



International Press Conference during HYPERTENSION Berlin 2008

Date: 18th June 2008, 12:30 to 13:30 p.m.

Place: ICC Berlin, room 43

Topics and Speakers:

Translating ONTARGET into clinical practice

Professor Dr. med. Thomas Unger, Hypertension 2008 Vice-President,
Center for Cardiovascular Research (CCR) and Institute of Pharmacology
Charité University Clinic, Berlin

Experimental research in the field of hypertension:

Development of a renin-inhibitor based on transgene rats

Professor Dr. rer. nat. Michael Bader, Max-Delbrück-Centre for Molecular
Medicine, Berlin Buch (MDC)

Pulse wave velocity and central blood pressure

Professor Stéphane Laurent, President of the European Society of
Hypertension (ESH), Head of Department of Clinical Pharmacology, Hôpital
Européen Georges Pompidou, Paris

Global burden of cardiovascular disease:

A major public health problem

Professor Richard Horton, Editor-in-Chief of The Lancet, London

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The importance of prevention and research in combating hypertension

Berlin, 18th June 2008 – Co-hosted by the European and the International Society of Hypertension at the ICC in Berlin from 14th to 19th June 2008, HYPERTENSION 2008 bring together around 7,000 scientists and physicians from all over the world to discuss the latest findings in the field of hypertension. Some of the main topics are the prevention of strokes, kidney and heart disease and hypertension in the elderly and in developing countries. Speakers from Germany and abroad also present significant recent studies on hypertension treatment. In plenary sessions, experts are dealing with evolutionary aspects of cardio-vascular biology, stem cell therapy, and the worldwide significance of cardiovascular disease.

About 50 percent of the adult population have high blood pressure. An aging population, obesity and lack of exercise are all factors that contribute to the rising incidence of hypertension. Chronic stress and an unhealthy diet are also contributory factors, as is reduced vascular elasticity in the elderly.

The consequences are many and varied: Hypertension sufferers not only have a higher cardiovascular risk, they also tend to develop cerebrovascular disorders, which increase the likelihood of developing vascular dementia.

One of the most important weapons in the battle against hypertension is prevention, a fact that is reflected in the congress program: "The success story of medicinal prevention in combating hypertension is almost unparalleled among the major widespread diseases," comments Professor Dr. med. Detlev Ganten, congress president and chairperson of Berlin's Charité University Clinic. "It should serve as a model for the treatment of the other major widespread diseases, too. Drug-based therapies, for example, significantly reduce the incidence of linked diseases such as stroke and kidney or heart failure. But more than anything, it's lifestyle choices such as eating a healthy diet, maintaining normal body weight, taking regular exercise, reducing alcohol intake, and giving up smoking that significantly reduce the development of hypertension and organ disease," adds Professor Ganten.



The majority of hypertension sufferers, approximately 90 percent, have primary hypertension, i.e. no organic problems such as kidney disease or hormonal dysfunctions of the thyroid or adrenal glands are involved. Besides the above-mentioned contributory causes, hypertension in these patients is frequently triggered by hereditary factors. "This is why fundamental genetic research is so important in developing new forms of diagnostics, prevention and therapy," says Ganten. At the congress experts are also presenting the latest findings in molecular biology and discussing how best to ensure their transfer into clinic and practice. "Many successes that have been the result of effective and safe drug-based treatments would have been inconceivable, were it not for the excellent research that has been done," emphasizes Professor Ganten.

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Metabolic syndrome – Does it confer pathophysiological or prognostic information?

Berlin, 18th June 2008 – The concept of the metabolic syndrome has gained much attention during recent years. Although others have proposed similar entities, the Reaven Banting lecture 1988 introduced the concept of syndrome X as a fundamental factor in the pathogenesis and clinical cause of type II diabetes, hypertension, and atherosclerotic cardiovascular disease.

In Reaven syndrome X resistance to insulin-stimulated glucose uptake (insulin resistance) and hyperinsulinemia was defined as key variables for the risk of cardiovascular diseases. The basic hypothesis was, that insulin resistance with compensatory hyperinsulinemia was the culprit in syndrome X. Later others, including leading organizations and associations turned syndrome X into the metabolic syndrome. A number of definitions for the metabolic syndrome was put forward – maybe too many! – and not always well founded based on pathophysiological or cardiovascular epidemiology.

Recently this has led to intense discussion about the importance of the metabolic syndrome as a riskfactor for cardiovascular diseases – to such an extent that the “father” of the syndrome suggested to let the metabolic syndrome rest in peace (GM Reaven: The metabolic syndrome: Requiescat in pace,. Clin. Chem. 2005; 51:;931).

We recently published data (J. Jeppesen et al J.Am Coll cardiol 2007; 49; 2112-9) from a large population based study. We were particularly interested in clarifying whether insulin resistance (IR) would predict incident CVD independent of the metabolic syndrome and how two different definitions of the metabolic syndrome would impact on the risk of CVD. We used the homeostasis model assessment (HOMA) to assess IR and we defined metabolic syndrome according to the International Diabetes Foundation (IDF) criteria and to the National Cholesterol Education program (NCEP) criteria.

The HOMA – IR value has been shown to correlate well with the “gold standard” clamp technique for insulin sensitivity. Insulin resistance predicted CVD indepen-

dent of the metabolic syndrome based on either IDF or NCEP criteria. Metabolic syndrome based on NCEP criteria remained a significant predictor for CVD when adjusted for IR, however IDF criteria did not remain a significant predictor for CVD. HOMA-IR predicted CVD independent of the Framingham risk score. Risk score programs such as the Framingham risk score provides more information about global risk of CVD than metabolic syndrome. Even though insulin resistance is key variable for development of metabolic syndrome in our population based study the concordance among individuals with metabolic syndrome and insulin resistance amounted to some 50 percent, i.e. insulin resistance is not the only cause for development of metabolic syndrome.

In our population the prevalence on metabolic syndrome was 20.6 percent according to IDF criteria and 16.4 percent according to NCEP criteria – the two definitions do not identify exactly the same population. It is noteworthy that the NCEP criteria identify risk for CVD to a higher extent than IDF criteria. In cross sectional data we also found (Marina K Kristensen: Phd-thesis) that in a general population atherosclerotic plaques in the carotid arteries was much less related to the metabolic syndrome than to traditional risk factors.

In conclusion:

In our hands insulin resistance seems to represent a basic pathophysiological pathway leading to potentially preventable CVD in the community. It carries risk information independent of the metabolic syndrome as well as Framingham risk score. The metabolic syndrome defined by NCEP criteria carries information about CVD risk, even when adjusted for insulin resistance. This was not the case with IDF criteria. It is obvious that risk score programs such as the Framingham risk score provides more information about global risk of CVD as compared to the metabolic syndrome. The metabolic syndrome should not be considered as a pathophysiological entity, but a pragmatic approach to achieve improvement in clinical outcome. The metabolic syndrome seems to be helpful, especially for the evaluation of individuals at low or moderate risk by a risk score program, adding help to identify individuals who warrant intervention.

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Source: Current Congress, Hypertension Berlin 2008.

The weight of evidence with ASCOT

Berlin, 18th June 2008 – The Blood Pressure Lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT-BPLA) was relatively unique among hypertension trials in that it was designed to compare the effects of two totally different combinations of drugs – a standard combination starting with atenolol and adding a thiazide as needed to reach target blood pressures, and a newer combination starting with amlodipine and adding perindopril as needed.(i)

The rationale for the design of ASCOT was firstly, that as of the mid-1990's, there had been insufficient outcome data on newer types of BP-lowering agents (e.g. calcium channel blockers [CCBs] and ACE-inhibitors) especially in specific combination treatment regimens and secondly, that the coronary (CHD) prevention associated with diuretics and β -blockers in meta-analyses of 17 major trials was suboptimal.(ii)

The primary outcome of the trial was non-fatal myocardial infarction and fatal CHD and by means of a 2 x 2 factorial design, two comparisons were made. Firstly, the impact of β -blocker + / - diuretic was compared with CCB + / - ACE inhibitor and secondly in those with total cholesterol \leq 6.5 mmol/L atorvastatin was compared with placebo.

Because the newer regimen was associated with a significant reduction in all-cause mortality the Data Safety Monitoring Board recommended that the trial be stopped early. The study executive and steering committee were unanimous in accepting this recommendation, whilst acknowledging the fact that all-cause mortality was a secondary end point and that by early termination of the trial it became underpowered to evaluate the primary end point (non-fatal myocardial infarction and CHD).

Nevertheless, compared with the standard regimen, the newer regimen was associated with a significantly superior effect on the primary end point excluding silent myocardial infarctions, or including revascularisation procedures, on total coronary events, cardiovascular mortality, fatal and non-fatal strokes, unstable angina, total cardiovascular events and procedures, new-onset diabetes, and development of renal impairment (Figure 1)(iii). Benefits were apparent and significant for total cardiovascular events and procedures in all 18 pre-specified subgroups. (Figure 2)

The newer regimen was associated with an average in-trial blood pressure which was 2.7/1.9mmHg lower than that of the standard regimen. Whilst it seems likely that this blood pressure difference contributed to the superior prevention of all cardiovascular events by the newer regimen, extensive in-trial analyses suggested that other advantages of the newer regimen also contributed to the more effective prevention of events^(iv). These analyses are in keeping with other findings which suggest ACE-inhibitors may have benefits beyond blood pressure-lowering in relation to coronary heart disease events and that calcium channel blockers may have benefits beyond blood pressure-lowering in relation to stroke protection (v).

Current national and international guidelines are inconsistent with regard to optimal first-line agents. It is therefore no surprise that guidelines are even less consistent regarding optimal combinations of therapies. However, along with the recently presented ACCOMPLISH trial, the results of ASCOT-BPLA provide strong support for the preferential use of “A + C” drugs (ACE-inhibitor / ARB + Calcium channel blockers) (vi) when two agents are needed to reach BP targets.

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By: Neil R Poulter, International Centre for Circulatory Health, Imperial College London
Abstract for Servier Satellite entitled 'Seeking efficacy in managing hypertension in 2008', held during the ESH-ISH Meeting, Berlin 14-19 June 2008
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Aliskiren—mode of action and preclinical data

Dominik N. Müller · Wolfgang Derer · Ralf Dechend

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Abstract Hypertension is one of the major health care problems worldwide since it markedly increases the risk for development of heart disease, stroke, generalized vascular disease, and renal failure. The renin–angiotensin system (RAS) with its major end-product angiotensin II (Ang II) plays a fundamental role in blood pressure regulation through direct and indirect mechanisms. Pharmacologically, we can inhibit the RAS using angiotensin-converting enzyme inhibitors and AT1 receptor blocker. Inhibiting renin directly with a clinically useful drug eluded pharmacologists until recently. However, the once-daily, orally effective, small-molecule, direct renin inhibitor aliskiren has recently changed this state of affairs. Aliskiren, with its 40-h half-life and ideal pharmacokinetics, can now address angiotensin production directly at its rate-limiting step. A novel transgenic rat model outfitted with the human renin and angiotensinogen genes allowed the testing of aliskiren in an animal model. Preclinical data demonstrated that aliskiren prolonged survival, decreased cardiac hypertrophy and the inducibility of arrhythmias, proteinuria, and attenuated inflammation. All these features might result in

improved target-organ damage. Studies in humans attest to an effective blood pressure-lowering action, a largely side effect-free profile, and the option of several combination therapies. Aliskiren is the first of a novel antihypertensive drug class. The preclinical data is very promising. Nevertheless, for the evaluation of its potency in humans, we have to wait for more clinical data.

Keywords Renin · Renin–angiotensin system · Hypertension

Introduction

The renin–angiotensin system (RAS) is important in regulating sodium levels and intravascular volume. It is also involved in the pathophysiology of hypertension, cardiovascular disease, diabetes and renal disease. Aliskiren is the first direct renin inhibitor which is approved for the treatment of hypertension (for review please see [1, 2]). RAS activity is initiated by the cleavage of angiotensinogen to angiotensin (Ang) I by the enzyme renin. This novel antihypertensive therapy offers the potential to inhibit the mechanisms which have induced the end-organ damage. The aim of this minireview is to summarize the mode of action and the preclinical data of aliskiren.

Mode of renin inhibition action

Direct renin inhibitors (DRIs) were explored years ago but failed to reach full clinical development for various reasons. Peptides proved pharmacologically inappropriate. Toxicity, poor bioavailability, and insufficient efficacy were all issues. In the absence of an available DRI, angiotensin-

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converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARB) were developed even though they do not address the rate-limiting step. Nonetheless, blocking or reducing Ang II has developed into a cornerstone of treatment. The aforementioned obstacles have been addressed with the introduction (and approval in many countries) of aliskiren, the first available direct renin inhibitor. Aliskiren differs from previous DRIs as it has an improved half-life (40 h) and acceptable bioavailability (2.6%). Thus, the drug is suitable for oral, once-daily dosing. The pharmacokinetics of aliskiren are unique since the drug's half-life is not affected by renal function, liver function, age, gender, concomitant medications, or activities of P450 micro-oxidases. Aliskiren binds to the active site of renin, preventing angiotensinogen from binding and being cleaved to form Ang I, thereby inhibiting the activation of the renin system at the rate-limiting step.

DRI offers a number of advantages over ACE inhibitors and ARB. Theoretically, inhibiting the renin system at the point of activation with a DRI will provide comprehensive Ang II suppression. In addition, since angiotensinogen is the only known renin substrate, direct renin inhibition should have minimal side effects. Cough would not be expected. Furthermore, the edema associated with calcium channel blockers should not occur.

One not completely answered question involves the possible aliskiren-induced inhibition of Ang breakdown products aside from the octapeptide Ang II. Indeed, the heptapeptide Ang(1–7), Ang3–8, and a series of other breakdown products have been implicated in the regulation of vascular physiology but has not yet proved to be physiologically significant. A second angiotensin conversion enzyme (ACE2) has been described. The nature of these breakdown products and their putative receptors is an area of much interest with similar amounts of confusion. ARB treatment actually increases Ang II levels and presumably the breakdown products. Thus, ARBs stimulate AT₂ receptors which might trigger a vasodilatory and natriuretic response. ACE inhibition also promotes vasodilation by increasing Ang(1–7) and NO release. However, they often lose their long-term effect in decreasing circulating Ang II. Aliskiren, in contrast to ARBs and ACE inhibitors, blocks very upstream and thus prevents the Ang peptide formation (Fig. 1). More basic research about beneficial and detrimental actions of Ang peptides and more long-term clinical studies will demonstrate whether early blockage will be an advantage or disadvantage.

The kidney releases active renin that is not equipped with the handle region peptide sequence that distinguishes active renin from prorenin. Aliskiren increases the amount of circulating immunoreactive renin while it decreases plasma renin activity (PRA). High PRA per se is a cardiovascular risk factor, albeit shown only in a large

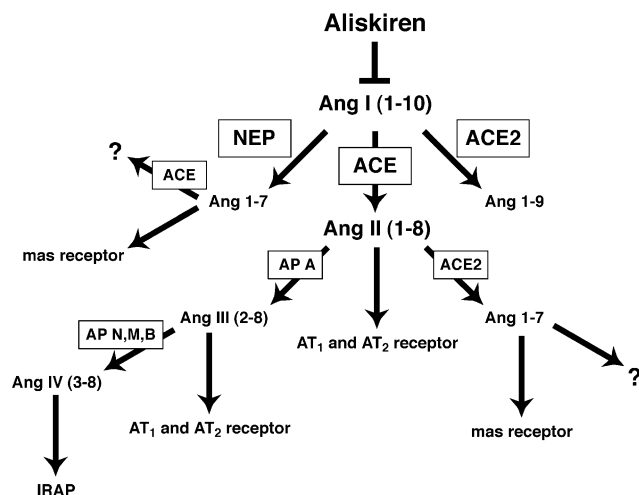


Fig. 1 Scheme of Ang peptide formation. Renin inhibition inhibits Ang I generation which leads to suppressed Ang II formation as well as reduced Ang peptides formation. (AP aminopeptidase, IRAP insulin-regulated aminopeptidase)

cohort of untreated hypertensive patients. This study showed that pretreatment PRA was independently and directly associated with the risk of myocardial infarction, even though the patients subsequently achieved blood pressure control with antihypertensive therapy [3]. However, the study did not investigate whether or not the effects of PRA were independent of Ang II. Nevertheless, elevated PRA has also been associated with the presence of target-organ damage, including renal dysfunction [4] and left ventricular hypertrophy in other studies [5]. Alderman et al. recently reported that although African Americans, the elderly, diabetics, and women patients are said to more commonly exhibit low-renin hypertension, this may not invariably be the case [6].

Preclinical aliskiren data

Renin is a species-specific enzyme. The drug exhibits an IIC₅₀ of 0.6 nM for human renin and 100-fold that value for rat renin. This creates challenges for profiling aliskiren in preclinical models. To get around this problem, Ganten et al. generated two transgenic rat strains [7]. One strain harbors the human renin gene with its own promoter; the second harbors the human angiotensinogen gene with an albumin promoter. Rat renin will not cleave human angiotensinogen and human renin will not cleave rat angiotensinogen. Thus, the double-transgenic (dTGR) offspring are under the influence of two transgenes that generate large quantities of Ang II in the circulation, the vasculature, the heart, and the kidneys (Fig. 2). Untreated dTGR die of cardiac cachexia [8] and renal failure at age

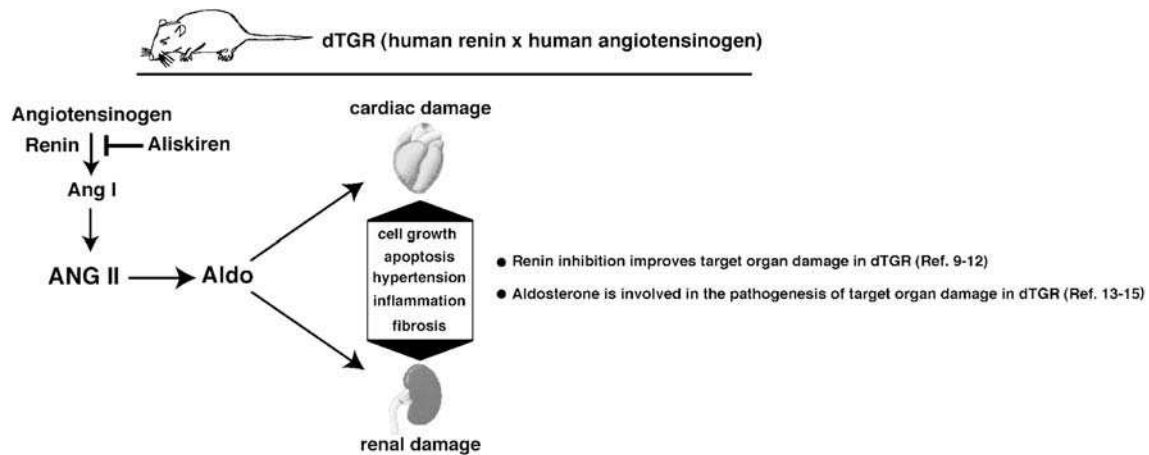


Fig. 2 Scheme of the double-transgenic rat model (dTGR). dTGR overexpress the human renin and angiotensinogen genes leading to increased Ang II and aldosterone levels. Renin inhibitors ameliorate renal and cardiac target-organ damage

8 weeks. This model is suitable to test human renin inhibitors in terms of mechanisms related to target-organ damage and subsequent repair. The first studies with aliskiren in dTGR demonstrated that aliskiren normalizes blood pressure and provides blood pressure control for >24 h [6].

In a regression study design [9], 6-week-old dTGR were matched in terms of albuminuria (2 mg per day) and divided into five groups. Untreated dTGR were compared with aliskiren-treated (3 and 0.3 mg/kg per day) and valsartan-treated (10 and 1 mg/kg per day) dTGR. The purpose of the low-dose valsartan group was to prolong survival sufficiently to permit the animals to be studied after 7 weeks. Treatment was conducted from week 6 through week 9. Untreated dTGR showed increased blood pressure, serum creatinine, and albuminuria at week 7. By week 9, both doses of aliskiren normalized blood pressure, albuminuria, and serum creatinine. Mortality was 100% in untreated dTGR and 26% in low-dose valsartan (1 mg/kg per day)-treated rats, whereas in all other groups, survival was 100%. Blood pressure levels were similar to those expected for a normal non-transgenic rat. dTGR treated with low-dose valsartan had cardiac hypertrophy, increased left ventricular wall thickness, and diastolic dysfunction. We concluded from this study that in dTGR, equally effective antihypertensive doses of valsartan or aliskiren attenuated end-organ damage.

In another study that included aliskiren, we assessed complement expression as well as C-reactive protein (CRP) production in this dTGR model [10]. We found that elevations in levels of CRP, macrophages, and T cells as well as the expression of tumor necrosis factor (TNF)-alpha, C1q, C3, C3c, and C5b-9 all preceded albuminuria in untreated dTGR. C1q, C3, C3c, and C5b-9 were observed in the dTGR vessel media. C5b-9 colocalized with interleukin-6. Aliskiren and the ARB losartan reduced

albuminuria and expression of TNF-alpha, CRP and complement C1q, C3, C3c, and C5b-9 to control levels. Recently, we observed that low-dose aliskiren and low-dose losartan effectively reduced mortality and target-organ damage with minimal, non-significant, effects on blood pressure [11]. Furthermore, we demonstrated that renin inhibition also reduced cardiac hypertrophy, fibrosis and inflammation, and the inducibility of arrhythmias [12].

Besides Ang II, aldosterone (aldo) plays an important role in the pathogenesis of Ang II-induced target-organ damage. We showed earlier that blockade of the mineralocorticoid receptor with spironolactone, eplerenone, and an aldo synthase inhibitor improves renal and cardiac damage [13–15]. Even more impressive was the fact that adrenalectomy leading to an abolished aldo synthesis resulted in an improved mortality and target-organ damage despite high Ang II and high blood pressure [13]. These results indicate that Ang II develops its major effect only in the presence of aldo. Unfortunately, there is not much data available about the role of aliskiren on aldo production. Nussberger et al. demonstrated that aliskiren decreased plasma and urinary aldo in a short-term study [16]. No data is so far available about the role of aliskiren and aldo escape.

The effect of aliskiren in diabetic nephropathy was demonstrated in a rat model expressing mouse renin (mRen-2 rats) by Kelly et al. [17]. These rats are made diabetic by injecting streptozocin. They subsequently develop nephropathy in a fashion that was similar to human nephropathy. Aliskiren, at the dose employed, did not reduce systemic blood pressure to the degree observed with the ACE inhibitor perindopril. Nevertheless, both compounds were equally effective in reducing albuminuria and glomerulosclerosis in the diabetic animals. Notably, the magnitude of interstitial fibrosis was attenuated to a greater degree by aliskiren than by perindopril.

Future perspective

Aliskiren is the first orally active DRI to be approved for the treatment of hypertension. Clinical studies in patients with hypertension have shown that aliskiren is effective in lowering blood pressure. Concerning the mode of action, direct renin inhibition decreases plasma renin activity and inhibits the formation of Ang I and Ang II and most likely also Ang peptides. Adequate RAS blockade is often not achieved with ACE inhibitors or ARB. Future studies will show if suppression of the RAS system by DRI is more complete and whether Ang peptides are not generated. In line with this question, it will be important to find out if direct renin inhibitors prevent an aldosterone escape phenomenon as observed with other RAS inhibiting agents. Another interesting alternative approach to suppress Ang II has been introduced by Ambuhl et al. [18]. Recently, they introduced the clinical development and the phase I clinical trial for active immunization against Ang II. They could show that blood pressure is reduced in spontaneously hypertensive rats after immunization comparable to treatment with an ACE inhibitor. The immunization was also well tolerated in healthy volunteers.

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Pulse wave velocity and central blood pressure

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Arterial stiffness and wave reflections are now well accepted as the most important determinants of increasing systolic and pulse pressures in ageing societies. The noninvasive measurement of aortic stiffness, through carotid-femoral pulse wave velocity (PWV) has been recommended by the 2007 ESH/ESC Guidelines for the management of Hypertension, in order to evaluate the extent of arterial damage and adapt the intensity of antihypertensive treatment.

The measurement of PWV is generally accepted as the most simple, non-invasive, robust, and reproducible method with which to determine arterial stiffness. Carotid-femoral PWV, measured along the aortic and aorto-iliac pathway, is the most clinically relevant. Pressure waveforms are obtained transcutaneously at the common carotid artery and the femoral artery. The time delay (Δt , or transit time) is measured between the feet of the two waveforms. PWV is calculated as $PWV = D \text{ (meters)}/\Delta t \text{ (seconds)}$. Carotid-femoral PWV has been used in most epidemiological studies demonstrating the predictive value of aortic stiffness for CV events.

The arterial pressure waveform is a composite of the forward pressure wave created by ventricular contraction and a reflected wave. Waves are reflected from the periphery, mainly at branch points or sites of impedance mismatch. In elastic vessels of young subjects, because PWV is low, reflected wave tends to arrive back at the aortic root during diastole. In the case of stiff arteries in older subjects, PWV rises and the reflected wave arrives back at the central arteries earlier, adding to the forward wave, and augmenting systolic and pulse pressures. This phenomenon can be quantified through the augmentation index (AIx) – defined as the difference between the second and first systolic peaks (P2-P1) expressed as a percentage of the pulse pressure. Central augmentation index and central pulse pressure have shown independent predictive values for all-cause mortality in patients with end-stage renal disease, and CV events in patients undergoing percutaneous coronary intervention and in the hypertensive patients of the CAFÉ study.

The damaging effect of local pulse pressure (PP) has been well demonstrated on large arteries, and to a lesser extent on small arteries. Elevated central PP is associated with left ventricular hypertrophy (LVH), reduction in glomerular filtration rate (GFR), and white matter lesions, this to a larger extent than brachial PP. A vicious circle between small and large artery damage can be exemplified by the following: (a) increased wall-to-lumen ratio and rarefaction of small arteries are major factors for an increase in mean BP; (b) the higher mean BP in turn increases large artery stiffness, through the loading of stiff components of the arterial wall at high BP levels; (c) the increased large artery stiffness is a major determinant of the increased PP, which in turn damages small artery, as seen above, and favours the development of left ventricular hypertrophy, carotid intima-media thickening and plaque rupture. These various types of target organ damage have been shown to be related with CV events.

Antihypertensive treatment should break this vicious circle, to increase the possibilities of reversing target organ damage and reducing the risk of CV events. Not all pharmacological classes are equal in this respect. Pharmacodynamic data and the results of large clinical trials suggest that therapy based on brachial artery recordings may overestimate the effect of beta-blocking drugs on central aortic systolic BP and underestimate the effectiveness of ACE inhibitors, angiotensin II receptor antagonists, diuretics and calcium channel blockers.

(The spoken word prevails!)
Berlin, June 2008

Curriculum Vitae

Professor Dr. med. Thomas Unger
Hypertension 2008 Vice-President, Center for Cardiovascular
Research (CCR) and Institute of Pharmacology Charité University
Clinic, Berlin

*1950



Professor Thomas Unger holds the Chair of Pharmacology and is Director of the Institute of Pharmacology at the Charité – Universitätsmedizin Berlin.

From 2001 until 2006 he was Director of the Institute of Pharmacology and Toxicology, Campus Mitte of the Charité Berlin.

He is also the Director of the Center for Cardiovascular Research (CCR) at the Charité, Berlin and the Chairman of the German Institute for High Blood Pressure Research in Heidelberg.

Between 1994 and 2001, he was Director of the Institute of Pharmacology at the University of Kiel, Germany.

Professor Unger studied medicine in Germany and the UK, and gained his MD from the University of Heidelberg, Germany. He then carried out postdoctoral research at the Clinical Research Institute of Montreal, Canada, and the Department of Pharmacology in Heidelberg, where he received his PhD in Pharmacology.

Until 1994, Professor Unger held professorships in pharmacology and hypertension research at the University of Heidelberg.

In recognition of his work, Professor Unger has received the German Hypertension Society's Franz Gross Award for Hypertension Research, the Meilahti Lecture Award of the Medical Faculty, University of Helsinki, Finland, the Björn Folkow Award of the European Society of Hypertension, and the Robert Tigerstedt Award of the Finnish Hypertension Society.

He is a member of the German Societies of Pharmacology, Cardiology and Hypertension (Council Member 1995–2001), the International Society of Hypertension, the European Society of Hypertension (Council Member 1989–97), the European Council for Blood Pressure and Cardiovascular Research (President, 2000–2) and the Inter-American Society of Hypertension. He is also a Fellow of the American Heart Association and was Chairman of the Angiotensin Gordon Research Conference in 1999.

Professor Unger has authored more than 600 scientific publications. He is or has been a member of the Editorial Boards of the *American Journal of Physiology*, *Biochemical Pharmacology*, *Blood Pressure*, *Cardiovascular Drugs and Therapy*, *Clinical and Experimental Hypertension*, *Hypertension*, *Hypertension Research*, *Journal of Hypertension*, *Fundamental and Clinical Pharmacology*, *Physiological Genomics*, *Regulatory Peptides*, *High Blood Pressure & Cardiovascular Prevention*.

Curriculum Vitae

Professor Dr. rer. nat. Michael Bader
Max-Delbrück-Centre for Molecular Medicine, Berlin Buch (MDC)



University Exams:

- 1984 Diploma (Biology) at the University of Freiburg, Germany
1989 Ph.D. at the University of Freiburg, Germany
 Habilitation in Pharmacology and Toxicology, Free University Berlin
2003 Professorship in Pharmacology and Toxicology, Charité–University Medicine Berlin

Academic Appointments:

- 1989–1993 Research assistant in the lab of Prof. Dr. Detlev Ganten at the Department of
 Pharmacology and German Institute for High Blood Pressure Research,
 University of Heidelberg
since 1994 Group Leader in the Hypertension Research at the Max-Delbrück-Center for
 Molecular Medicine (MDC), Berlin Buch
 Vice-Coordinator of the Hypertension Research at the MDC

Awards:

- 03/1998 Schmiedeberg-Award of the „Deutsche Gesellschaft für Experimentelle und Klinische
 Pharmakologie und Toxikologie“
12/2000 Research Award of the Medical Faculty of the Free University Berlin

Main Research Interests:

- Molecular biology of genes coding for cardiovascular hormones
- Generation and characterization of genetically altered animal models for the functional analysis of cardiovascular hormones
- Development of transgenic technology in mouse and rat / Embryonic stem cell technology

Curriculum Vitae

Professor Stéphane Laurent

President of the European Society of Hypertension (ESH),
Head of Department of Clinical Pharmacology, Hôpital Européen
Georges Pompidou, Paris



Current position:

Head, Department of Clinical Pharmacology, Hôpital Européen Georges Pompidou, Paris
Professor of Pharmacology, Paris Descartes Medical School
Hypertension Specialist
Head, team 1, INSERM UMRS 872 ("*Vascular and renal physiology and pharmacology*").

Special area of interest and expertise:

Arterial hypertension and cardiovascular diseases.
Pathogenesis and regression of structural and functional changes of large arteries (arterial stiffness, central pulse pressure, carotid intima-media thickness, endothelial dysfunction)..
Clinical investigation and pharmacology of large arteries.
Clinical trials on large artery changes under treatment (CELIMENE, DAPHNET, CASHMERE, PERFORM vascular,...)

Other activities:

Has lectured widely to international audiences on hypertension, cardiovascular diseases, and non invasive clinical investigation of large arteries
Visiting Professor (1999) in Cardiology at Harvard Medical School and Brigham and Women's Hospital, Boston
Past President of the French Society of Hypertension (2001–2002)
Chairman of the Scientific Council of the 14th Meeting of the European Society of Hypertension (ESH, Paris, June 2004)
Member, Council of the European Society of Hypertension (ESH), 2005–2007
Member, Scientific Council of the French Foundation for Hypertension Research (since 2006)
Member of several international scientific societies, including the European Society of Hypertension (ESH), the AHA Council for High Blood Pressure Research, the International Society of Hypertension (ISH), and the European Council for Cardiovascular Research (ECCR)
Vice-President of the Artery Society (since 2006)
President of the European Society of Hypertension (ESH)

Editorial boards and publications:

Member of the editorial board of *Hypertension, Journal of Hypertension*

Deputy Editor of *Artery Research*

More than 200 original papers in refereed journals, 60 review publications including editorials and book chapters, and 350 reports, including abstracts.

More than 150 invited lectures at international venues.

Curriculum Vitae

Professor Richard Horton
Editor-in-Chief von "The Lancet", London



Richard Horton qualified in medicine from the University of Birmingham in 1986. He completed his general medical training in Birmingham before moving to the liver unit at the Royal Free Hospital. In 1990, he joined *The Lancet* as an assistant editor and moved to New York as North American editor in 1993. Two years later he returned to the UK to become Editor-in-Chief.

He was the first President of the World Association of Medical Editors and is a Past-President of the US Council of Science Editors. He is an honorary professor at the London School of Hygiene and Tropical Medicine, University College London, and the University of Edinburgh.

He is a Fellow of the Royal College of Physicians and a Founder Fellow of the UK's Academy of Medical Sciences. In 2005 he was a member of the working party and subsequently wrote the report for the Royal College of Physicians' inquiry into the future of medical professionalism – *Doctors in Society*. He currently chairs the Royal College of Physicians' Working Party on Physicians and the Pharmaceutical Industry; co-chairs a WHO Scientific Advisory Group on Clinical Trials Registration; is a Council Member of the Global Forum for Health Research; is a Board Member of the Health Metrics Network; sits on the External Reference Group for WHO's Research Strategy; and is an External Advisory Board Member for the WHO European Region.

In 2004, *The Lancet* won the UK's Medical Publication of the Year and, in 2007, he received the Edinburgh Medal for professional achievements judged to have made a significant contribution to the understanding of human health and wellbeing. In 2008, he was appointed a Senior Associate of The Nuffield Trust, a think tank for research and policy studies in health services. He has a strong interest in issues of global health.

He has been a medical columnist for *The Observer* and writes regularly for the *Times Literary Supplement* and *New York Review of Books*. A book about controversies in modern medicine, *Second Opinion*, was published in 2003.

Order Form for Photographs of the Speakers

**International Press Conference
during HYPERTENSION Berlin 2008**

Date: 18th June 2008, 12:30 to 13:30 p.m.

Place: ICC Berlin, Room 43

Please provide me the following photo(s) via email:

- Professor Dr. med. Thomas Unger
- Professor Dr. rer. nat. Michael Bader
- Professor Stéphane Laurent
- Professor Richard Horton

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