What’s new in hypertension 2008?

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Introduction

This editorial comment intends to inform readers of NDT about new information in the field of hypertension from mid-October 2007 to September 2008 that has not been published in nephrological journals. PubMed lists 2514 citations in the last 12 months with ‘hypertension’ as major topic including 353 reviews.

Human studies

Antihypertensive drugs in people over 80 years of age

It is unclear whether we should treat hypertensive people above the age of 80 years with antihypertensive drugs. This hypertensive subgroup on the one hand is liable to adverse events of drug treatment and may die of many diseases unrelated to hypertension, but on the other hand the absolute cardiovascular risk increases dramatically with higher blood pressure. The HYVET study [1] randomized people above the age of 80 and with sustained systolic blood pressure >160 mmHg to placebo or to indapamid, 1.5 mg/day, to which perindopril, 2–4 mg/day, could be added if the target blood pressure of 150/80 was not reached. In other words, the investigators did not examine initial stages of hypertension, let alone high-normal blood pressure, and did not target so-called normal blood pressure <140/90 mmHg. In 3845 participants with a mean age of 84 years and a blood pressure of 173/91 mmHg at baseline, a remarkably high diastolic blood pressure for that age, blood pressure was lowered by 30/13 mmHg with active treatment versus 15/7 mmHg with placebo. Over a follow-up of only 2 years, total mortality was significantly reduced by 21% or 39 deaths were prevented by active treatment, 22 from cardiovascular causes. Risk of stroke was also significantly reduced, by 30% or 18 strokes prevented in 2 years, and risk reduction of new heart failure was striking, 64% or 35 cases prevented in 2 years. Serious adverse events were much more frequent with placebo (448 versus 358 instances). There are few limitations to that study except that the authors report no details of subjective adverse events such as dizziness or syncope that may impact on quality of life. In daily practice we must, however, consider that the general hypertensive population at that age is considerably sicker than in the HYVET study, exhibits isolated systolic hypertension as a rule (only 33% in HYVET) and reports frequently a history of cardiovascular events (only 12% in HYVET). It is uncertain whether the HYVET results can be translated into a population of the same age, but with a more widespread vascular damage that nephrologists often see. Results in sicker populations may be better because of a higher event rate and a potentially higher absolute benefit but may also be worse because risks may be less dependent on blood pressure.

Combining ACE inhibitors and angiotensin receptor blockers does not help

Inhibition of the renin–angiotensin system by ACE inhibitors and by angiotensin receptor blockers is beneficial in people with hypertension, with vascular disease, in heart failure and in proteinuric nephropathies. The combination of both drugs inhibits the renin system more effectively with some further benefits in people with heart failure and in reducing proteinuria to a greater extent than monotherapy with either drug. Adverse events of the combination in heart failure are worrisome as we have detailed in this comment a year ago. The ONTARGET study enrolled 25,600 people with vascular disease, and compared ramipril 10 mg/day with the combination of telmisartan 80 mg/day plus ramipril 10 mg/day and with telmisartan 80 mg/day over 5 years [2]. Although combination therapy had a greater effect on blood pressure (differential 2.4/1.4 mmHg to ramipril), it had no benefits on major cardiovascular outcomes. Renal outcomes were more frequent with combination therapy, including the often used combined endpoint of dialysis plus doubling of serum creatinine, while proteinuria was less with combination therapy [3]. No doubt that we should not use the combination to treat hypertension or to prevent major cardiovascular or renal outcomes in people with vascular disease in
general, but how about renal subgroups? ONTARGET included 3000 people with microalbuminuria, almost 1000 individuals with macroalbuminuria including 300 people with macroalbuminuria > 1 g/g creatinine. We could not detect in any of those proteinuria-based subgroups a signal of renal benefit. Subgroup analyses are fraught with statistical problems and there are issues of power when going to sub-subgroups such as macroalbuminuria > 1 g/g. Until further long-term studies dedicated to major renal outcomes are available, we should base our judgements on the ONTARGET trial. The use of combination therapy to lower proteinuria should be restricted to people with albuminuria in excess of 1 g/g and should be discontinued when there is no antiproteinuric effect or when eGFR decreases substantially. In the end, ONTARGET questions the use of proteinuria as a surrogate marker and suggests that we need hard renal outcomes to accept interventions and medications for our patients. The COOPERATE study is no good argument here because that study should no longer be cited until extremely serious concerns about its conduct and analysis have been dealt with [4,5].

Should we screen asymptomatic people for carotid artery stenosis?

It has been argued that people with hypertension should be screened with carotid duplex ultrasound for an increase in intima-media thickness and for carotid artery stenosis even in the absence of cerebrovascular symptoms. The last guidelines of the European Society of Hypertension also favour such screening. The US Preventive Services Task Force, funded by but independent from the US government, has now issued recommendations not to screen in asymptomatic people. The USPSTF performed a systematic review of the evidence for benefit and harm of the screening [6]. The review is revealing; duplex ultrasound is a reliable technique with a sensitivity and specificity ∼ 90% to detect stenoses of > 60–70%. However, only a minority of disabling strokes is due to carotid artery stenosis. In centres of vascular surgery with a low complication rate, high-risk people with high-grade carotid stenosis will have a 5% absolute risk reduction over 5 years for stroke and death combined. This risk reduction must be weighted against the harms of screening, namely the risks of angiography when stenosis is suspected on ultrasound and the complications of unnecessary surgery in people with false-positive screening results. It is also noted that a 60–99% stenosis of the carotid artery in asymptomatic people above age 65 may be found in 1% of the population. No single risk factor or predictive rule is known to reliably predict clinically important carotid artery stenosis. It is, however, clear that the prevalence of such stenosis increases with hypertension, male gender, smoking and known heart disease. Based on these considerations and in the absence of a study comparing stroke as an outcome and screening or no screening as interventions, USPSTF does not recommend screening for carotid artery stenosis in asymptomatic people.

Obesity is not a lack of discipline

Obesity may be a major cause of hypertension as indicated by epidemiological and interventional studies. Many physicians assume that losing weight is only a matter of discipline. We may be wrong. Everyone interested in the subject should read a controversy [7] that reviews all aspects of that matter. There is impressive evidence that body weight is strongly genetically determined. Body weight in identical twins is closely correlated if they are raised in different families; their body weight is not related to their family if it is not the genetic family. The correlation of body weight is weaker in non-identical twins. Apart from rare monogenic disorders like Leptin deficiency or Leptin receptor deficiency, obesity is a multigenetic disorder. In addition, epigenetic effects, like body weight and fat intake of the mother during pregnancy, play a role. The question then comes up, why does overweight (BMI 25–30/m²) and obesity (BMI > 30/m²) increase in recent years, affecting now far more than 50% of adults? The hypothesis is that obesity genes are susceptibility genes, i.e. genes that cause a disease only in a ‘toxic’ environment. With the abundant availability of fat food and the sedentary lifestyle, such genes break their way. Such gene–environment interactions can be shown in animal models of genetic obesity and in humans. These interactions also explain why abundance of fat food has little influence on the proportion of lean people, who are genetically immune against weight gain, but has a major influence on the massive increase of morbid obesity in recent decades. Given the strong genetic background, it comes as no surprise that the long-term efficacy of weight control programmes is fraught with failure. The majority of interventional weight control studies ended before 1 year; the mean weight loss was 2–5 kg and could be maintained by a minority only. Similarly, attempts to increase physical activity, which may explain about half of the overweight problem, are usually not maintained whenever a specific programme ends. Small changes in weight admittedly result in a significant decrease in blood pressure that matches antihypertensive drug monotherapy. Whether these changes of blood pressure are maintained for more than 1–2 years is unknown. Maybe research of the few patients that successfully maintain a substantial weight loss (everyone of us knows a handful of those) may teach us more. The sad conclusion is that obesity as a genetically determined disease in modern environment has no cure. What to do in our hypertension clinics? We should inform patients about the effects of diet and exercise on blood pressure with prudent guidance of what they can expect. The strong genetic background should be made clear, and failure of a weight reduction programme, which is the rule, should not be blamed on the patient. In morbid obesity, bariatric surgery is effective over many years and has recently been associated with a reduction in cardiovascular outcomes and death with minor effects on blood pressure.

Subtle kidney damage first, hypertension later?

The kidneys play a major role in regulating blood pressure, and severe diseases of the kidney are commonly accompanied by hypertension. Whether the kidneys play a role in the genesis of primary hypertension is less clear, but there is evidence that people with primary hypertension have a lower number of glomeruli per kidney. The MESA (Multi Ethnic Study of Atherosclerosis) recruited between 2000 and 2002 adults aged 45–84 in the community to study subclinical cardiovascular disease in 6814 participants [8].
Of these, 2767 did not have hypertension or kidney or cardiovascular disease; microalbuminuria and estimated GFR <60 ml/min/1.73 m² were absent in particular. Over 3 years, 20% developed primary hypertension. Of all parameters, a higher baseline cystatin C serum level was associated with the new development of hypertension; a 15 nmol/l higher cystatin C indicated a 15% increase in risk for the development of hypertension. This relationship was absent for serum creatinine or eGFR calculated on the basis of serum creatinine. If anything, participants with a serum creatinine level of 0.8–1.5 mg/dl had a lower incidence of hypertension than those with a serum creatinine <0.8 mg/dl! The association of serum cystatin C with new onset hypertension was remarkably robust; it was independent of baseline blood pressure and persisted when participants with high-normal blood pressure were eliminated from the analysis. Diabetes, age, race and body mass index did not materially alter the association. The urinary albumin excretion rate did not correlate with the incidence of hypertension. That association was less robust and was eliminated when adjusted for other variables. Serum cystatin C and urinary albumin excretion were not related to each other, but this study purposefully excluded participants with elevated urinary albumin excretion (microalbuminuria) and with a low eGFR. The MESA study measured blood pressure three times with an automated sphygmomanometer at each visit. However, there were only three such visits, which certainly limits the precision to detect and classify chronic hypertension. The latter was not only diagnosed on the basis of blood pressure but also on medication and history. The authors adjusted extensively for covariates that do not exclude resistant confounding, and they state that uric acid was not measured. Recent preliminary evidence from one small and short-term pilot study opens the possibility that allopurinol lowers blood pressure [8a]. The MESA study provides solid evidence that indeed subtle kidney damage contributes substantially to elevated blood pressure, hence to primary hypertension. Still that does not say that any hypertension is a kidney disease and we do not know why in the first place kidney function was reduced in MESA participants developing hypertension and why blood pressure increased subsequently. Further understanding of the pathophysiology may lead to new treatments or, better, prevention of hypertension.

How to use ACE inhibitors and angiotensin receptor blockers with renal artery stenosis?

Many textbooks and package inserts list renal artery stenosis indiscriminately as contraindication for the use of ACE inhibitors or angiotensin receptor blockers (collectively called ‘angiotensin inhibition’ in this paragraph). There are data, however, suggesting that people with renal artery stenosis may specifically benefit from both types of drugs given the fact that (a) they are more effective in lowering blood pressure in renovascular hypertension than other antihypertensives and (b) they lower cardiovascular risk in people with atherosclerotic vascular disease. The latter condition is highly prevalent in people with renal artery stenosis. Hackam et al. [9] note that trial registries show that there are no randomized trials underway testing angiotensin inhibition in renal artery stenosis. The authors, therefore, performed a longitudinal population-based cohort study to evaluate the impact of angiotensin inhibition on renal and cardiovascular outcomes in all people 65 years of age or older in the province of Ontario, Canada. These people are entitled to free, i.e. tax-financed, health care including drug coverage. Data on hospital admissions, discharge diagnoses and interventions, on drug use, on all physician claims and on vital statistics of these Ontario residents are in central registers and were used for the present manuscript. Between 1995 and 2005, 3570 people were detected with a diagnosis of renal artery stenosis, excluding those that concomitantly were on dialysis. Total years of follow-up were 6959, so the mean follow-up time was 2 years. Angiotensin inhibition was defined as a filled prescription of one of these drugs after 3 months of the initial diagnosis of renal artery stenosis (n = 1877). The two groups, treated and not treated with angiotensin inhibition, were remarkably similar in baseline characteristics; if anything, baseline risk was somewhat higher in those treated with angiotensin inhibition. The annual incidence of a primary event (818 events), defined as death, myocardial infarction or stroke, was high, namely 11.8%, but significantly less in those treated with angiotensin inhibition (25% by unadjusted, 30% by adjusted analyses). The absolute benefit was 3 per 100 patient-years for the primary outcome. The population experienced more cardiovascular than renal events, and the single most frequent event was hospitalization for heart failure, occurring in 8%. Treatment with angiotensin inhibition also significantly reduced mortality by 44% (666 deaths) and chronic dialysis (146 cases) by 38%, but increased the risk of hospital admission for acute renal failure; 36 of those episodes were reversible, 24 unfortunately were not. The authors indicate that they cannot offer any data on follow-up serum creatinine or on severity of renal artery stenosis and its lateralization (uni- or bilateral?). Results were independent of intensity of diagnostic or interventional procedures and of number of visits with family doctors or specialists. The authors caution that other antihypertensive agents should be used first in people with renal artery stenosis and if angiotensin inhibitors are used, renal function should be very frequently monitored. I would come to slightly different conclusions because of the striking benefits of angiotensin inhibition in this study and recommend using angiotensin inhibition in most cases of unilateral renal artery stenosis and to strongly consider its use in bilateral renal artery stenosis if blood pressure is not normalized (which is rather the rule). No doubt that we need careful control of kidney function, especially early after initiation of therapy but also later on because renal artery stenoses tend to become tighter with time.

Experimental studies

**T-cells mediate angiotensin-induced hypertension and vascular damage**

Interaction of hypertension and hypertensive damage with the immune system is an attractive though underrepresented subject. We had alluded to involvement of tumour necrosis factor alpha (TNF alpha) in a complex model of hypertensive renal damage in last year’s commentary. Guzik et al. [10] studied the role of T-cells in angiotensin II-induced
blood pressure in these mice was drastically elevated by respective diseases following severe hypertension. In fact, thy and kidney damage in these mice is reminiscent of as in humans with the Costello syndrome. Cardiomyopathy, mammary gland hyperplasia and cardiomyopathy has been developed [11]. These mice display facial dysdevelopmental changes of the heart, the skin and the brain. Costello syndrome. That syndrome is characterized by constitutive activation of a member of the RAS oncogene superfamily. Oncogenes play pivotal roles in cell differentiation. Constitutive activation of a member of the RAS oncogene superfamily, H-RAS, results in a rare genetic disease, the Costello syndrome. That syndrome is characterized by developmental changes of the heart, the skin and the brain. A mouse model for that constitutive activation of H-RAS has been developed [11]. These mice display facial dysmorphia, mammary gland hyperplasia and cardiomyopathy as in humans with the Costello syndrome. Cardiomyopathy and kidney damage in these mice is reminiscent of respective diseases following severe hypertension. In fact, blood pressure in these mice was drastically elevated by ∼60 mmHg at an early age. Furthermore, local renin–angiotensin systems in the heart and vascular wall exhibited signs of activation and plasma levels of angiotensin II more than doubled. Inhibition of the renin–angiotensin system, but not of endothelin, blunted left-heart cardiomyopathy and prevented renal and vascular damage concomitant with a normalization of blood pressure. The authors intensively investigated, but to no avail, in which organs or in which cells H-RAS would activate the renin–angiotensin system. Their hypothesis is that the H-RAS-dependent activation of renin in the brain is the culprit. The results are of interest not only to unravel the mysteries of a rare syndrome but also to understand regulation of the renin system and possibly hypertension associated tissue injury. There is a large gap in our understanding why tissue damage in patients may be vastly different at identical levels of blood pressure.

Malignant hypertension is one example of excessive tissue damage at blood pressure levels that are associated with minor damage in the majority of patients.

Unravelling pre-eclampsia

Kanasaki et al. [12] hypothesized that placental hypoxia is the determining factor for the development of many cases of pre-eclampsia and that alterations in hypoxia-driven imbalance in vasculogenic factors such as soluble FMS-like tyrosine kinase (s-FLT-1) and VEGF are only secondary to hypoxia. Searching for factors possibly responsible for hypoxia, the authors noted that 2-methoxyoestriadiol (2-ME), a metabolite generated by catechol-o-methyltransferase (COMT), is reduced in women with pre-eclampsia, as is placental COMT. In fact, 2-ME is a strong inhibitor of hypoxia inducible factor 1-alpha (HIF-1alpha), i.e. its absence will boost hypoxia-sensitive gene transcription. The authors genetically engineered mice with a reduced expression of COMT and hence 2-ME. These mice developed all features of pre-eclampsia. Treatment with 2-ME reversed the syndrome to a normal pregnancy without any notable adverse effects. Other oestradiol metabolites did not imitate the effects of 2-ME. Hopefully these results will alter diagnosis and treatment of pre-eclampsia in the near future. However, the syndrome of pre-eclampsia may not be initiated by a single factor and we should not expect that one treatment will cure all women with this syndrome that may affect 5–10% of pregnancies.

H-RAS oncogene associated with angiotensin-dependent hypertension

Oncogenes play pivotal roles in cell differentiation. Constitutive activation of a member of the RAS oncogene superfamily, H-RAS, results in a rare genetic disease, the Costello syndrome. That syndrome is characterized by developmental changes of the heart, the skin and the brain. A mouse model for that constitutive activation of H-RAS has been developed [11]. These mice display facial dysmorphia, mammary gland hyperplasia and cardiomyopathy as in humans with the Costello syndrome. Cardiomyopathy and kidney damage in these mice is reminiscent of respective diseases following severe hypertension. In fact, blood pressure in these mice was drastically elevated by

Activation of the renin–angiotensin system in diabetes is driven by hyperglycaemia

It is known that the renin–angiotensin system is activated at early stages of diabetes in animal model and in humans. Diabetic complications have been linked to renin activation, specifically to pro-renin. It proved to be difficult to sort out metabolic and haemodynamic effects that govern renin release with diabetes. Toma et al. [13] now provide evidence that altered metabolism play the major role in diabetes-associated activation of renin release. The authors studied the G-protein coupled metabolic receptor GPR91. This receptor is present in glomerular endothelium (and in many other organs) and its ligand is succinate. Succinate as part of the Krebs
cycle is normally present in the mitochondria but will be released from there to the extracellular space when there is an energy supply-demand imbalance. Succinate will bind to membrane bound GPR91. Toma et al. now convincingly show that high glucose perfusion of a kidney will induce succinate formation and activation of GPR91. Glucose releases renin and prorenin within minutes and decreases stored renin by > 50%. A high proportion of these glucose effects are direct, and a third is due to changes in osmolality of hyperglycaemia. GPR91 was shown to be present on glomerular endothelial cells and not on juxtaglomerular (JGA) or vascular smooth muscle cells. Signal transduction from the vascular endothelial cells to the renin-producing cells involves intracellular calcium release, NO formation and prostaglandin E2 production and their paracrine effects. Animal models with diabetes (streptozotocin model) exhibit enhanced renin release that is blunted in animals lacking GPR91, interestingly blunted to a level that correspond to the osmotic component of renin release in the kidney perfusion experiments alluded to above. Interference with succinate production in whole animal models of diabetes confirms its specific role in renin release. These extensive data, backed by splendid imaging results at a subcellular level, provide new information where and how metabolism interacts with vasoactive hormones and, hence, haemodynamic pathophysiology. The authors allude to former data that propose GPR91 as a mediator of ischaemia-induced renin release in renovascular hypertension. The role of this receptor may go beyond metabolism and it may be a target for drug development to prevent diabetic complications.

Hypertension is driving cellular senescence

People do not age at the same speed and hypertension speeds up senescence! Senescence of cells leads to reduced capacity to react to stress and to upregulate repair mechanisms, limiting regenerative capacity of organs. Senescence may be induced by stress and aberrant signalling and by dysfunctional telomerases. Westhoff et al. [14] provide interesting data that stress-dependent cellular senescence in the kidney and in the heart is modulated by hypertension. The authors studied a main switch of stress-induced senescence, p16-INK4a, a cyclin-dependent kinase inhibitor that arrests cells cycle at the G1 phase. Results in two hypertensive rat models, mineralocorticoid (DOCA-salt) hypertension and (mRen2) 27 transgenic rats, were very consistent; in both models, expression of p16-INK4a in kidney and heart (including coronary arteries) was massively elevated as compared to controls, and antihypertensive therapy reduced this expression to almost normal levels. The expression of p16-INK4a was shown at the RNA, protein and histopathological level. Spironolactone at doses that had no measurable antihypertensive activity also reduced expression of p16-INK4a. Hypertensive damage to the kidney and heart was extensive in both rat models and antihypertensive therapy reduced this damage. The authors also studied kidney biopsies of several patients diagnosed with hypertensive nephrosclerosis. As compared to other biopsies, the expression of p16-INK4a in these human specimens was substantially enhanced. These data will not alter our approach to our patients, but will indicate new avenues in the search for drug treatment. So far there are no inhibitors of p16-INK4a or its upstream modulators.

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Conflict of interest statement. I receive grants and speakers honoraria from several companies that produce antihypertensive drugs. I collaborate in several international trials on antihypertensive medications and on non-pharmacological treatments in CKD that are co-sponsored by companies that produce antihypertensive drugs.

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