

International Society of Hypertension HYPERTENSION NEWS



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Notes from the Editor

- Lars H. Lindholm

Again, it is my great pleasure to present you with a new issue of Hypertension News, which I hope you will enjoy reading.



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Let me first thank Helen and her wonderful team at our Secretariat in London for their outstanding help during 2015, without which there would not have been any newsletters. I would also like to thank the other members of the ISH Communications Committee, Thomas Kahan (Sweden), Dylan Burger (Canada), and Neil Poulter (Chair, UK) for their help.

These are exciting times for hypertension researchers and authors of hypertension guidelines around the world. The results of the long awaited Systolic Blood Pressure Intervention Trial (SPRINT), recently published in NEJM, make it necessary to reassess systolic blood pressure goals for high risk patients for whom a lower systolic goal now seems appropriate. One problem, however, is how to translate the attained blood pressure values in that trial to general practice around the world, with widely variable standards in blood pressure measurement. Another concern is that patients with diabetes mellitus and those who have already suffered a stroke had been excluded. In this issue of HT News "We give you a HINT how to interpret SPRINT" on pages 6-7. For those of you who want a comparison of the results of the ACCORD (which includes patients with diabetes mellitus) and SPRINT (which did not), I recommend the excellent Editorial in NEJM written by Vlado Percovic and Anthony Rogers at The George Institute in Sydney, Australia.

The institute focus in this issue of the newsletter is on Thomas Kahan and his group at the Danderyd University Hospital in Stockholm, Sweden which is part of the Karolinska Institute. On pages 9-12, you will find a summary of the excellent projects ongoing in that institute. We have also included greetings from Professor Kim in Seoul, who gives his views on hypertension with a special focus on the upcoming ISH Biennial Scientific Meeting to be held there in September 2016, on pages 24-25.

Among the Commissioned papers, you will find a review of the difference between the terms sex and gender which may be of interest to you. We have asked two very experienced gender researchers Katarina Hamberg, Umeå, Sweden and Susan Phillips, Ontario, Canada to help us here and they have sent us the enclosed paper (pages 13-14) entitled "Sex or gender – Conceptual confusion is common".

Finally, if you are interested in how impact factors are calculated and how well a number of hypertension, and other medical, journals have been rated over the last five years, please find an update on pages 20-21 entitled: Where to publish - the role of the Impact Factor.

Best wishes, and to all of you: **Merry Christmas and a Happy New Year!**

Lars H Lindholm,
Editor, Hypertension News

From the ISH President - Rhian Touyz



As the year comes to an end, it is time to reflect on the many exciting activities and new initiatives that your leadership has worked so hard on during 2015. Some highlights include:

1. Women in Hypertension Research initiative

This programme is focused on promoting awareness, opportunities, mentoring, networks, support groups, and so forth for women at all stages of their careers in hypertension research. We will launch this officially at the 2016 ISH Biennial Scientific Meeting in Seoul. Not only will the programme provide support for women in their research careers but it will also offer a platform to advance awareness and research related to cardiovascular disease in women.

2. Hypertension Summer School in China

The Summer School took place in Beijing in August over a period of 5 days and was attended by 11 faculty members and 31 scholars from the Asia Pacific region (from Bangladesh, China, India, Indonesia, Japan, Malaysia, Nepal, Philippines, Singapore and Thailand).

[View reports of this initiative.](#)

3. Regional Advisory Group (RAG) activities

RAG initiatives have been expansive and have included participation of ISH representatives at meetings globally, to include Argentina, Australia, Brazil, China, Egypt, Indonesia, Italy, Japan, Korea, Lebanon, Mauritius, Russia, South Africa, Sudan and USA. We are pleased to have worked closely with several of our affiliated national and regional societies of hypertension and Councils of Hypertension during the year. We hope that you have enjoyed the activity reports provided via the monthly e-Bulletins, previous issues of ISH Hypertension News and the Society website.

4. Expanding horizons for the New Investigator Committee

A very successful partnership was held with the Trainee Advocacy Committee of the Council on Hypertension, American Heart Association (AHA), in Washington in September at the annual AHA Council meeting. View a report on pages 17-18.

In addition the NIC is forging stronger links with other young investigator groups based around the world including Argentina ([with the Argentine Society of Hypertension](#)).

5. Close interactions with the World Hypertension League

A number of joint publications have resulted from this partnership including a fact sheet an infographic on hypertension for Sub-Saharan Africa.

6. New communications platforms and growing engagement in social networking

Of note, you will see that we have introduced a monthly e-Bulletin for members in the months when Hypertension News is not produced. With this Bulletin, we aim to streamline Society news and provide you with regular updates. Thanks to our very active and hardworking New Investigator Committee, our presence on social media networks (Facebook, LinkedIn, Twitter and YouTube) is also growing.

7. Working with the Local Scientific Organising Committee (LOC) in Seoul

The Executive has been working closely with the Seoul LOC to help create an exciting scientific programme for the 2016 ISH Biennial Scientific Meeting (Hypertension Seoul 2016). Our Korean colleagues are working hard to ensure a great meeting. Please save the dates - 24-29 September 2016.



ISH/APSH Asia and Australasia Summer School Attendees

From the ISH President - Rhian Touyz

Revised ISH Constitution

In addition to the above, I would like to bring the following to your attention.

You will have received an invitation from me over the last few weeks to vote on changes to the ISH Constitution (deadline, Friday 6th November). 44% of membership agreed to the changes and forthwith we very much look forward to implementing the revised Constitution. We were delighted with the response rate, which was markedly greater than the required 10%.

Changes were proposed to modernise the Constitution, to reflect the changing Society and to prevent it from being too rigid and overly prescriptive. The new Constitution is more user-friendly and easier to understand. With the new format, separate policy documents contain the specific rules and regulations governing relevant areas including membership, delegation by the Council of its functions to committees and awards and prizes.

All revised Constitution and policy documents can be viewed below.

- [ISH revised Constitution](#)
- [ISH Awards and Prizes Regulations](#)
- [ISH Committee Policy](#)
- [ISH Membership Regulations](#)

Of note, you will notice important changes to the membership categories laid out in the Membership Regulations document (as summarised below).

- Regular Member title change to Professional Member
- Introduction of an Emerging Leaders category:

The Emerging Leader membership category is a new initiative from the ISH where we want to help Research Fellows to progress during their career to being a Professional Member.

This category has been designed to accommodate early to mid-career research and clinical scientists (junior faculty members) who have completed their doctoral degree (or other qualifying research degree) and are in the process of establishing themselves as scientists or hypertension experts. Membership in this category is limited to three years and Emerging Leaders will enjoy identical benefits to Professional Members, but at a much lower fee.

- Extension of Research Fellow tenure to up to 6 years on application
- Distinguished Member title change to Distinguished Fellow
- Honorary Member title changes to Honorary Fellow
- Emeritus Member title change to Emeritus Fellow
- Emeritus criteria update:

A Professional Member who has been a longstanding member of the Society, who is over the age of 65, and who has retired from full-time active work may seek status as an Emeritus Fellow.

In summary, I am sure you agree that 2015 has been an exciting year for ISH. Your leadership continues to work hard on your behalf to ensure that the mission of the Society is realised and that our efforts are reflected globally.

I would like to take this opportunity to wish you and your loved ones all the very best for the holiday season. May this time be filled with joy, happiness, smiles and peace for all.

I am looking forward to welcoming you to Seoul in 2016!

- Rhian Touyz, ISH President



Join us at the ISH Biennial Scientific Meeting in Seoul in 2016!

Peter Sever

International Centre for Circulatory Health
National Heart and Lung Institute
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PATHWAYS to Optimal Treatment of Hypertension: A commentary on the British Hypertension Society PATHWAY Programme of Trials

Background

Despite the fact that the treatment of hypertension is one of the most extensively investigated areas of clinical medicine, there remains a number of important questions, the answers to which would affect guidelines for hypertension management and a change in clinical practice. Some of these questions were addressed by the PATHWAY Programme of trials conducted under the auspices of the British Hypertension Society (BHS). The results of two of these trials have recently been presented at the European Society of Cardiology Meeting in London and published in the *Lancet*.^{1,2}

Trial design and outcomes

PATHWAY 2¹ was designed to investigate optimal treatment for patients with resistant hypertension. Guidelines, notably the NICE Guidelines,³ provide treatment algorithms for hypertensive patients which specify the first 3 drugs (an angiotensin converting enzyme inhibitor [ACEI], or an angiotensin receptor blocker [ARB], a calcium channel blocker [CCB], and a thiazide like diuretic) together with recommendations for add on therapy for those who fail to achieve BP goals on 3 drugs. There are, however, no trials of additional drug treatment to provide insight into optimal treatment. This is particularly important, for there remains a substantial number of resistant hypertensive patients at high residual cardiovascular risk for whom there are no clear guidelines for preferred treatment, but an increasing number of costly, invasive interventions, advocated by many, but for which there is doubtful objective evidence of real benefit.

PATHWAY 2 was a double-blind, placebo-controlled, cross-over study carried out in 335 hypertensive patients receiving 3 antihypertensive drugs in optimal or best tolerated doses, and whose BP was uncontrolled (clinic SBP > 140 mmHg, home SBP > 130 mmHg) following observed drug ingestion and subsequent BP monitoring. Patients received sequential treatment with spironolactone (25-50mg), bisoprolol (5-10mg), doxazosin MR (4-8mg) or placebo, assigned in random order, in addition to their baseline treatment. Each cycle was for 12 weeks duration with dose force titration at 6 weeks. The hierarchical primary endpoints were the difference in home SBP between spironolactone and placebo, followed by the difference in home SBP between spironolactone and the average of the two other active drugs and, finally, the difference in home SBP between spironolactone and each of the two other active drugs.

Spironolactone was substantially more effective than placebo (-8.70 mmHg), and significantly more effective than doxazosin (-4.03 mmHg) or bisoprolol (-4.48 mmHg).

A critical finding in this trial was that spironolactone controlled home SBP in almost 60% of patients (and an even greater percentage if clinic pressures were used). In addition, over 75% of patients had a > 10 mmHg reduction in SBP.

These observations, in conjunction with the fact that BP responses to spironolactone were inversely related to plasma renin, confirm the view that sodium retention plays a major role in the pathophysiology of resistant hypertension.

These results should be viewed in the context of the many invasive intervention trials in so-called drug resistant hypertension, particularly in the light of the fact that many recruits into these trials were not receiving, or had not received, a trial of spironolactone.

In PATHWAY 2, concerns about hyperkalaemia with spironolactone were not realized. Discontinuations due to renal impairment, hyperkalaemia and gynaecomastia were not increased in those assigned to spironolactone compared with the other drugs.

PATHWAY 3² was designed to explore whether the addition or substitution of a potassium sparing diuretic would prevent the glucose intolerance associated with a thiazide diuretic and improve blood pressure control. Many guidelines have advocated the use of low dose thiazide diuretics in the treatment of hypertension, yet the evidence for cardiovascular event reduction was based on trials of higher doses of thiazides, thiazide-like diuretics (chlorthalidone, indapamide) or combinations of diuretics such as hydrochlorothiazide (HCTZ)/amiloride.

The development of glucose intolerance associated with thiazides appears linked to the development of hypokalaemia, and PATHWAY 3 addressed this issue with a comparison of the metabolic effects of a thiazide, amiloride and the combination.

441 hypertensive patients with one component of the metabolic syndrome, on background antihypertensive drugs requiring additional therapy, were randomized to HCTZ 25mg, amiloride 10mg or the combination of HCTZ 12.5mg/amiloride 5mg. Doses were doubled after 12 weeks of treatment for a further 12 weeks.

The primary endpoint was the difference in blood glucose measured 2 hours after a 75g oral glucose load. Secondary endpoints included differences in home SBP, plasma electrolytes and renin.

Two hour glucose rose on HCTZ, and fell on both amiloride and the combination. A greater fall in home SBP at 24 weeks treatment was seen on the combination (-19 mmHg), than either HCTZ (-14 mmHg) or amiloride (-16 mmHg) despite the combination being used in half the doses of the individual components.

Importantly serum potassium fell on HCTZ, rose on amiloride and was unchanged on the combination.

These observations clearly demonstrated that the glucose intolerance associated with thiazides was closely linked to hypokalaemia and could be abolished when the thiazide was combined with amiloride. Given the well-established benefits of the HCTZ/amiloride combination on cardiovascular outcome reported in the Medical Research Trial in Older Patients⁴ and the International Nifedipine GITS Study Intervention as a Goal in Hypertension Treatment (INSIGHT),⁵ PATHWAY 3 provides compelling evidence for this combination to replace thiazide and thiazide like diuretics in clinical practice, particular in those patients at increased risk of developing new onset diabetes (NOD). No doubt some will argue that NOD induced by thiazides does not carry the cardiovascular risk associated with non- drug induced diabetes,⁶ however, this remains a highly controversial issue. Logic surely dictates that if you can prevent major metabolic consequences of a drug treatment by replacement with an alternative that carries no such risk, and for which there is excellent evidence for outcome benefits, a combination of thiazide/amiloride should be the preferred choice diuretic for most hypertensive patients.

Conclusions

These trials were carried out over a period of 5 years, in 12 secondary and 2 primary care centres in the UK. All were part of a framework established by the BHS. The working party was established to address a number of important but unanswered questions in hypertension management at a time when most antihypertensive drug classes were available in generic formulation and there seemed little hope for industry sponsorship. In comparison with industry funded trials they were carried out at substantially lower cost despite the requirements for meeting the rigorous demands of the drug regulatory bodies for trial oversight and management. The trials were supported by a grant from the British Heart Foundation and the UK National Institute for Health Research through infrastructure support at regional level to the recruiting centres. The BHS working party is now challenged with the design and funding for new studies to provide further insight into optimal management of patients with hypertension.

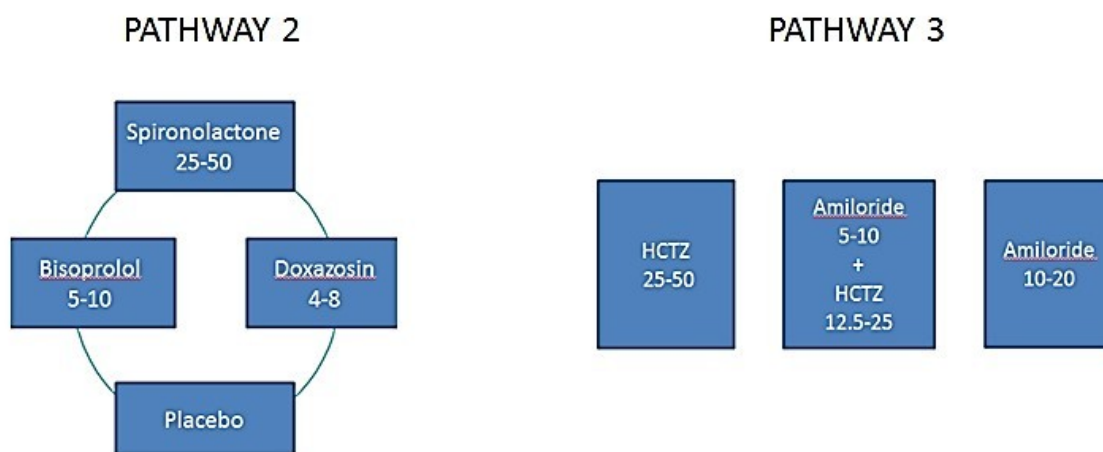
One objective of the PATHWAY Programme of trials was to provide an evidence base for new guidelines for the management of hypertensive patients.

PATHWAY 2 clearly establishes the case for recommending spironolactone as the optimal 4th line drug in the treatment algorithm for patients with resistant hypertensive patients, whilst PATHWAY 3 provides an important insight into the different metabolic effects of the diuretics commonly used in hypertension treatment strategies and evidence for the benefits of a thiazide/amiloride combination.

A brief commentary on the third PATHWAY trial (PATHWAY 1) will be included in a future newsletter .

Schematic of PATHWAY Trials.

PATHWAY 2 randomised cross-over design. PATHWAY 3 parallel group comparison.

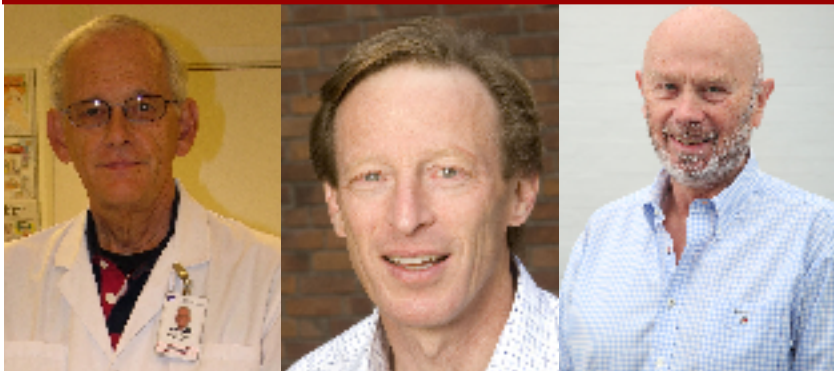


- Peter Sever

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Hot off the Press



Lars H Lindholm¹, Thomas Kahan²
and Neil Poulter³

(for organisations, see end of report)

Can we translate the results of SPRINT into clinical practice?

Observational studies have shown a linear relationship between systolic blood pressure (SBP) and cardiovascular disease (CVD) risk rising from 115 mm Hg. Randomised controlled trials have shown that lowering the SBP by approximately 10 mm Hg reduces the risk of stroke by 35-40%, myocardial infarction by 15-25% and heart failure by up to 65%. The target for blood pressure lowering has, however, been uncertain. Previously available data have clearly shown the benefits of lowering SBP to below 150 mm Hg, whilst most hypertension guidelines have recommended lowering SBP to below 140 mm Hg (below 150 mm Hg in patients aged 80 years or above).

The much awaited results of the Systolic Blood Pressure Intervention Trial (SPRINT) have recently been published¹. In this landmark study, 9361 high risk patients without diabetes mellitus or a previous stroke (mean age 68, 65% men), with a SBP of 130 mm Hg or higher, were randomised to intensive (SBP <120 mm Hg) or standard (SBP <140 mm Hg) blood pressure control.

More than 90% in both randomised groups were receiving blood pressure lowering drug treatment at baseline. The mean number of drugs was 1.8 at baseline, increasing to 2.8 in the intensive-treatment group during the study period. Medications for patients in the intensive-treatment group were adjusted on a monthly basis to a SBP target of less than 120 mm Hg. For those in the standard-treatment group, medications were adjusted to a SBP target of 135-139 mm Hg; the dose was reduced if SBP was less than 130 mm Hg at a single visit. Mean SBP at baseline was 140 (SD 16) mm Hg in both groups. Throughout the follow-up this dropped to 121 mm Hg in the intensive-treatment group compared with 135 mm Hg in the standard-treatment group - a 14 mm Hg difference. Importantly, blood pressure was recorded with an automated device, (Model 907, Omron Healthcare) after five minutes rest in an office free from staff. The mean of three recordings was calculated and used in the analyses.

SPRINT was stopped ahead of time after a median follow-up of 3.3 years, owing to a significantly lower rate of CVD events (primary outcome - a composite of myocardial infarction, acute coronary syndrome, stroke, heart failure or cardiovascular death) and all cause mortality in the intensive-treatment group. CVD events were confirmed in 562 participants - 243 in the intensive-treatment group and 319 in the standard-treatment group. In total, 365 deaths occurred - 155 in the intensive-treatment group and 210 in the standard-treatment group. The relative risk reductions in the primary endpoint and all-cause mortality associated with intensive treatment were 25% (95% CI: 11 to 36) and 27% (95% CI: 10 to 40), respectively. The numbers needed to treat during the study period were 61 for a CVD event and 90 for a death of any cause. Some serious adverse events including hypotension (but not orthostatic hypotension or injurious falls) and acute kidney failure were higher in the intensive-treatment group than in the standard-treatment group, but the rates were low and were clearly outweighed by the morbidity and mortality benefits. It should be underlined that patients with diabetes mellitus or a previous stroke were not included in SPRINT and that we therefore cannot necessarily extrapolate the results to those groups of patients.

However, these SPRINT results make it necessary to reassess SBP goals for high risk patients for whom a lower systolic goal now seems appropriate, which is in keeping with a recent report on the benefit of intensive blood pressure lowering in high risk patients². Nevertheless, one major problem is how to translate the SBP values achieved in SPRINT to inform clinical practice around the world given widely variable standards in blood pressure measurement.

The white coat effect on recorded blood pressure levels is variable and may be large and other conditions of measurement also impact greatly on the level recorded. For example, it has been shown that blood pressures recorded whilst strictly following guideline-recommended methods are significantly lower than when measured in usual clinical practice³. The level of blood pressure recorded is also affected by the presence or absence of clinic staff although some patients are "cuff" rather than just "white coat" responders⁴.

So - it seems likely that automated recordings after 5 minutes rest with no medical staff present are likely to be lower than "usual" clinic or office measurements (as frequently practiced) and may equate more closely to home and/or ambulatory blood pressure levels³. Consequently automated office blood pressure recordings, as performed in SPRINT, may be approximately 10/5 mm Hg lower than those obtained in more usual clinical practice³.

How then do we interpret the SPRINT findings in the context of less rigorous clinical practice, which is perhaps "the norm"? Ideally clinic blood pressures should be measured as in SPRINT, and if so, the findings appear robust in suggesting we should aim for an SBP of <120 mm Hg. With less rigorous measurement techniques - as most commonly practiced - the SBP values achieved in the intensive treatment arm (121 mm Hg) may well be equivalent to 131 mm Hg!

Proponents of home and/or ambulatory blood pressure monitoring will no doubt argue that these difficulties in interpretation and extrapolation to typical clinical practice would have been largely overcome had home or ambulatory blood pressure recordings been used in SPRINT. Meanwhile, whilst these difficulties are debated, and assuming it is agreed that SBP targets are lowered at least for high risk patients - this has clear implications for lowering treatment thresholds!

Finally, whilst SPRINT undoubtedly challenges us to rethink blood pressure targets, at least in high risk patients, as pointed out at the first presentation in Orlando, don't expect the patients to thank you when you discuss adding an extra tablet!

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Hot off the Press



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Empagliflozin: a paradigm shift or just another diuretic?

Type 2-diabetes is one major risk factor for cardiovascular morbidity and mortality. Hypertension and type 2-diabetes are common and they often coexist. Blood pressure lowering treatment in patients with diabetes reduces cardiovascular events. However, the effects of blood glucose lowering on cardiovascular morbidity and mortality are less well demonstrated. Furthermore, there has recently been some concern of increased risk for cardiovascular complications with some newer antidiabetic drug classes, such as thiazolidinediones [1,2].

Drugs that inhibit the sodium-glucose cotransporter 2 (SGLT2 inhibitors; gliflozins) decrease renal glucose reabsorption. The increase in urinary glucose excretion will reduce blood glucose levels in patients with type 2-diabetes. Treatment with SGLT2 inhibitors is also associated with reductions in body weight and blood pressure, and an increase in genital infections. Recently, the results of the randomized placebo controlled cardiovascular outcome trial of the SGLT2 inhibitor empagliflozin (EMPA-REG OUTCOME) was presented [3]. The authors reported a lower rate of the primary composite cardiovascular endpoint (cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke), and of all cause mortality with active drug added to standard care therapy, as compared to placebo.

This study randomized 7020 patients with type 2-diabetes and coexisting atherosclerotic cardiovascular disease to either 10 or 25 mg empagliflozin or placebo with a median observation time of 3.1 years. The primary outcome was reduced by 12.1 vs. 10.5 %, with a hazard ratio and 95 % confidence interval in favour of active treatment (pooled data for both doses as results were similar) of 0.86; 0.74 to 0.99. Active treatment also reduced cardiovascular mortality, heart failure hospitalizations, and all-cause mortality by 38, 35, and 32 %, respectively. The rates of non-fatal myocardial infarctions and non-fatal strokes, when analysed separately, did not reach significance. Patients in the empagliflozin groups had on average about 0.4 % lower haemoglobin A1c values, 4/2 mm Hg lower blood pressure, and lost 2 kg more in weight; and had more genital infections but no increase in other adverse events.

The results of the EMPA-REG OUTCOME study are important as they provide us with a drug that can reduce cardiovascular morbidity and mortality in high-risk type 2-diabetic patients. However, the reduction in haemoglobin A1c was quite modest and it is unlikely that this change in glycaemic control could affect cardiovascular events within such a short period of time. Previous studies suggest that the effects of glucose control on cardiovascular events will take much longer time [4]. Of note, the effects on blood pressure, body weight (likely to reflect fluid loss and reduced tissue mass), and cardiovascular events in the empagliflozin groups were observed already within a few months of treatment, suggesting that these beneficial effects represent a hemodynamic mechanism. The effects of gliflozins to reduce blood pressure are well established [5].

Thus, this study suggests that gliflozins may be an attractive drug class with beneficial effects on haemoglobin A1c, blood pressure, body weight, and with diuretic effects, which can reduce cardiovascular morbidity and mortality in high risk type 2-diabetic patients. The results could be mediated by hemodynamic changes and give little support for a major role of the improved glycaemic control. The mechanisms behind the improved outcome warrant further study.

- Thomas Kahan

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Muhammad Oneeb Rehman Mian

ISH New Investigator Committee Media Working Group member
Montreal, Canada

Sex-Specific Effect of Endothelin in the Blood Pressure Response to Acute Angiotensin II in Growth-Restricted Rats

Intapad S, Ojeda NB, Varney E, Royals TP, Alexander BT.

Hypertension. 2015 Dec;66(6):1260-6

Endothelin (ET)-1, a potent 21 amino acid vasoconstrictor, is a household name in the field of pulmonary arterial hypertension (PAH) implicated in vascular remodeling associated with the disease. ET-1 receptor antagonism is a common therapy for PAH and has been demonstrated to improve morbidity and mortality in patients (1). More recently, experimental and clinical studies have linked ET-1, independently or in association with an activated renin-angiotensin-aldosterone system, to the development and progression of systemic hypertension due to its vast effects on the vasculature and the kidneys (2,3). However, the role of the ET system in a model of developmental programming of a greater risk for blood pressure elevation and cardiovascular disease later in life remained unexplored.

This recent publication by Intapad et al. demonstrates a sex-specific role for the ET system in hypersensitivity to acute angiotensin (Ang) II in male growth-restricted rats via the endothelin type A (ETA) receptor. Blood pressure elevation in response to acute Ang II infusion was greater in male growth-restricted rats compared to controls, a differential response that was abolished by the ETA receptor antagonist, atrasentan. Ang II-induced decrease in glomerular filtration rate and increase in renal vascular resistance were also reversed by atrasentan in male growth-restricted rats. Consistent with previous reports (4,5,6), in this study, female growth-restricted rats responded to acute Ang II infusion only when ovariectomized but the Ang II effects were not affected by ETA receptor blockade. Interestingly, expression of ETA and ETB receptors was increased in the renal cortex and medulla of male growth-restricted rats whereas in female growth-restricted rats the medullary ETB receptor expression was slightly decreased, relative to respective controls. There was no difference in whole kidney preproendothelin mRNA expression and 24-hour urinary excretion of endothelin in either sex.

Although this study presents exciting new evidence, the mechanisms behind ET-1 mediated amplification of Ang II responses in male growth-restricted rats remains unknown. The expression of the ET system was not directly compared between males relative to females, however, the fact that renal expression of ET receptors was enhanced only in male growth-restricted rats could explain the sex-specific effect of ETA receptor blockade. Measurement of circulating plasma ET-1 levels in males and females may have revealed if enhanced systemic production could have influenced the sex-specific differences observed.

Over the past decade or so, the potential of targeting the ET-1 signaling pathways for the treatment of essential hypertension has repeatedly been explored, debated, and clinically tested but has so far failed to live up to expectations due to reasons reviewed extensively elsewhere (7,8). Essential hypertension is multifactorial with developmental programming and sex differences important influencers of blood pressure control (9,10). This study adds a new dimension to an already complex problem by showing that ET signaling may be an important contributor to sex differences in the developmental programming of blood pressure. It is prudent to take into account evidence of this novel role of ET system in determination of blood pressure control, and the sex-specific differences thereof, when rationalizing and planning for the ideal clinical targets in this signaling system.

- Muhammad Oneeb Rehman Mian

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Institute Focus



Thomas Kahan

Danderyd University Hospital Hypertension Excellence Center
Division of Cardiovascular Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet; and Department of Cardiology, Danderyd University Hospital, Stockholm, Sweden

BACKGROUND

Karolinska Institutet in Stockholm, Sweden, is one of the leading medical universities in the world. It accounts for over 40 % of the medical academic research conducted in Sweden and offers the broadest range of education in medicine and health sciences in the country. There are three major university hospitals in Stockholm affiliated to Karolinska Institutet, where basic and translational research meets clinical research: Karolinska University Hospital, Danderyd University Hospital, and Stockholm South General Hospital.



Danderyd University Hospital, Stockholm, Sweden

CLINICAL ACTIVITY

Danderyd University Hospital, with a current and rapidly growing catchment area of approximately 500 000 people, is the sixth largest hospital and second largest emergency room in Sweden; the maternity unit is the largest in Northern Europe. The hospital has 460 beds, and approximately 45 000 hospitalizations and 242 000 physician outpatient visits annually. The Department of Cardiology (head, Karin Malmqvist) is the largest in the country, and is ranked number one for coronary care in Sweden according to the 2014 Swedeheart quality index. Main areas of clinical activity are process oriented and divided into coronary artery disease and cardiovascular risk assessment including blood pressure and vascular disease, haemostasis, heart failure, and arrhythmias. The Karolinska Institutet Cardiorenal Theme Center and a devoted outpatient unit for patients with complex concomitant cardiac, diabetic, and renal disease (head, Jonas Spaak) are also within the Department of Cardiology.

The Cardiovascular Risk Assessment Unit (started by Ulf de Faire in 1980) is an important part of the Department of Cardiology. Thomas Kahan has been head of the unit since 1988. The initial focus was on treatment of high blood pressure, but the scope has since expanded into global cardiovascular risk assessment and treatment. The unit has been identified as a Hypertension Centre of Excellence by the European Society of Hypertension since 2007, and is a well-recognized regional referral centre for hypertension, lipid disorders, and peripheral artery disease, including activities for smoking cessation, dietary counselling and stress management. At the unit there is a special clinical interest in patients with renovascular disease, obstructive sleep apnoea, and neurohormonal disorders associated with hypertension, and this is the second largest centre in Sweden for renal denervation in difficult to treat hypertension.

Institute Focus

TRANSLATIONAL RESEARCH AS A KEY TO SUCCESS

Our focus areas of cardiovascular research (figure) nicely follow the main clinical processes. We believe that a strong academic profile in everyday clinical work is an important feature for high quality translational and clinical research. Thus, among the clinical staff (including also those in training) in cardiology of about 70 physicians are five professors, 29 with a PhD, and 20 engaged in their personal PhD research doctoral programs. Supported together by Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, and by Danderyd University Hospital, the hospital Clinical Research Centre provides important core facilities for research, staffed by trained research nurses, laboratory technicians, and study coordinators. There is a Cardiovascular Research Laboratory with state of the art equipment for non-invasive and invasive cardiac and vascular imaging and assessment of cardiac, arterial, and endothelial function in man (Thomas Kahan, Jonas Persson, Reidar Winther). Methods available for studies of autonomous cardiac and vascular control include measurements of regional and systemic endogenous plasma catecholamine concentrations and overflow and radiotracer methodology, single fibre muscle sympathetic neurography, heart rate variability, and measurement of components of the renin-angiotensin-aldosterone system and neuropeptides (Thomas Kahan, Jonas Spaak). The Microcirculatory and Metabolic Laboratory provide methodologies for human skin microcirculatory and capillary microscopy studies, insulin clamping, and other techniques for studies in diabetes (Gun Jörneskog, Majid Kalani). The Biochemistry Research Laboratory focuses on the development of new assays to assess thrombotic and fibrinolytic activity, thrombocyte function, and biomarkers of endothelial function, including cutting edge flow cytometry equipment methodology (Håkan Wallén). Other hospital core facilities support obstetric/gynaecology, and stroke and neurorehabilitation.

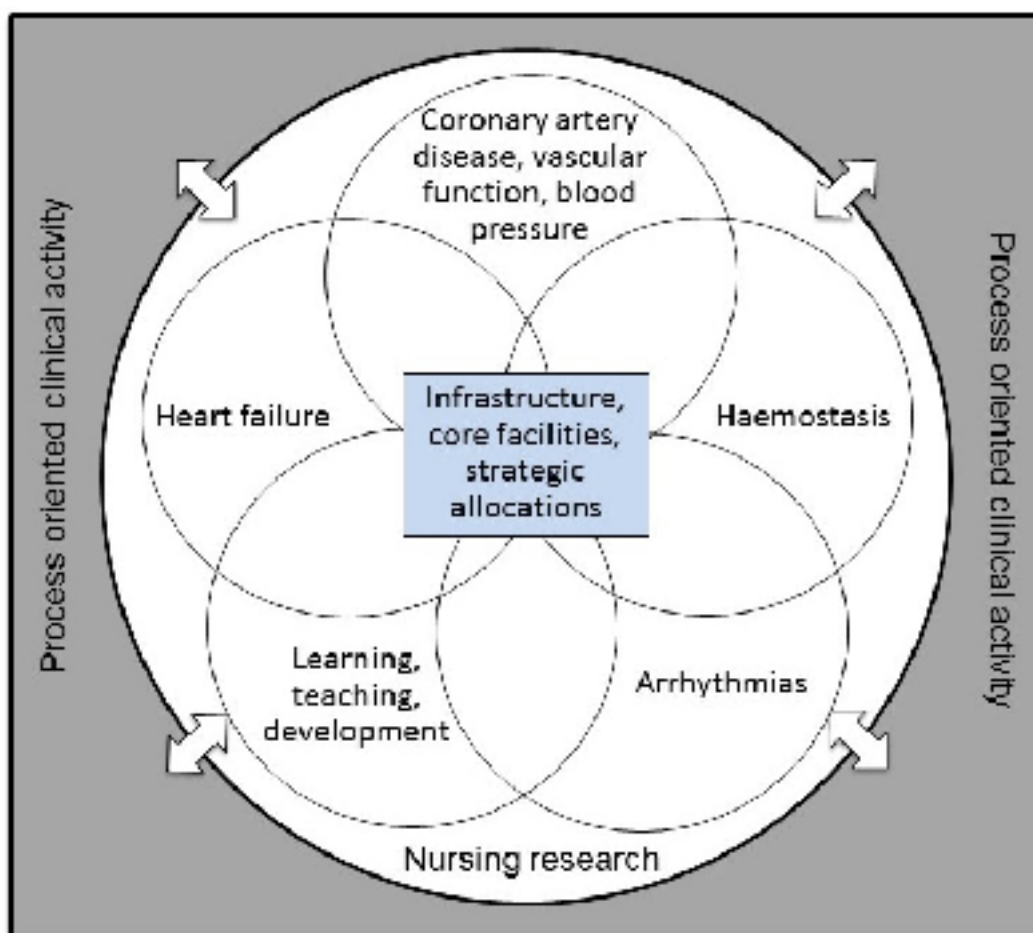


FIGURE LEGEND

Focus areas of cardiovascular research at the Division of Cardiovascular Medicine, Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet. There is facilitated exchange with the process oriented main areas of clinical activity (coronary artery disease and cardiovascular risk assessment including blood pressure and vascular disease, haemostasis, heart failure, and arrhythmia) at the Department of Cardiology, Danderyd University Hospital, Stockholm, Sweden.



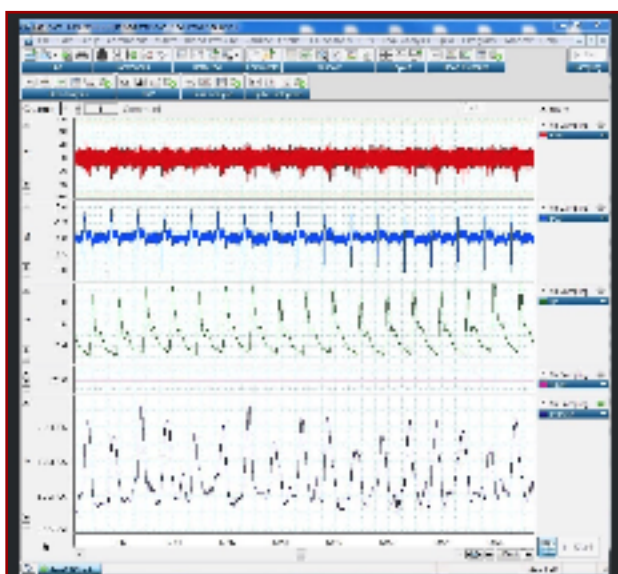
Danderyd University Hospital Hypertension Excellence Center has biochemistry facilities with focus on hemostats and vascular biomarkers

HYPERTENSION RESEARCH ACTIVITIES

Our previous animal experimental experience of sympathetic adrenergic and non-adrenergic peptidergic vascular control, and interactions with the renin-angiotensin-aldosterone system, have translated into studies of neurohormonal control of cardiac and vascular function in healthy individuals and in patients with hypertension and heart failure. Structural vascular changes and endothelial dysfunction are early findings in hypertension and in atherosclerotic disease, and hypertension increases the risk of atherothrombotic events. We study the effects beyond the influence on blood pressure of stimulating and blocking the renin-angiotensin-aldosterone system on vascular structure and function, microcirculation, and endothelial function (Thomas Kahan). Studies are performed in healthy subjects, in patients with familial hyperlipidaemia, and in hypertension. Other studies examine the interplay of sympathetic activation and blood pressure control in patients with obstructive sleep apnoea, and in difficult to treat hypertensive patients before and after renal denervation (Jonas Spaak).

Furthermore, effects of the sympathetic nervous system and the renin-angiotensin system on inflammatory pathways and on thrombotic and fibrinolytic mechanisms are studied in patients with hypertension, lipid disorders, and diabetes, with focus on the potential impact of antihypertensive drug therapy (Bruna Gigante, Håkan Wallén). Haemostatic control and abnormalities in patients with atrial fibrillation and in patients with a previous atherothrombotic event such as stroke or myocardial infarction, and new methods to evaluate antithrombotic and anticoagulant therapy, are also studied (Mårten Rosenqvist, Mika Skeppholm).

Hypertensive complications during pregnancy are associated with an increased risk for maternal cardiovascular disease in later life. Preeclampsia is characterized by endothelial dysfunction and cardiac functional impairment, and an increased risk for pregnancy related complications for mother and offspring. We study pregnancy related alterations in macrovascular, microvascular and endothelial function, and cardiac function, and how this relates to the outcome of offspring (Ellika Andolf, Thomas Kahan). Furthermore, we have reported that patients with preeclampsia eventually normalize vascular, endothelial and cardiac abnormalities, suggesting that preexisting cardiovascular risk factors may play an important role for the increased risk for future cardiovascular complications in women with a history of preeclampsia.



ABOVE: Dr Jonas Persson studying coronary artery endothelial function
LEFT: non-invasive cardiovascular assessment and studies of neurohormonal mechanisms by e.g. sympathetic nerve recordings with microneurography

Institute Focus

Hypertension causes alterations in cardiac structure and function as a response to increased workload, a condition often summarized as hypertensive heart disease. We have studied the contribution of the sympathetic nervous system and the renin-angiotensin-aldosterone system to the evolution and maintenance of hypertensive heart disease. Our results suggest that the renin-angiotensin-aldosterone system is important for the development of hypertension induced myocardial fibrosis, which precedes cardiomyocyte hypertrophy. Our current focus is on mechanisms involved in the transition from an elevated blood pressure to hypertensive heart disease and to heart failure with either preserved or reduced left ventricular ejection fraction (Thomas Kahan, Hans Persson). This may help to identify subjects at risk for the new onset heart failure, and the appropriate treatment. Other studies in patients with established heart failure disease examine extracellular matrix and cardiomyocyte turnover and neurohormonal activation (and their interrelation) and prognosis.

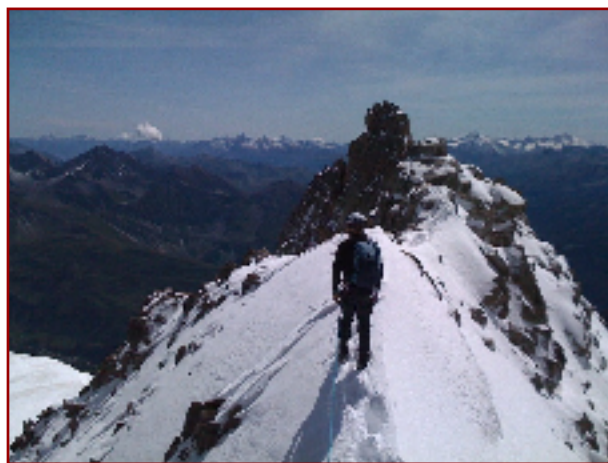
About half of the patients attending primary care with treated hypertension do not achieve target blood pressure, and a major problem in hypertension treatment is the implementation of guideline recommendations. We and colleagues founded the Swedish Primary Care Cardiovascular Database, containing about 75 000 patients attending primary care in Sweden with a diagnosis of hypertension. Data from medical records are linked to several national health registers. This comprehensive database allows us to study demographics including socioeconomic factors, comorbidity, treatment, blood pressure control, drug persistence, and morbidity and mortality. More important, this will clarify areas of improvement to achieve better control of blood pressure and risk factors. Results published on time trends show improved blood pressure control, but important and persistent gender differences in drug treatment, with fewer women achieving target blood pressure than men; and factors that determine antihypertensive drug discontinuation. A database on approximately 88 000 heart failure patients from the Stockholm region is investigated in a similar way.

TEACHING ACTIVITIES

Danderyd University Hospital is a teaching hospital for many health professional categories. At the Department of Cardiology both academic staff and clinical staff are engaged in teaching of medical students, interns in medicine, residents in cardiology, and in our postgraduate educational courses. The Hypertension Excellence Center contributes to these activities with their expertise. Furthermore, we contribute with several courses within the cardiovascular research doctoral program at Karolinska Institutet, and are part of the organisation of the biannual Nordic PhD course on cardiovascular research. There is also active research on learning and teaching of patients and relatives, health professionals, and on implementation of knowledge into clinical practice (Peter Henriksson, Anna Kiessling).

INTERNATIONAL AND LEARNED SOCIETIES

The Hypertension Excellence Center has conducted or coordinated national and international multicentre studies phase 2-3 studies (ASCOT, CUPID, DORADO, SILVHIA, SPIRE) and is active in the Swedish Society for Hypertension, Stroke and Vascular Medicine, where Jonas Spaak is secretary and Thomas Kahan is immediate past president. Thomas Kahan is board member of the European Society of Hypertension, on the Communications Committee of the International Society of Hypertension, nucleus member of the European Society of Cardiology Council on Hypertension, board member of the International Society of Cardiovascular Pharmacology, and on the Research Council of the Swedish Society of Medicine. We are founding members of the Swedish Registry on Renal Denervation (Jonas Spaak); and in the ENCOREd European network on renal denervation (Thomas Kahan), the IDACO (Kristina Bodegård Björklund) and ARTEMIS (Thomas Kahan) international networks on ambulatory blood pressure monitoring.



LEFT: Thomas Kahan in scientific discussions RIGHT: or in the mountains (fresh snow at Tour Ronde, above Courmayeur, Italy); both favorite occupations!

- Thomas Kahan

Sex or gender? – Conceptual confusion is common

Katarina Hamberg¹ (left) & Susan P. Phillips² (right)

¹Department of Public Health and Clinical Medicine, Family Medicine, Umeå University, Sweden

²Departments of Family Medicine and Public Health Sciences, Queen's University, Ontario, Canada



When researchers study sex or gender differences in health outcomes they often find significant disparities. But what do sex or gender actually mean and measure? The simplest answer is to consider that all subjects are either women or men and to group them accordingly. Historically differences between the women and men were thought to arise from biology, reproductive organs, hormones or biological processes. This is what the term 'sex' generally means. The division between sex and gender in social science research developed in the 1960s. The split highlighted the need to move beyond a narrow focus on biology and recognize that socioeconomic conditions and cultural norms also shape and constrain education, career choices, salaries, and health. The term, gender refers to social aspects of being a man and woman, features that are formed in relation to upbringing, conditions in daily life, norms and culture. ¹

In medical research interest in sex/gender analyses grow slowly and it was, for instance, not until 1998 that the US Food and Drug Administration decided that all new drugs, before being accepted for use, should be analysed for safety and efficacy by sex.² Later, health organisations and research foundations in many countries stressed the importance of including both men and women in medical studies and analysing sex and gender differences in outcome, and many organisations also formulated their own definitions of the terms sex and gender.³⁻⁵

However, still in 2015, medical researchers time and again neglect sex/gender aspects in their studies and when including 'sex' or 'gender' in their publications are often unaware of the meanings of the terms. It is common for 'gender' to be seen as the modern word to use instead of 'sex', or that the terms are used as interchangeable synonyms, without being defined. The July 2015 issue of *Atherosclerosis* included a section about sex related differences in CVD. In an accompanying commentary Spence & Pilote stated that there was initially unwarranted confusion about how to use sex and gender in many of the submitted papers.⁶ They then explained differences between the two concepts by quoting the current definition of 'sex' and 'gender' used by the Canadian Institutes for Health Research:⁷

"**Sex** refers to a set of biological attributes in humans and animals. It is primarily associated with physical and physiological features including chromosomes, gene expression, hormone levels and function, and reproductive/sexual anatomy. Sex is usually categorized as female or male but there is variation in the biological attributes that comprise sex and how those attributes are expressed.

Gender refers to the socially constructed roles, behaviours, expressions and identities of girls, women, boys, men, and gender diverse people. It influences how people perceive themselves and each other, how they act and interact, and the distribution of power and resources in society. Gender is usually conceptualized as a binary (girl/woman and boy/man), yet there is considerable diversity in how individuals and groups understand, experience, and express it."

However, the commentary left out the last and most innovative part of the definition. This part is inspired by the latest development in gender theory which comprises biomedical research achievements in, for example, psychoneuroimmunology and epigenetics:

"**Gender and sex are interrelated.** There is no simple "recipe" for integrating sex and gender in health research (or for accounting for the complex interrelationships between them and other factors or determinants of health). "

This passage signifies a shift from strict splitting between biology and social factors and is important for readers of *Hypertension*. In medical research and clinical practice it is often impossible to differentiate between biological and social causes to health problems. Living conditions and environment affect the body and biological processes, i.e. they cause biological changes. Physicians can seldom define how much of a patient's disease, be it carotid artery stenosis, stroke, hypertension, psoriasis or tuberculosis, is related to or caused by behaviour, living conditions, infectious agents or heredity. This means that a dichotomy between sex and gender is problematic in medicine - although both sex and gender might be important they are always interacting. Therefore, some researchers use the combined term 'sex/gender' to recognize that neither sex nor gender can be examined independent of the other as the two concepts are intertwined.⁸⁻⁹

Does this mean that we can skip the whole discussion of 'sex' versus 'gender'? No, 'sex' and 'gender' are useful concepts in that they pinpoint the need to assess biological as well as social conditions when investigating similarities and differences between men and women. But as the last part of the definition above suggests, our comprehensions need to reach beyond simple dichotomies of either biological sex or social gender. This means that even if 'sex' is still assigned to biological characteristics, greater research accuracy is achieved by recognizing that biological processes are interacting with and influenced by social and psychological conditions, i.e. gender.⁸ Likewise, the way 'gender' is created and expressed by individuals is related to biological conditions like muscle strength, body weight, disease or physical handicap. Social and cultural influences on biological processes are well recognized in epidemiology and as determinants in oncology and cardiovascular research. Further, expanding knowledge of epigenetics teach us that genes, previously seen as innate and fixed, can be activated or shut down (temporarily or permanently) by environmental factors and ways of living.^{10,11} Since men and women often live different lives with different duties, demands and resources, epigenetic knowledge contributes new insights into how gender and sex are intertwined.

To conclude, there is no short and simple answer to when to use 'sex' and when 'gender' is the more appropriate term. Due to the current confusion about the use of 'sex' and 'gender', we recommend that researchers always explain what they mean by whatever term they choose. Even more important is to realize that 'sex' and 'gender' are not interchangeable synonyms, nor can they be isolated from each other. Although

it may be suitable to talk about sex differences in animal experiments and laboratory research, in clinical studies it is more realistic to see biology as entangled with social circumstances and to highlight this interconnection by using the term 'sex/gender'.

- Katarina Hamberg and Susan P. Phillips

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PCSK9 inhibitors



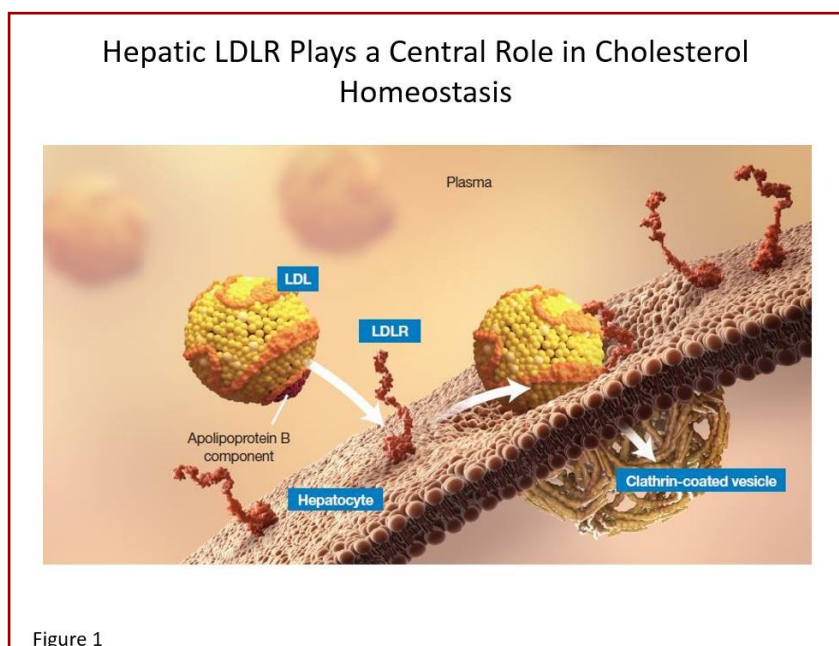
Peter Sever (pictured left) and Judy Mackay (pictured right)

International Centre for Circulatory Health.
National Heart and Lung Institute.
Imperial College London, UK.

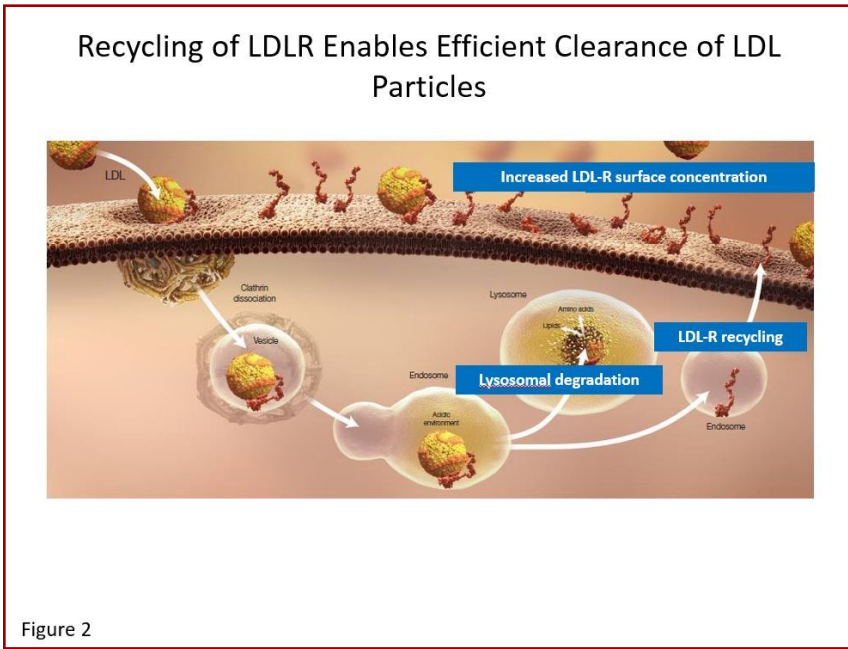
Lowering cholesterol with statins has shown consistent cardiovascular (CV) outcome benefits across a wide range of baseline cholesterol levels. One of today's challenges, however, is to establish whether it is possible to improve CV outcomes by additional lipid-lowering therapy, which will enable lower levels of cholesterol to be attained, particularly in patients at higher CV risk, including those with established CV disease, and those with hypercholesterolaemia, in whom optimal levels of cholesterol cannot be achieved with existing statin therapies. A further unmet need is the optimal management of subjects who are statin intolerant although, as I pointed out in a previous commentary for this News Letter, true statin intolerance is much less common than has been claimed by some reviewers¹

PCSK9 (Proprotein Convertase Subtilisin Kexin Type 9) and Inhibitors of PCSK9

The LDL receptor on the surface of hepatocytes plays a central role in cholesterol homeostasis. Circulating LDL-cholesterol binds to the LDL receptor and the complex is internalized in the hepatocyte in clathrin coated vesicles, the contents of which undergo lysosomal degradation (Figure 1).



The LDL receptor is, however, recycled to the cell surface where it can bind with more LDL-cholesterol molecules (Figure 2). PCSK9 is a protein synthesized by the hepatocytes which binds to the LDL receptor component of the LDL receptor/LDL-cholesterol complex. However, when this complex is internalized in the hepatocyte, the resultant lysosomal degradation does not permit the LDL receptor to be recycled to the cell membrane (Figure 3). Thus, the number of LDL receptors on the surface of the hepatocytes is reduced and serum levels of LDL-cholesterol increase. The more PCSK9 produced by the liver, the higher the LDL-cholesterol level.



Genetic variations in PCSK9 are associated with high or low levels of the protein which, in turn, relate to high and low levels of LDL-cholesterol (Figure 4) and, not surprisingly, high and low risks of CHD respectively. PCSK9 is therefore a novel regulator of hepatic LDL receptor expression and an obvious target to influence levels of LDL-cholesterol.



Monoclonal antibodies have been developed which bind PCSK9 and prevent its interaction with the LDL receptor (Figure 5), thereby preserving receptor numbers and lowering LDL-cholesterol. In Phase 2 clinical trials the administration of human monoclonal antibodies to PCSK9 has been associated with impressive reductions of LDL-cholesterol (50-70%), not only in patients who were statin naïve, but also in patients receiving optimal doses of high intensity statins, including those with heterozygous hypercholesterolaemia^{2,3}. In these studies highly significant reductions were also seen in ApoB, Lp(a) and triglycerides.

Overall, the monoclonal antibodies tested thus far have been shown to be not only effective, but safe and well tolerated. Because of their nature they have to be administered by subcutaneous injection either 2 weekly or 4 weekly. Novel autoinjector devices make subcutaneous administration of the antibody relatively simple and cause minimal discomfort.

Long term efficacy and safety trials are now the major challenge and three large Phase 3 morbidity/mortality outcome trials are currently ongoing, designed to establish whether, in patients with established CV disease or at high risk of CV disease, the administration of a monoclonal antibody to PCSK9, confers additional protection against CV events on top of optimal statin therapy.

PCSK9 is a Novel Regulator of Hepatic LDL Receptor Expression

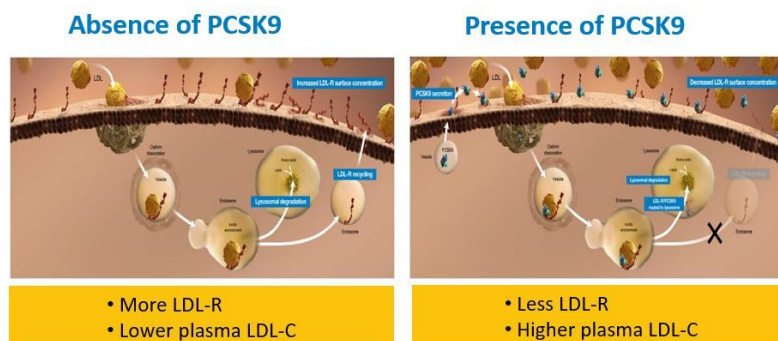


Figure 4

Monoclonal Antibodies Against PCSK9 Block PCSK9/LDL-R Interaction

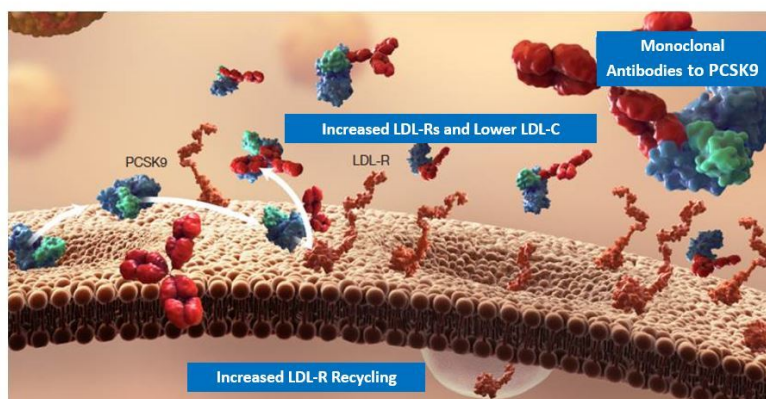


Figure 5

FOURIER (sponsored by Amgen Inc.) is a trial of 27,500 patients with established CVD, recruited on the basis of a past history of myocardial infarction, stroke or symptomatic peripheral vascular disease. Patients enter the study on optimal background statin therapy (usually atorvastatin 40-80mg), with an LDL-cholesterol $>1.8\text{mmol/L}$ or non-HDL cholesterol $>2.6\text{mmol/L}$. They are randomized to the monoclonal antibody, evolocumab, or placebo administered by subcutaneous injection 2 or 4 weekly. Patients will be followed up for an average of about 4 years until approximately 1630 hard endpoints have occurred (non-fatal myocardial infarction, non-fatal stroke and fatal CVD). The trial is designed to detect a 15% reduction in this combined endpoint in the active treatment group compared with placebo. The current projection, based on endpoint rates in the trial to date, is that the trial may be completed by mid 2016.

ODYSSEY OUTCOMES (sponsored by Sanofi and Regeneron) is a trial of 18,000 patients recruited within one year of an acute coronary syndrome (ACS) and who, despite high intensity or maximum tolerated dose of statin, have an LDL-C $>1.8\text{mmol/L}$. Patients are randomised to alirocumab or placebo as a 2 weekly subcutaneous injection. The principle outcome is the composite of CHD death, non-fatal myocardial infarction, ischaemic stroke or unstable angina. The expected duration of the study is 4 years by which time approximately 1650 primary events are predicted to have occurred. With a placebo event rate of 11.4% at 4 years, the study is powered to test a 15% reduction in the primary endpoint.

SPIRE 1 and 2 (sponsored by Pfizer) comprise two combined studies in patients with established CV disease or at high risk of CV disease, receiving highly effective statin therapy –SPIRE 1 of 17,000 patients with entry LDL-cholesterol $<2.59\text{mmol/L}$, and SPIRE 2 of 9000 patients with entry LDL-cholesterol $>2.59\text{mmol/L}$. Statin intolerant patients may also be included. Patients are randomized to bococizumab or placebo to receive 2 weekly injections. The principle outcome is a composite of CV death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina with urgent revascularization. Follow up is for 4.1 years with an expected placebo event rate of 2.7% per year.

Clearly these trials are carried out in high risk patients with established CVD or at high CV disease risk, who are already receiving optimal or best tolerated statin treatment. The main difference is in the patient population. The focus of ODYSSEY OUTCOMES is limited to subjects with recent ACS, whilst FOURIER includes subjects who have suffered an MI or ischaemic stroke at any time, and patients with peripheral vascular disease. In SPIRE, high risk patients in primary prevention and statin intolerant patients are included.

Further information on these trials is available on clinicaltrials.gov

Earlier this year both evolocumab (AMGEN) and alirocumab (Sanofi-Regeneron) were approved by the EU and the FDA, and both drugs launched in the US and Europe . The licensed indications are similar and include adults with primary hypercholesterolaemia (heterozygous familial or non-familial) or mixed dyslipidaemia, as an adjunct to diet: a) in combination with a statin or statin with other lipid-lowering drugs in patients unable to reach LDL goals with maximum tolerated doses of a statin, or b) alone or in combination with lipid- lowering drugs in patients who are statin intolerant or for whom a statin is contraindicated.

In the UK, AMGEN has launched at a fraction of its cost in the US (UK \$6780 a year compared with \$14,100 in the US). A preliminary analysis estimates cost effectiveness at around \$1700 per year.

Conclusions

The rate of development of these drugs has been extraordinary, from the first discovery of PCSK9 in 2003 to the launch of the monoclonal antibodies into clinical practice in 2015. They represent the most dramatic advance in lipid-lowering therapy since the statins were introduced in 1987. The outcome of the first of the major morbidity/mortality trials is anticipated in 2016 and the impact on clinical practice will be immense. For the first time we will have a realistic opportunity to treat effectively patients with familial hypercholesterolaemia and to achieve cholesterol goals in other high risk patients for whom statins are less than optimally effective or who are statin intolerant.

- Peter Sever and Judy Mackay

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Disclosure: PS is a member of the Executive Committee for the FOURIER Trial.
Acknowledgment: Figures 1-5 are reproduced with permission from Amgen Inc.



XXIII ARGENTINE HYPERTENSION MEETING | APRIL 14-16TH | HOTEL PARAMERICANO BUENOS AIRES | 2016

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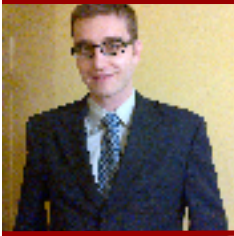


INTERNATIONAL SOCIETY OF HYPERTENSION - NEW INVESTIGATOR COMMITTEE, (ISH-NIC)



ARGENTINE SOCIETY OF HYPERTENSION

Spotlight on the ISH New Investigator Programme, AHA Hypertension Council Scientific Sessions, September 2015



Report compiled and introduced by
Dylan Burger - Lead for Media Working Group of ISH NIC
Ottawa, Canada



In September, the ISH New Investigator Committee (NIC) worked alongside the Trainee Advocacy Committee of the American Heart Association (AHA) Hypertension Council to build a New Investigator-centred programme. The programme continued to grow a longstanding relationship between the two committees and featured poster and oral communication sessions, awards and social interactions. The programme was a huge success with the largest participation of any ISH-sponsored symposia and was well received by all participants. Here we present three perspectives on the programme from members of the ISH New Investigator Committee Working Groups.

ISH/AHA Trainee Advocacy Committee Social Interactions



Fady Hannah-Shmouni (pictured left)
Member of ISH NIC Recruitment Working Group, Washington, D.C, USA

It was lovely to participate in the social gathering where many familiar faces (and new ones) were engaged in dancing and singing. These activities reinforced the collaborative efforts that we rely on in science to help advance the field. Gatherings such as this one bring together like minded individuals for the same goal: building new relationships through the arts. I am glad to have made new friends and collaborators during this unforgettable social event and hope we will continue advocating for these extra-curricular activities during our conferences.

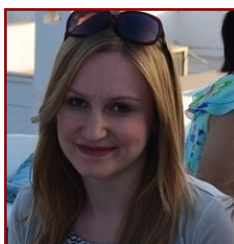
Poster Sessions



Cesar Romero (pictured left)
Member of ISH NIC Media Working Group, Troy, Michigan, USA

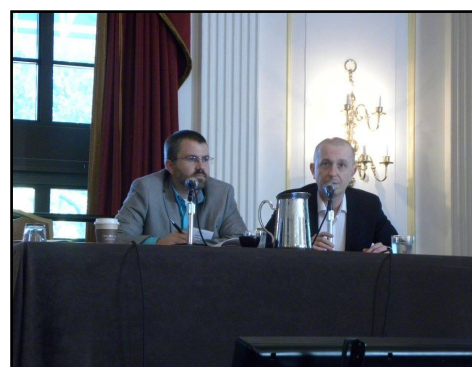
The trainee on-site poster competition and reception was a highlight of the Hypertension Council Sessions. In a collegial atmosphere, almost 140 students, fellows, and trainees presented their work receiving feedback from colleagues and established senior investigators. The judges contributed to poster evaluations and maintained a constructive and friendly mood whilst sharing their valuable experiences. Overall I found the poster competition to be a great opportunity to meet people, build relationships and promote the activities of the ISH New Investigator Committee.

Oral Communications



Lucinda Hilliard (pictured left)
Member of ISH NIC Media Working Group, Melbourne, Vic, Australia

This year the ISH New Investigator Committee and Trainee Advocacy Committee of the Council on Hypertension co-hosted, and together with Hypertension journal jointly sponsored, the Top Trainee Abstracts Oral Session. The scientific program featured high quality presentations and cutting edge research from 6 outstanding trainees who were competing for the newly developed "Hypertension Early Career Award". Many thanks to Professor Anna Dominiczak, Editor-in-Chief of Hypertension, who participated in the judging process of this prestigious award. Congratulations to our awardee, Ellen Gillis from the University of Mississippi, USA, for her presentation entitled "Preeclampsia in the Dahl salt sensitive rat is associated with increased uterine artery resistance and reduced placental microvascular density".



LEFT: Oral Presentation Session, CENTRE: Chair, AHA Trainee Advocacy Committee, Aaron Trask and Chair, ISH NIC - Maciej Tomaszewski, RIGHT: Oral presentation Session

Award Winners

Hypertension Early Career Award Sponsored by Hypertension, AHA TAC and ISH NIC

(Top Trainee Oral Presentation Award)

Winner:

Ellen Gillis **University of Mississippi Medical Center (USA)**
Abstract title: **Preeclampsia in the Dahl Salt Sensitive Rat is Associated with Increased Uterine Artery Resistance and Reduced Placental Microvascular Density**

Runners up:

- Balyssa Bell University of Iowa (USA)
- Hana Itani Vanderbilt University (USA)
- Jordon Kho Baylor College of Medicine (USA)
- Marc Mazzuca Brigham and Women's Hospital and Harvard Medical School (USA)
- Maria Pitra Georgia Regents University (USA)

Poster Presentation Award Winners

- Stacy Robertson Heart Research Institute (Australia)
- Gautam Shah Cleveland Clinic (USA)
- Sathnur Pushpakumar University of Louisville (USA)
- Candace McNaughton Vanderbilt University Medical Center (USA)
- Amrita Pai Georgetown University (USA)
- Faisal Rahman Boston University Medical Center (USA)
- John Henry Dasinger University of Mississippi Medical Center (USA)
- Ninitha Asirvatham-Jeyaraj University of Minnesota (USA)
- Justin Van Beusecum University of Alabama (USA)
- Katie Hood Institute of Cardiovascular and Medical Sciences (UK)
- Nathan Campbell University of Mississippi Medical Center (USA)
- Wissam AbouAlaiwi University of Toledo (USA)
- Erin Bruce University of Florida (USA)
- Katrin Nather University of Glasgow (UK)
- Johnathan Ebben Medical College of Wisconsin (USA)
- Steven Forrester Temple University (USA)
- Sabine Kossman University Medical Center Mainz (Germany)
- Masashi Mukohda University of Iowa Carver College of Medicine (USA)
- Amanda Soler New York Medical College (USA)
- Sanghamitra Sahoo Vascular Medicine Institute (USA)
- Guang Yang Heinrich-Heine-University (Germany)

View an interview with the winner of the top trainee oral session - Ellen Gillis



Where to publish - the role of the Impact Factor

Lars H. Lindholm
Editor, Hypertension News



New data on the Impact Factor (IF) of medical journals were released in September 2015, giving barely moderate changes for most hypertension journals, as shown below in the table. The Lancet, however, has had a marked increase since 2010, almost halving the gap to the New England Journal of Medicine.

The IF of an academic journal is a measure reflecting the mean number of citations to recent articles published in that journal. It is frequently used as a proxy for the relative importance of a journal within its field, with journals with higher IF deemed to be more important than those with lower ones. Numerous criticisms have been made of the use of IF, and there is a general debate on the validity of the IF as a measure of a journal's importance. As a result, it is often said, that it doesn't matter where you publish, as long as the journal is included in the Journal Citation Reports. I disagree since, at least in my part of the world, we have an activity based funding of our departments (based on publications, number of doctorate theses, and external grants) and only papers with an IF above 2 (or 3 at some universities) give us full funding for that paper. Some universities use a basket of several factors such as the IF, the 5-year-impact factor, and others. However, the IF should be used only - and cautiously - for measuring and comparing the influence of entire journals, but not for assessment of single papers and certainly not for the assessment of researchers and research programmes (European Society of Science Editors EASE, 2007).

How to calculate IF (adapted from: en.m.wikipedia.org)

In any given year, the IF of a journal is the average number of citations received per paper published in that journal during the two preceding years. For example, if a journal has an IF of 3 in 2014 (released in September 2015), then its papers published in 2012 and 2013 received 3 citations each on average in 2014.

The 2014 IF of a journal would be calculated as follows:

$$IF = A/B$$

A = the number of times that all items published in that journal in 2012 and 2013 were cited by indexed publications during 2014.

B = the total number of "citable items" published by that journal in 2012 and 2013.

"Citable items" for this calculation are usually articles, reviews, proceedings, but not editorials or letters.

Journal	2010	2011	2012	2013	2014	2010-2014
NEJM*	53.5	53.3	51.7	54.4	55.9	+2.4
Lancet	33.6	38.3	39.1	39.2	45.2	+11.6
Science	31.4	31.2	31.0	31.5	33.6	+2.2
Nat. Med.	25.4	22.5	22.9	28.1	27.4	+2.0
Brit. Med. J.	13.5	14.1	17.2	16.4	17.4	+3.9
Circulation	14.4	14.7	15.2	14.9	14.4	0
Hypertension	6.9	6.2	6.9	7.6	6.5	-0.4
J. Hypertens.	4.0	4.0	3.8	4.2	4.7	+0.7
Am J Hypertens	3.1	3.2	3.7	3.4	2.9	-0.2
JASH	N/A	2.1	2.8	2.7	2.6	N/A
J Hum. Hypertens.	2.2	2.8	2.8	2.7	2.7	+0.5
Blood Press	1.3	1.4	1.4	1.6	1.8	+0.5

*New England Journal of Medicine (New Engl J Med)

Comment

When deciding where to send an article, it should be remembered that the Journal of Hypertension is the official journal of the International Society of Hypertension (and the European Society of Hypertension) and has a reasonable IF of 4 or above. Hence, it is a natural home for many papers on high blood pressure. Also, it is far from easy to get articles published in the top two journals. During 2010-14, "hypertension" was mentioned in the text of 14 Lancet papers per year, compared with 15 in the New England Journal of Medicine; including "high blood pressure" added little. "Hypertension" was only found in the title of a limited number of those papers. Undoubtedly, one reason for the paucity of papers is that both are general medical journals and have to cover all aspects of medicine; but perhaps it also reflects the quality of research in terms of how much the results will influence clinical practice around the world.

The narrowing of the gap between the New England Journal of Medicine and The Lancet can hardly be explained by the policies discussed above. Both journals publish high quality original papers every week and both give priority to randomised control trials. To some extent, the Lancet may have been favoured by the excellent group of papers on the Global Burden of Disease published in December 2012 by Chris Murray and co-workers, but those papers were published late in the year so the effect would have been muted. A likely contributing factor to The Lancet's increase in IF may be their launching of nine daughter journals over the last decade; the first ones with an IF above 25 (!) today. Clinically interesting, high profile papers can now be published in the weekly journal and other good papers can be accommodated in their monthly daughter journals. Living in the Bordeaux area of France five months the year, this makes me think on how Grand Cru chateaux in Medoc have increased the quality (and the rating by Robert Parker) of their first wines by making very good second wines made from grapes grown on younger wine stocks.

- Lars H Lindholm



On behalf of the ISH Leadership, I would like to wish you and your family all the very best for the festive season


Rhian Touyz
ISH President





www.ish-world.com

Christmas Menu

As the festive season is upon us, we take a look at a traditional British Christmas menu using products commonly available in the UK. You will see two versions : high salt and low salt .

This information was made available to the ISH courtesy of Consensus Action on Salt and Health (CASH). We would like to extend a special thanks to Graham MacGregor and Sonia Pombo for their assistance. Please note that data was compiled in 2011. For further information please see <http://www.actiononsalt.org.uk/less/surveys/2011/Christmas/>

High Salt Christmas Menu 	Salt (g) per portion	Low Salt Christmas Menu 	Salt (g) per portion
Pre-lunch snacks	2.2	Pre-Lunch snacks	0.5
Sherry / champagne	0	Sherry / champagne	0
Salt & vinegar crisps	0.7	Lightly salted or no added salt crisps	0.2
Green Olives	0.8	Black Olives	0.3
Salted Peanuts	0.7	Unsalted Mixed Nuts or Nuts and Dried Fruits	Trace
Starter	3.30	Starter	2.12
Smoked salmon	2.55	Smoked salmon	1.67
Kraft Light Philadelphia	0.3	Supermarket Light cream cheese	0.10
Thick sliced bread	0.53	Medium sliced bread	0.27
Main meal	0.87	Main meal	2.24
Prepared, Basted Turkey Breast Joint	0.79	Home-cooked Roast Turkey	0.3
Pork Cocktail Sausages	0.48	Ready-prepared Pigs in Blankets	0.45
Dry Cured Streaky Bacon	0.60		
Ready prepared Roast Potatoes	1.03	Home-made Roast Potatoes	Trace
Ready-prepared Parsnips	0.43	Home-made Roast Parsnips	Trace
Ready-prepared Brussels Sprouts	0.8	Home-cooked Brussels Sprouts	Trace
Ready-prepared Mashed Carrot and Swede	0.6	Home-made Mashed Carrot and Swede	Trace
Sausage Meat Stuffing	1.38	Vegetarian Stuffing e.g. Cranberry & Bramley Apple Stuffing	0.47
Aunt Bessie's 12 Yorkshire Puddings (frozen)	0.3	Supermarket Yorkshire Puddings (frozen)	0.1
Poultry Gravy	1.1	Poultry Gravy	0.27
Colman's Bread Sauce Mix	0.72	Marks & Spencer Bread Sauce (fresh)	0.33
Cranberry Sauce	0.03	Cranberry Sauce	0.03
Colman's English Mustard	0.42	Essential Waitrose English Mustard	0.25
Dessert	1.22	Dessert	0.80
Christmas pudding	0.3	Christmas pudding	0.3
Fresh custard	0.1	Fresh custard	0.1
Stilton Cheese	0.62	Cheese with fruit in e.g. <u>Wensleydale</u> with apricot	0.28
Crackers or Biscuits for Cheese	0.2	Crackers or Biscuits for Cheese	0.2
Total Salt Content	15.67	Total Salt Content	5.7

Council's Corner: Hypertension Issues - a personal view



Hermann Haller
Hannover Medical School
Clinic of Nephrology and Hypertension
Carl-Neuberg-Straße 1
30625 Hannover, Germany

I have not always been a “vascular “person. When I first entered the field of hypertension research as a young doctoral fellow my research topic was the effects of the hypothalamus on the kidney.

Under the supervision of Wolfgang Oelkers who had trained at the MRC Unit in Glasgow I tried to find out whether and how ACTH influenced RAAS. Besides the fact that we found a small but significant effect of ACTH on the renin-angiotensin system, the most important lesson was the rigorous training of clinical research and the enthusiasm of working with patients. So I entered hypertension research as an endocrinologist with a profound belief in the importance of the RAAS in hypertension. However, when I entered Nephrology and the research group of Armin Distler and Thomas Philipp in 1983, it was all blood vessels, and contraction which mattered in the pathogenesis of hypertension. As today, the concept of hypertension in 1983 was that it is either (1) an increased vaso-constriction in arterioles or (2) an increased activity in the heart or (3) the increased sodium uptake in the kidney or (4) a mechanism influenced by the altered circuits in the brain. So, as of today, the kidneys, vascular tone and the brain were supposed to be the culprits either alone or together in the pathogenesis of hypertension. My research group was concentrating on increased contractility. Thomas Philipp had described that vascular receptors in hypertensive patients were more responsive to catecholamines and my first task was to address intracellular signalling in vascular smooth muscle cells. It was well-known that calcium is important in the regulation of cellular contractility and since the first measurements of intracellular free calcium had just been made possible by the introduction of fluorescent dyes I tried to measure intracellular free calcium in patients with essential hypertension. The hypothesis was that a disturbance in intracellular calcium signalling, either by calcium influx through membrane channels or by an increased release from intracellular stores is altered in hypertensive patients. This assumption was supported by the antihypertensive effects of calcium channel blockers in patients with essential hypertension. Since vascular smooth muscle cells were not accessible in our hypertensive patients, we used what we thought at that time to be a circulating contractile cell type i.e. the platelet from hypertensive patients. I learned the method in the laboratory of Fritz Bühler and Paul Erne in Basle and we were able to demonstrate that intracellular free calcium concentration in patients with essential hypertension was increased and that it could be manipulated both to increase and to decrease in accordance with changes in blood pressure. I still believe that a disturbance in vascular smooth muscle cells is important in the pathogenesis of hypertension. At the time there was a raging debate whether this is an intrinsic alteration of contractility or whether there are structural alterations in the vessel wall which mediate the increase in resistance. The excitement of the scientific discussions and the battles which were fought between functional and structural believers is still a fond memory.

The vascular hypothesis of hypertension, although still important, has lost some ground in the era of genetics. Most genetic alteration and possible candidate genes which have been associated with high blood pressure and hypertension have been found in the kidney. The last example is uromodulin which shows a strong association both with hypertension and the progression of renal disease. Most likely uromodulin, which is a tubular surface molecule interacts with transporters in the renal tubules and influences thereby sodium uptake and, possible, fibrosis. This indicates that at least in some patients with hypertension the kidney and sodium still play a major role. This hypothesis is strongly supported by the fact that most monogenetic forms of hypertension have been associated with sodium transport and renal mechanisms. However, recently the first monogenetic disease which is caused by a dysregulation in vascular smooth muscles has been described. Friedrich Luft and his research group, where I had the privilege to be a member of 20 years ago, found and described the first “vascular” gene in a monogenetic form of hypertension and brachydactily. The gene codes for phosphodiesterase-3 and, in families with hypertension, is hyperactive and leads to an increased breakdown of cyclic GMP. To what extent these genetic disturbances contribute to the increased vascular resistance in patients with so-called essential hypertension remains to be identified. At least in one genome-wide analysis PDE-3A has been found to be associated with hypertension. This makes it possible that some patients have a vascular disturbance as the cause of hypertension.

The vascular hypothesis of hypertension was dramatically influenced by the identification of NO and its role in vascular regulation in the early nineties. All of a sudden, the endothelium and its altered state in hypertension were of central interest. The endothelial cells are not only important in regulating vascular tone by secreting NO but also basic constrictive substances bound as an interface between the blood and the vessel wall they play a role in cardiovascular disease in general. These cells and their regulation became of central interest to my research group. We strongly believe that unravelling the disturbances of the endothelial cells will not only help us to understand hypertension but also the pathogenesis of chronic vascular disease. Numerous studies have shown that the endothelium is changed in patients with hypertension. However, it was and still is much more difficult to find out whether these are primary intrinsic differences or whether the endothelial cells are the first culprit of an increase in hypertension. After a long time in endothelial cell research I tend to believe that endothelial cells do not have a primary alteration in patients with hypertension but are suffering from the increased stress by hypertension and other risk factors in these

patients. However, it cannot be ruled out that the endothelial cells may have a different responsiveness in patients with a genetic basis for hypertension and are more susceptible to damage. After all, PDE-3 is also strongly expressed in endothelial cells.

One property of the endothelium which has been a research interest of mine in the last few years may be of central importance in the pathogenesis of hypertension. It is only recently that the early reports of inflammation and its relationship with hypertension have been confirmed and extended in a more rigorous manner. We now have a multitude of studies demonstrating that the pathogenesis of hypertension is intricately linked to specific inflammatory mechanisms. This work which was pioneered by Harrison and others suggests that hypertension is a specific immunological response and that T-lymphocytes and monocytes are directly linked to an increase in blood pressure. In this inflammatory response the endothelium also plays a major role. Leucocytes within the blood stream have to enter the vascular wall through the endothelial cell layer. The secretion of chemokines and the expression of adhesion molecules are important steps in this set of events. How the inflammatory cells induce an increase in high blood pressure and whether the endothelial cells are involved in either the generation of epitopes which induce the immunological response or whether they are mostly responsible for the immigration of white blood cells into the vessel wall remains to be solved. However, I believe that the interaction between the inflammatory mechanisms and the vessel wall are of wider importance in the pathogenesis of hypertension.

In recent years the neuronal circuits especially the sympathetic system have become more important in the pathogenesis of hypertension. As always, the introduction of a novel device to interfere with a specific pathogenetic mechanism has led to a lot of activity. Without addressing first the issues of the underlined pathophysiology we (especially in Germany) embarked enthusiastically on interventional procedures in patients with severe hypertension. I strongly believe that the sympathetic nervous system plays an important role in hypertension. The intimate relationship between neuronal cells and the vasculature, the tubulus system and other organs makes it more likely than not that the nerve fibres strongly influence the behaviour of sodium reabsorption and contractility. This relationship has been shown in elegant pathophysiological studies by DiBona and others. However, because this relationship is so delicate and balanced, it is important to find out which mechanisms are responsible and to define patients most likely to have hypertension on the basis of increased sympathetic tone and who therefore may benefit from medical therapy.

So based on my view of hypertension, what role does the kidney play? As I am a nephrologist I believe that this is most likely a central one. Classically, it was the increase in sodium absorption on the one hand and the release of ACE-active hormones on the other which kept the kidney in the centre of blood pressure regulation and hypertension. Genetic studies in families with monogenetic hypertension have strongly shown that a variety of elements are involved in tubular sodium reabsorption and the pathogenesis of hypertension. We have been concentrating on specific defects in transport systems and signalling molecules. However, in the last couple of years we have found that these mechanisms may be even more complicated.

In summary, my view on hypertension has been strongly influenced by my scientific life with hypertension. I was once fully convinced that vascular resistance is the culprit in the disease and my centre of the hypertensive universe. However, over the years, endothelium, nerve fibres and renal cells have appeared and make a more complex picture. It is like in a museum: the older I get the more I am interested in the complexity of baroque paintings and consider my favourite renaissance paintings to be one-dimensional. However, complexity is no excuse for not finding out how it works. And that is still the real challenge: which of these mechanisms we have so successfully described and characterized over the last 30 years is active in our hypertensive patient?

- Hermann Haller

Council's Corner: Hypertension Issues - a personal view



Cheol-Ho Kim

Seoul National University Bundang Hospital
Seoul National University College of Medicine
Seoul, South Korea

It was my great pleasure to be elected as an ISH Council Member in 2012. One of my main aims of joining Council was to act as a link between the ISH 2016 Seoul Biennial Scientific Meeting Local Organising Committee and the ISH leadership and maximise the opportunities for scientific exchange at this event. Since my election, I have been working with my local colleagues to determine the main theme and topics to be discussed at the meeting (Hypertension Seoul 2016).

Hypertension Seoul 2016
The 26th Scientific Meeting of the
International Society of **Hypertension**
September 24(Sat) - 29(Thu), 2016
Coex, Seoul, Korea

As you may be aware, the main theme of Hypertension Seoul 2016 has been confirmed as **"working together for better BP control and CV reduction."** I believe that hypertension meetings should create numerous opportunities for information exchange on recent developments, as well as being a place for participants to think about the way in which high blood pressure can be better managed. In practice, high blood pressure is not adequately managed. This is more often from a lack of interest from the patient or doctor than from a lack of information provision, although cases differ for patients based in countries with varying economies. The cooperation of health professionals is indispensable in order to effectively control and manage high blood pressure. The ISH 2016 Seoul meeting will be an ideal occasion for clinicians and scientists from all over the world to come together for the good management of persons with high blood pressure.

The landscape of hypertension burden in the world is changing. There is a high burden of high blood pressure in Asia in areas including China, India and Southeast Asia. The epidemiology of this region is totally different from Europe, even though data from different areas within Asia differs. Subsequently, the first topic of the meeting will be the difference in cardiovascular (CV) risk factors and outcomes in Eastern and Western areas. This will be a chance to discuss the reasons for the lower incidence of CV outcomes in the eastern world and give good insights into reduced CV outcomes in the western world. In addition, it will allow eastern countries to share their experience of high blood pressure control from a western perspective.

The global population is ageing.

Many developed countries are facing previously unexperienced problems of hypertension in the elderly. Hence, this will be the second topic for the meeting. Management of high blood pressure in the future will be targeted at the prevention of small vessel disease in central nervous system (CNS) leading to geriatric syndrome such as cognitive impairment, depression and Parkinson Syndrome with gait abnormality. Better prevention of small vessel disease in CNS will lead to reduction of disability in the elderly, reducing the health economic burden of the world. In addition, target blood pressure, use of medication in frail elderly patients should be included for discussion. There will be many related topics to be discussed in the elderly such as prevention of diastolic heart failure or chronic kidney diseases.

Information technology may change hypertension management in the future.

Having a longer life-expectancy, every individual should have the ability to manage his or her medical conditions including high blood pressure. With the introduction of simple appliances at home or during activity, blood pressure, glucose or the amount of exercise taken can be measured and data can be used to manage a person's health status in clinical practice. Data can be stored in mobile phones and transferred to clinics for further reference. This will be a new mode of managing chronic problems in the future. This subject will be covered as the 3rd topic for the meeting and up to date applications will be presented.

Hypertension still remains the leading cause of CV diseases in the world. We are equipped with good therapeutic treatments but due to various reasons, control of blood pressure levels remains inadequate in almost all parts of the world. Hypertension specialists, in collaboration with other health professionals including general practitioners, must work together to reduce global blood pressure levels. I hope the next meeting in Seoul to be a good chance to achieve this goal.

- Cheol-Ho Kim



Hypertension Seoul 2016

The 26th Scientific Meeting of the International Society of Hypertension
September 24(Sat) - 29(Thu), 2016 Coex, Seoul, Korea



Plenary Session: Perspective of hypertension in the future



Yutaka Imai, Japan
Remote BP monitoring
in hypertension care



Friedrich Luft, Germany
Tailored drug therapy for
arterial hypertension



Steven Steinhubl, USA
Hypertension management
in the era of digital information
and communication technologies

Seminar on Hypertension

Lars H. Lindholm
Editor, Hypertension News



Neil Poulter, Dorairaj Prabhakaran and Mark Caulfield recently published a Seminar on Hypertension in The Lancet [1]. The Seminar summarizes our current recommendations on how to interpret the risks of having high blood pressure as well as how to reduce these risks. It also compares current guidelines from different parts of the world and points at gaps in evidence and need for future trials.

Raised blood pressure is, after all, the biggest single contributor to the global burden of disease and to global mortality. Moreover, the number of people affected worldwide is expected to increase over the next decades. However, three-drug combinations of blood pressure lowering medication can control hypertension in about 90% of patients, but only if the drugs are affordable. Assessment of optimal therapy for different ethnic groups are needed but sadly often lacking today.

Management guidelines, presumably referring to the same databases, are inconsistent in terms of key areas of hypertension management. This is discussed in the Seminar where the different recommendations are compared. For example, the latest European guidelines differ from those from the UK in drug selection. They also differ from those issued by our Society (ISH) and the American Society of Hypertension (ASH), as shown in the table below. The continued promotion of beta-blockers as first line agents in the European guidelines is surprising in light of many reviews which came out against it, but, as pointed out in the Seminar, the European guidelines recommend beta-blockers only for subgroups of patients with compelling indications, such as angina, heart failure, or atrial fibrillation.

	Recommended drug combinations
NICE ^a	A+C
ESH/ESC ^b	A+C, A+D, C+D
ASH-ISH ^c	
Black	A+C, A+D, C+D
Non-black	A+C, A+D
JNC8 ^d	
Black	C+D
Non-black	A+C, A+D, C+D

NICE—National Institute for Health and Care Excellence. ESH—European Society of Hypertension. ESC—European Society of Cardiology. ASH—American Society of Hypertension. ISH—International Society of Hypertension. JNC8—Eighth Joint National Committee. A—ACE inhibitor or angiotensin-receptor blocker. C—calcium channel blocker. D—diuretic (including thiazides or thiazide like/type).

Table 2: Recommended two-drug combinations of antihypertensive drugs

[1] Reprinted with permission from Elsevier (The Lancet, [Volume 386, No. 9995](#), p801–812, 22 August 2015)

Another interesting observation made in the Seminar is that as development begins in a population, high blood pressure tends to emerge in the higher socioeconomic strata but when the country is developed, the relation inverts and low socioeconomic status is associated with higher blood pressure.

This is an excellent Seminar which I strongly recommend the ISH members to read.

- Lars H Lindholm

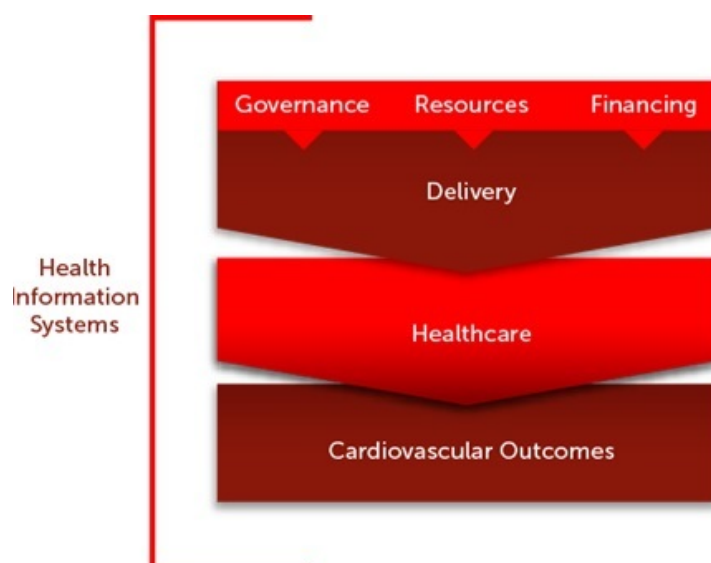
World Heart Federation Hypertension Roadmap: INTRODUCTION

Alma Adler, Science Officer, World Heart Federation - www.worldheart.org

The World Heart Federation (WHF) Roadmaps provide guidance for policymakers, healthcare professionals, patients, the private sector and the public on reducing premature mortality from cardiovascular disease (CVD), in alignment with the eight key targets proposed by World Health Organization (WHO) in 2013, which includes a 25% improvement in hypertension control.

The WHF Roadmaps serve as models for countries to develop or update national noncommunicable disease (NCD) action plans, using the framework provided by the World Health Organization's Global Action Plan (GAP) 2013-2020 [1]. They translate existing knowledge of best practices, barriers and solutions in hypertension control into practical strategies for improving cardiovascular health. We have focused on improved hypertension control as the most effective means to reach the overall mortality target, rather than the broader target related to reducing the prevalence of raised blood pressure, because of the clear evidence that blood pressure control in hypertensives will reduce CVD and there are large opportunities for avoiding premature CVD by such a focused approach. Although numerous guidelines and consensus statements recommend strategies for achieving hypertension control, globally the control of hypertension remains poor. The Roadmap aims to help countries, communities and stakeholders in changing these statistics by dramatically accelerating action to prevent and control hypertension.

The Hypertension Roadmap is primarily focused on health system issues and identifies roadblocks on the care pathway for patients with hypertension. To identify roadblocks and potential solutions, a framework has been adopted that was previously used to examine the relationship between the various health system levels and other cardiovascular conditions (Figure) [2].



We searched for systematic reviews in three online sources of evidence synthesis for policy, health system and knowledge translation evidence: the McMaster Health Systems Evidence portal; the Rx for Change database; and the Cochrane Effective Practice and Organization of Care (EPOC) Review Group. We received feedback from 91 participants who attended a meeting at the World Congress of Cardiology in Melbourne, Australia in May 2014. Furthermore, through an iterative online process and an online survey, we consulted with the WHF membership network of over 200 organizations. The final recommendations were reached by consensus of the Roadmap Writing Group.

The WHF Roadmaps give an overall picture, provide general recommendations and suggest a menu of policy options. To be applicable at a national level, the recommendations should be tailored (through local health system appraisals and multi-stakeholder policy dialogue) to that country's circumstances, achievements and capacity to create appropriate national action plans [3]. The Roadmaps provide general guidance but each country and region will need to customize the strategy to local economic and social circumstances and the particular structures of their health care systems.

- Alma Adler

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WHF Hypertension Roadmap: Global Perspectives



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An analysis of the World Heart Federation Raised Blood Pressure Roadmap for prevention and management of raised Blood Pressure using a health system approach - African commentary.

Hypertension constitutes a major health concern worldwide.¹ According to recent estimates, the worldwide prevalence of hypertension in 2000 was approximately 26% totalling about 1 billion people,² and along with the aging population, hypertension prevalence has been projected to increase to $\geq 29\%$ by 2025.²

Even though the problem of hypertension is a global one, the consequences are said to be more devastating in low and middle income countries (LMIC) like those of the sub-Saharan Africa region with nearly 80% of all cardiovascular mortality occurring also in these regions.³

Whereas the high income countries have been able to develop guidelines and policies towards blood pressure control, there are very few nations in LMIC that either have hypertension guidelines or documented policies to control blood pressure. Therefore this roadmap by the World Heart Federation which focuses on presenting practical steps for hypertension control is a welcome one, which will go a long way in bridging the gap between high and middle income/low income nations in terms of hypertension management control policy.

The Roadmap identifies roadblocks and potential solutions. For effective control of hypertension, this Roadmap precisely identifies four population groups: people who are unaware of their blood pressure status, those who are aware that they have raised blood pressure but their blood pressure remains uncontrolled, those who are aware that they have blood pressure but now controlled and finally those who are aware they do not have raised blood pressure.

After identifying the target population, the Roadmap went further to give practical steps for improving hypertension management which includes opportunistic screening so that people are aware of their blood pressure status, effective drug treatment for persons with systolic BP ≥ 160 mm Hg or diastolic BP ≥ 100 mm Hg, and individuals with systolic BP ≥ 140 mm Hg or diastolic BP \geq if they considered to be high risk.

On anti hypertensive medications, the use of generic rather than proprietary medications is encouraged to substantially reduce the cost of care, but with a caveat for the need to ensure quality generic medications.

Bearing in mind the holistic nature of health care delivery, this guideline identified health-system requirements to achieve blood pressure management targets and include human, physical and intellectual resources; healthcare delivery; healthcare recipients; financing; governance and information system.

With the availability of information technological tools globally, we found the suggestion for the use E-health particularly m-health in patient education in the guideline to be a very feasible one that if well applied could be a very useful tool in hypertension control. The simplicity in the presentation of this document makes it a very appealing one, and easy to adapt by different LMIC especially those in sub-Saharan African countries. However, bearing in mind the complexity of governance in these parts of the world and with fact that the health system is still often bedevilled by high burden of communicable diseases like human immunodeficiency virus infection, malaria and tuberculosis, and with the challenge of limited resources, there is a need for high power advocacy by both national hypertension and cardiac societies of various countries in order to put pressure on the various governments and regional organisations like African Union to adapt and modify this Roadmap to suit individual needs of each country. Finally, with the leadership of the Pan African Society of Cardiology (PASCAR) and dynamism of all other professional organizations, the WHF Roadmap sounds like the right tool at the right time to turn the big challenges of hypertension in Africa into immense opportunities.

- Dike Ojji and Anastase Dzudie

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WHF Hypertension Roadmap: Global Perspectives



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An analysis of the World Heart Federation Raised Blood Pressure Roadmap for prevention and management of raised Blood Pressure using a health system approach - Australasian commentary.

Hypertension Prevalence data still confirm that raised blood pressure remains an important risk factor both for high, middle and low income countries in the Asia-Pacific region. The Roadmap developed by the World Heart Federation certainly has value as a template for improved blood pressure care in the Asia Pacific region as it includes population and not just clinical approaches to the problem, and also recognises systemic factors that may mitigate against both areas to gain good population and individual blood pressure outcomes. It also contains modest, pragmatic and achievable goals for blood pressure control but from an Australasian perspective it represents a missed opportunity (1). The document is comprehensive and has due deference to varying healthcare systems and the ability to pay but by continuing to consider raised blood pressure as an isolated risk factor it 'short-changes' the purpose of blood pressure reduction which is to prevent major adverse cardiovascular events (MACE) rather than to just reduce blood pressure per se. The benefit of blood pressure reduction is reported in terms of relative risk reduction without reference to absolute risk reduction which better communicates who can have their MACE avoided.

The document starts well by using the term raised blood pressure in the heading rather than 'hypertension'. This fits with the recognition of the importance of risk stratification for treatment decision making rather than just simple blood pressure thresholds. It then reverts to the term 'hypertension' due to its historic and extensive use. This is the first opportunity missed. The second is the authors not taking an absolute risk approach because of "... uncertainty regarding how best to implement it in practice ..there are no randomized controlled data to support its use" and "may be too complicated (particularly in low and middle income countries)". The overall risk approach is included in recommendations when considering the blood pressure threshold to initiate medical treatment as well as the use of risk scores for cardiovascular prevention. Blood pressure lowering medication is recommended for all individuals with systolic blood pressure ≥ 160 mmHg or diastolic blood pressure ≥ 100 mmHg and all individuals with systolic blood pressure 140-159 mmHg or diastolic blood pressure 90-99 mmHg but if they are considered to be at overall high-risk, though just how this is determined is not specified. If it is physician estimation we know this is highly unreliable (2). Such stratification in the region requires recalibrated risk algorithms such as the Framingham Risk Score or local algorithms developed from good local datasets (3). We can see such initiatives in action in Australia and New Zealand (4, 5). Significantly the included guidelines do not contain any reference documents from the Western Pacific where a large proportion of humanity resides.

In summary while the Roadmap is a pragmatic and rational document, having threshold for treatments presented as a hybrid of blood pressure level and unquantified and unqualified risk status lets consumers in the Asia-Pacific down.

- Mark Nelson

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International Society of Hypertension

World Hypertension League



Dan Lackland

**President, World Hypertension League
Charleston, South Carolina, USA**

To help health care providers better care for the large population of hypertensive patients, World Hypertension League has led the development of a three-series education online program for global access the first series of 25 modules is now available for access and use. With hypertension detection, management and prevention as a true global public health and global issue, the availability of these education modules satisfies a critical need for health care providers throughout the world.

Presented by international experts, these modules are available online and are designed to improve healthcare providers' knowledge on specific areas related to hypertension. The on-demand modules can be completed online and offer free CME credit and low-cost to no-cost nursing credit.

"High blood pressure is a major factor and risk for strokes, heart disease, and end-stage renal disease, all conditions with excess risks around the world. The prevention, treatment and control of hypertension can have high impact on these conditions and risks. These modules present the state-of-the-art evidence for the management of elevated blood pressure and are presented by an internationally recognized faculty," according to Daniel T. Lackland, DrPH, president of the World Hypertension League.

The modules have been first made available through the online platform through the website at www.scahec.net/schools

The 25 education modules with 1.0 hour programs were organized and designed as enduring and available to any health professional. The next two 25-module series are currently being developed and will be available next year. The first series faculty are:

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Assessing Blood Pressure in the Clinic
- 2] Barry Carter, Pharm D
Team-Based Care to Improve Blood Pressure Control: The CAPTION Trial
- 3] William Cushman MD
Selection of Drugs in Hypertension: Does it make a difference?
- 4] William Cushman MD
Chlorthalidone versus HCTZ in Management of Hypertension
- 5] Gordon Defriese PhD
Enduring Hypertension Series: Quality Improvement Indicators and Management of Hypertension
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- Dan Lackland



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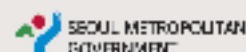
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