients because of hypertension, another three studies randomized patients with heart failure, and two trials were only reported as abstract, one of which, by Nakao et al., could not be found in the usual registries of trials. Baseline mean systolic blood pressure ranged from 133–155 mmHg, so many normotensive patients were included and mean lowering was -4.5/-2.3 mmHg. Given the inclusion criteria of the trials it is entirely possible that the antihypertensive drugs exerted their benefit through non-pressure dependent mechanisms, as in other trials of heart failure and left ventricular dysfunction. My personal conclusion is that we should seriously consider the use of inhibitors of the renin–angiotensin system and/or beta blockers in our dialysis patients if there is evidence of left ventricular hypertrophy or dysfunction. The latter is a typical diagnosis in a vast majority of our patients. However, whether we should lower blood pressure in hypertensive dialysis patients and more importantly, to which target level, remains an open question. It is important to answer this question and not consider it resolved by the present meta-analysis also because observational data on blood-pressure-dependent risk in dialysis patients is so vastly different from pressure-dependent risk in the general population.

Preventing microalbuminuria in people with diabetes
The DIRECT study programme examined the prevention of microvascular disease in type 1 and type 2 diabetes. The investigators now report the effects of candesartan at a high dose of 32 mg/day on the development of new microalbuminuria in over 5000 patients, about 2/3 with type 2 and 1/3 with type 1 diabetes and with normal urinary albumin excretion [8]. Candesartan had a no significant effect on the incidence of microalbuminuria and no effect on the change of urinary albumin excretion rate. As thoroughly reported by the authors, four other trials investigating the same question with ACE inhibitors came to opposite conclusions, namely a substantial reduction in the incidence of microalbuminuria. In the discussion the authors provide insightful hypotheses why the DIRECT data were negative while HOPE, EUCLID, BENEDICT and ADVANCE reported positive findings on the prevention of microalbuminuria. The key seems to be the fact that the DIRECT programme enrolled relatively healthy people with a low baseline blood pressure (mean systolic 117 mmHg), low urinary albumin excretion and a low burden of vascular disease. The possibility that there are differences between ARB and ACE inhibitors is also discussed but refuted. In fact, the ONTARGET trial reported a head-to-head comparison of ARBs versus ACE inhibitors on changes of urinary albumin excretion and found, if anything, slight advantages for the ARBs on that outcome. Thus, the question whether we should treat all people with diabetes, independent of underlying disease or independent of underlying urinary albumin excretion with an inhibitor of the renin–angiotensin system, remains unresolved. For us as physicians, the focus of the use of these drugs remains the high-risk patient.

Which antihypertensive regime?
On the basis of literally many hundred of thousand participants in outcome trials of antihypertensive therapy one can safely conclude that independent of the drug(s) used, lowering of blood pressure in hypertensive individuals lowers risk. Up to now there was no good evidence that one drug is much better than the other, despite some heated discussions. In the ACCOMPLISH trial [9], more than 11 000 participants with hypertension and a high vascular risk profile including many with diabetes, were all treated with the ACE inhibitor benazepril, and were randomized to additional therapy with either hydrochlorothiazide (HCT) or amlopidine. The trial was stopped early because of greater benefit with the amlopidine combination on recommendation of the data safety monitoring board (DSMB) when 75% of the predicted endpoints had accumulated. The data are surprising to many experts but robust on close scrutiny. Blood pressure if anything was slightly lower in the HCT group, in a subgroup with 24 h ABPM and slightly higher for office blood pressure, by about 1–1.5 mmHg. The trial was criticized because of the broad primary outcome that included soft outcomes such as coronary revascularization and hospitalization for unstable angina, the necessity of which may depend on personal judgement. Amlodipine may also be a better antianginal drug than HCT. However, there was a strong trend for cardiovascular mortality to be reduced by the amlopidine combination (20% relative reduction, 0.4% absolute) and the usual primary outcome of many cardiovascular trials, the combination of cardiovascular death, myocardial infarction and stroke, was also significantly reduced by about 1.3% in absolute terms and by 21% in relative terms by amlopidine. Was HCT the right choice as a diuretic? No doubt that data on outcomes in hypertension trials for chlorthalidone are far better than for HCT as are its pharmacokinetic characteristics (duration of action >24 h versus <12 h). However, in most countries typical combination therapy of ACE inhibitors with diuretics involves HCT, sometimes indapamide but almost never chlorthalidone. Furthermore, the blood pressure effects of both combinations in ACCOMPLISH argue against the idea that the choice of the diuretic was wrong. How about adverse events, often underreported in trials? There were more cases of peripheral oedema with amlopidine (31 versus 13%), as expected, and more cases of dizziness with HCT (25 versus 20%)
Any data about aliskiren, the new kid on the block?

It has been demonstrated that aliskiren reduced blood pressure as effectively as other antihypertensives, provides a duration of action well beyond 24 h and reduces urinary albumin excretion when added to a full dose losartan. Trials with more reliable endpoints are underway and new information indicates that the drug is effective in people with hypertension and left ventricular hypertrophy (LVH). Such participants \((n = 465)\) were randomized in the ALLAY study [10] to losartan 100 mg/day, aliskiren 300 mg/day or their combination. A change in LVH parameters, assessed by magnetic resonance imaging (MRI), was the primary outcome after 36 weeks. Note that in the LIFE study, losartan 100 mg/day reduced major cardiovascular events in comparison to atenolol in people with hypertension and ECG evidence of LVH. ALLAY now reports that aliskiren, losartan and their combination in that 3-arm study were equally effective in reducing blood pressure, reducing LVH and exhibited a similar profile of safety and of tolerability. In particular, there was no signal of a greater increase of serum creatinine or of hyperkalaemia with combination therapy, based on low absolute numbers of those events (2 and 14, respectively). Subgroup analysis generated the hypothesis that the combination arm may be advantageous in people with diabetes, but in the end, the strongest predictor of a change in LVH was the change in blood pressure as one would expect. The ALLAY study and other studies with aliskiren support the use of this new drug in outcome trials in comparison to and in combination with other inhibitors of the renin–angiotensin system.

Non-osmotic regulation of body sodium and blood pressure

The intake of a high sodium diet, especially in people with renal disease, does induce hypertension in some individuals. The associated mechanisms are not well defined and recent data suggest that non-osmotic mechanisms of sodium disposal play an important role. The latter mechanisms, in addition, open a new concept of sodium homeostasis. The classic concept of sodium homeostasis follows a 2-compartment model, where changes in sodium metabolism are associated with commensurate changes in intra- and extracellular water metabolism to achieve osmotic homeostasis. In contrast to this concept, Titze and collaborators had previously shown that sodium can be stored non-osmotically in the skin, attached to proteoglycans so that changes in body sodium are not associated with parallel changes in water metabolism. Titze et al. now show [11] that a high sodium intake leads to hypertonic sodium accumulation in the skin interstitium and intermediate growth of the lymphcapillary network. Why do these vessels grow and enlarge? Interstitial hypertonicity activates tonicity-responsive enhancer binding protein (TonEBP) of the mononuclear phagocytic system. TonEBP binds to the promoter of the vascular endothelial growth factor-C (VEGF-C) gene, activates its transcription and secretion by macrophages. In the experiments of Titze et al., the whole system functions locally and is blocked either by depletion of mononuclear phagocytes or by VEGF-C trapping, leading to augmented interstitial hypertonicity, a decrease in NO (nitric oxide) formation and finally to hypertension. Thus, volume-dependent hypertension of high sodium intake may be partly regulated by dermal interstitium! There are clinical ramifications of the new data from Titze et al., because it explains the rise in blood pressure that is often observed with anti-VEGF strategies in cancer therapy. The data on mononuclear phagocytes suggest that inhibition of those cells, often detrimental in cardiovascular organ damage, may elevate blood pressure under certain circumstances. In the end, the data of Titze et al. corroborate the implications of immune cells in blood pressure regulation and not only in the associated organ damage.

Genetic associations with hypertension

Enormous amounts of money and manpower have recently gone into the elucidation of the genetic basis of hypertension. Two of these studies were published as companion papers [12,13]. The list of institutions, let alone coauthors, engaged in these endeavours is in the hundreds. The obvious result from these genome-wide association studies is that there is no such thing as the ‘hypertension gene or genes’ in the general population. It is also clear that the search for the genetic foundation of hypertension, or better of blood pressure regulation, is still in its infancy. That limitation is acknowledged by the authors of those papers and they continue to point out that for each allele found to be associated with a change in blood pressure, the actual magnitude of change is only in the 0.05—0.5 mmHg range. Even if multiple allelic associations are combined, a blood pressure change of only 4–6 mmHg and less than 5–10% of the variation in blood pressure can be explained (for comparison, body mass index (BMI) has a similar explanatory power). It is possible that with refined genetic analyses of the detected alleles these associations become somewhat stronger. However, the goal of finding genetic variants that lead to more specific or even to new therapeutic approaches is still a remote dream. First of all, hypertension may be the end result of numerous mechanisms and, second, these mechanisms may be of vastly different quantitative importance in a given person. Environmental factors add risk, and interact with the genetic background. Hence, it is far from granted that the genetic approach would lead to clinically meaningful results. The authors of the above cited papers note that for example statins are very powerful drugs in treating hyperlipidaemia while the genetic variation in the HMGCR enzyme explains very little of the hyperlipidaemia associated cardiovascular risk. Ji et al. [14] used another approach to explain the variable incidence of hypertension in the population. They noted that monogenetic forms of hypertension are due to changes in genes that regulate renal sodium excretion. Those genes account for changes in blood pressure 10 times greater than the aggregated effects of multiple genes in the above population wide studies. Ji et al. reasoned that heterozygous genes of rare disorders of enhanced salt excretion, such as Bartter’s and Gitelman’s,
should be present in about 1–2% in the general population and may be associated with lower blood pressure. That is in fact what they found. In the 1–2% of the population who are fortunate to carry only one allele of the mutant Gitelmans or Bartters, NCCT, NKCC2 or ROMK genes, the incidence of hypertension at any age is about half the expected incidence. The latter avenue of research may explain less of a population-wide risk but may be much better for the quest to individualized therapy and for finding targets of new antihypertensive strategies.

Acknowledgements. I thank Drs C. Clase, A. Grosshennig and K. F. Hilgers for their help in the preparation of this manuscript.

Conflict of interest statement. I receive grant support from Boehringer Ingelheim and Roche, honoraria from Novartis, Bayer, Amgen, Roche, Boehringer Ingelheim.

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Received for publication: 24.11.09. Accepted in revised form: 24.11.09