HYPERTENSION NEWS

March 2020

International Society of Hypertension

Opus 59

DOI: 10.30824/2003-1

IN THIS ISSUE

FROM THE EDITOR

BP medication most effective at night – a bedtime story?

LARS H LINDHOLM
Editor

DOI: 10.30824/2003-2

Dear ISH member,

About five months ago, Ramón Hermida and co-workers published a paper from Spain on the findings of the large (n=19,000) 'HYGIA Chronotherapy Trial' in the European Heart Journal, online[1]. The authors found that taking blood pressure (BP) lowering drugs at bedtime instead of in the morning lowered the risk of 'mortality of all causes' by 45%, myocardial infarction by 34%, stroke by 49%, and cardiovascular mortality by 54%. Findings, somewhat difficult to believe! The idea to give BP lowering medication at night instead of in the morning, however, is not a bad one, since cardiovascular events like stroke and myocardial infarction often happen in the morning. Hence, good BP control during the night should be beneficial.

The coverage of these findings on television, in newspapers, and on social media has been considerable and many patients have asked their doctors to help them interpret the results. Surprisingly, the paper has not yet appeared in print. We have asked Bo Carlberg and Mattias Brunström from Umeå, Sweden, two experienced reviewers of cardiovascular papers, to take a close look at the paper and share their thoughts with our readers (page 17). In summary, Bo Carlberg and Mattias Brunström have concerns for the way the data have been reported and recommend that the results of two other ongoing studies (Bed Med and TIME) are awaited before a change of clinical practice is considered. Moreover, since many patients are on a diuretic, a possible negative effect on treatment compliance by night-time medication should be considered.

In this comprehensive issue of Hypertension News, we have tried to make the Newsletter more 'reader friendly' by using a new template. The first page will remain the same for a year (four issues normally, with a DOI number for each issue) and then change. The texts have been divided into two halves with red and blue bars on top and at the bottom. Papers in the first half (red bars) carry individual DOI numbers. In the second (blue bars) half, we publish reports from meetings, society committee reports, updates, and adverts. One of my problems as Editor today, is to keep the number of pages in each issue at a reasonable level. With the number of downloads per issue going up steeply we get more and more texts to consider for publication.

On page 26, you will find Dylan Burger's data on how many readers have accessed the November 2019 issue (Opera 57-58). The results are just great! About 11,500 readers – the highest number ever – have so far accessed that issue. A few years ago, we would have been glad if we had reached a thousand! The members of the Editorial Board feel greatly encouraged by these figures and I would like to express my thanks to all the Board members, the ISH Secretariat, and the authors for their dedicated work.

Finally, I would like to recommend you to read Murray Epstein's obituary (page 8) of Norman Hollenberg – a really great man and an outstanding scientist!

Have a good read!

Reference

1. Hermida RC, Crespo JJ, Domínguez-Sardina M et al. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J 2019; doi: 10.1093/eurheartj/ehz754

Lars H Lindholm: lars.h.lindholm@umu.se

FROM THE ISH PRESIDENT

ALTA SCHUTTE
Faculty of Medicine, School of Public Health & Community Medicine
University of New South Wales, Sydney, Australia
ISH President 2018-2020

DOI: 10.30824/2003-3

Dear Members,

This year started with a bang! There was no easing into it... The coronavirus (COVID-19) has taken the world by huge surprise, and with all on alert (or in quarantine), it made me realise once again what an important role the media can play in activating the world in times of crisis. Alarming outbreaks such as SARS, Ebola and now COVID-19 are approached proactively and with the help of wide-ranging collaborative networks. And usually this ends in success.

In the background, however, raised blood pressure and hypertension continue to have an enormous global impact remaining the leading cause of death in the world. Without any alarm bells. Often low on the agenda of influential global agencies or governments – as well as the pharmaceutical industry – I encourage everyone reading this letter to continue your hard work. Never before has the time been better to collaborate, to innovate and to impact the lives of more than a billion humans. The ISH – a charity organisation – is busy with many activities to facilitate this process, so please join forces! Some of these activities I wish to highlight are:

1. Our main event: **The Joint ESH-ISH Scientific Meeting to be held in Glasgow** from 29 May to 1 June 2020. In January this year the Programme Committee already met in Glasgow, and developed a programme that would be of great interest to delegates from low to high income regions alike. We also visited the beautiful Scottish Exhibition Centre – a fascinating venue on the banks of the river Clyde. For detailed information, please visit the website: https://www.hypertension2020.org/

a. One of the major highlights at the Glasgow meeting will be the release of the highly anticipated **ISH 2020 Global Hypertension Practice Guidelines.** A global team of ISH Council Members have now spent many months in the development of these guidelines, undergoing two rounds of extensive reviews including more than 20 international reviewers from low, middle and high income regions. A unique approach followed in the guidelines is the inclusion of ***essential and optimal standards of care,*** to be followed based on the availability of resources. I encourage you to attend the meeting in Glasgow and attend this highlight session!

b. For the first time the ISH will also recognise and honour members of the Society who have distinguished themselves through excellence in clinical practice or research in the field of Hypertension by becoming **ISH Fellows (ISHF)**. Only ISH Professional members who have been a member of the Society for at least 2 years are eligible. I am very excited to honour these colleagues during the Awards session. More information here https://ish-world.com/membership/fellowship.htm

c. I can not omit to mention the excitement surrounding the activities of our next generation of scientists. The **New Investigator and Mentorship Committee** has ensured a number of oral and poster sessions (and awards!) during the meeting, giving opportunity to more upcoming scientists to present than ever before. Look out for the social events, which has been some of the best features at previous ISH Scientific Meetings!!

d. Along similar lines the **Women in Hypertension Research Committee** has ensured that there are an abundance of opportunities to network and showcase work in this area. There will be several sessions throughout the programme highlighting cardiovascular disease in women, as well as awards and networking opportunities.

2. I am very pleased to announce that the ISH is now involved with two free online training platforms for GPs, nurses, pharmacists, community health workers and implementers. The Society first joined forces with the Omron Academy https://omron.platform.co.nl/#/. In February 2020 a new platform with interactive learning experiences will also be launched where the ISH collaborated with other organisations and the Johns Hopkins Bloomberg School of Public Health. The platform, titled ***Fundamentals for Implementing a Hypertension Program in Resource-Constrained Settings*** is freely available from the ISH website, and also here: https://globalhypertensionathopkins.org/ I firmly believe that such programmes are essential in improving informed decision making and task sharing particularly in low- and middle-income countries where significant intervention is required.

I trust you will once again enjoy our Newsletter. I want to personnally thank Lars Lindholm and the Editorial Team for their energy and continued efforts in making our Newsletter a delightful read!

See you in Glasgow!

With my very best wishes,

Alta Schutte - alta.schutte@nwu.ac.za

THE SECRETARY'S VOICE

THOMAS UNGER
CARIM – School for Cardiovascular Research,
Maastricht University, Maastricht, The Netherlands

DOI: 10.30824/2003-4

The British philosopher and mathematician Alfred North Whitehead (1861-1947) has left us the following statement on the problem of translation: "I have often noticed that, if in an assembly of great scholars the topic of translations be introduced, they function as to their emotions and sentiments in exactly the same way as to decent people in the presence of a nasty sex problem. A mathematician has no scholastic respectability to lose..." (in: The Aims of Education, 1929), and in another essay in the same book: "Imagination is a contagious disease. It cannot be measured by the yard or weighed by the pound, and then delivered to the students by the faculty. It can only be communicated by a faculty whose members themselves wear their learning with imagination."

Seems that AN Whitehead didn't like the translationists very much and, of course, his statements did not refer to translational medicine, but I think they bear some general truth. Here we are: on one side those of us who see the only benefit of biomedical research in translating research results into clinical practice (translational medicine: from bench to bedside), on the other side those who strive imagination for curiosity per se. Further down

in this issue of "Hypertension News" I try to discuss the apparent dichotomy which can be overcome through integration of both concepts into a common strategy.

When it comes to hypertension research and the development of new antihypertensive drugs, it is quite reasonable to ask for more imagination. The complex pathological issue that we call hypertension has been a research topic for decades, yet, if we want to explain the etio-pathology of the 'hypertension disease' to our students, we are lost in details of vascular, endocrine, nervous, renal, cardiac dysfunction without being able to put all the pieces of the puzzle together.

We desperately need more curiosity, more imagination in hypertension research to open up new horizons.

A European initiative with scholars from the universities of Maastricht, Glasgow, Madrid, Padua and Paris, aiming at the formation of a "European Hypertension School", is trying to 'shift the minds', i.e. to transcend existing standards of doctoral training in hypertension research by unifying vascular and endocrine approaches and establishing the dynamics of this network. A hopeful beginning.

Thomas Unger - thomas.unger@maastrichtuniversity.nl

New, imaginative approaches are also badly needed in the development of new antihypertensive drugs. The enormous translational success over the last seven decades beginning with sympatholytics up to the inhibitors of the RAAS has blinded us giving rise to the contention that translation from research to clinical use has done its job perfectly well and that novel antihypertensives are not necessary anymore. Indeed, the problem of lowering elevated blood pressure has been solved in most cases, undoubtedly an enormous success; however, the issue of the 'hypertensive disease' with all its complex pathological ramifications still needs to be addressed. The interplay of the pathological undercurrents such as genetics, inflammation, fibrosis, immunity in the context of neuronal, endocrine renal, vascular and cardiac dysfunction requires the development of treatment strategies beyond the mere blood pressure reduction. This has already begun with the RAAS inhibitors with their beneficial effects on some of the hypertension-related pathologies but needs to be followed by new, more comprehensive drug targets. The recent development of the SGLT2-Inhibitors, dealing with diabetes and hypertension at the same time, is a good example telling us where to go.

In the end, imagination or curiosity and translation are not necessarily mutually exclusive entities in hypertension research and the development of antihypertensives: They need each other to progress our understanding of the hypertensive disease in all its complexity and to help us developing drugs against novel cardiovascular/metabolic targets.

ISH 2020 GLOBAL HYPERTENSION PRACTICE GUIDELINES

The International Society of Hypertension (ISH) is delighted to announce the release of the 2020 ISH Global Hypertension Practice Guidelines

These new Guidelines are unique: In line with the mission of ISH to provide global assistance in our fight against hypertension, they divide for the first time diagnostic and treatment procedures into OPTIMAL (for the affl ent regions) and ESSENTIAL (for low resource settings) standards of care. Optimal care refers to evidence-based standards of care articulated in recent guidelines, whereas essential standards recognize that optimal standards would not always be possible. Hence essential standards refer to minimum standards of care.

We are convinced that these new hypertension guidelines will benefit health providers and patients and help to raise the standards of hypertension management around the world.

The new ISH Hypertension Guidelines will be presented at the upcoming ESH/ISH Scientific Meeting in Glasgow, UK, during the plenary session (10:30 – 12:30) on Monday, 1 June 2020. www.hypertension2020.org

Make sure to attend this highlight of the congress !

Alta E. Schutte (President ISH) Thomas Unger (Chair, ISH Guidelines Committee)

HOT OFF THE PRESS: CLINICAL

SGLT2 inhibition reduces blood pressure and left ventricular mass

THOMAS KAHAN

Karolinska Institutet, Department of Clinical Sciences, Danderyd Hospital, Division of Cardiovascular Medicine, & Department of Cardiology, Danderyd University Hospital Corporation, Stockholm, Sweden

DOI: 10.30824/2003-5

Sodium-glucose cotransporter 2 (SGLT2) inhibitors were developed to reduce blood glucose levels in patients with poorly controlled type 2 diabetes. More important, however, is their ability to reduce cardiovascular morbidity and mortality in patients with type 2 diabetes and atherosclerotic disease; and this benefit may be regardless of the presence or absence of diabetes (at least among patients with heart failure and a reduced ejection fraction). There are several proposed mechanisms by which SGLT2 inhibitors may exert their effects to reduce cardiovascular events, including improved glucose control, diuresis, vasodilatation with reductions in blood pressure, preload and afterload, and alterations in cardiomyocyte function [1,2].

Recently, Verma and colleagues[3] reported on the effects of the SGLT2 inhibitor empaglifozin on blood pressure and left ventricular mass in patients with type 2 diabetes and coronary artery disease. The EMPA-HEART Cardiolink-6 trial randomized 97 patients (93% men) to double blind treatment with 10 mg empaglifozin od or placebo for six months; 90 patients were available for outcome evaluation. Mean age was of 63 years, duration of type 2 diabetes 11 years, glycated haemoglobin 8.0%, estimated glomerular filtration rate 88 mL/min/1.73 m2. Mean 24 h ambulatory blood pressure was 139/80 and 138/88 mm Hg, and left ventricular mass index (by cardiac magnetic resonance imaging) 59 and 62 g/m2 in the empaglifozin and the placebo group, respectively. Primary outcome of the study was the change in left ventricular mass index during six months.

Compared to placebo, empaglifozin reduced 24 h ambulatory systolic and diastolic blood pressure by (mean between group difference and 95% CI) –6.8 [–11.2; –2.3] mm Hg (P=0.003) and –3.2 [–5.8; –0.6] mm Hg (P=0.016). Also left ventricular mass index was reduced more by empaglifozin than by placebo, –3.4 [–5.9; –0.8] g/m2 (P=0.01). The changes in glycated haemoglobin by empaglifozin and placebo were small (–0.4 and –0.3%, respectively).

This is the first randomized clinical trail to show that empaglifozin reduces LV mass. Furthermore, this study confirms findings of a reduction in ambulatory blood pressure by SGLT2 inhibitors[4]. The blood pressure reduction is not trivial. Of note, the reduction in left ventricular mass did not relate to changes in blood pressure, suggesting an effect beyond that of blood pressure reduction alone. A similar dissociation between effects on blood pressure and on myocardial geometry and function has also been observed when antihypertensive drug classes have been compared. Hypertensive heart disease is a strong cardiovascular risk factor, and regression of left ventricular mass reduces future cardiovascular events[5]. Thus, the results of the current study may help our understanding the mechanism(s) for the reduction in cardiovascular events in patients treated with SGLT2 inhibitors.

Thomas Kahan - thomas.kahan@sll.se

References:

1.Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia 2018; 61:2108–2117. doi: 10.1007/s00125-018-4670-7

2. Chin KL, Ofori-Asenso R, Hopper I, et al. Potential mechanisms underlying the cardiovascular benefits of sodium glucose cotransporter 2 inhibitors: a systematic review of data from preclinical studies. Cardiovasc Res 2019;115:266–276. doi: 10.1093/cvr/cvy295

3. Verma S, Mazer CD, Yan AT, et al. Effect of empagliflozin on left ventricular mass in patients with type 2 diabetes mellitus and coronary artery disease: The EMPA-HEART CardioLink-6 randomized clinical trial. Circulation 2019;140:1693-1702. doi: 10.1161/CIRCULATIONAHA.119.042375

4. Kario K, Okada K, Kato M, et al. 24-hour blood pressure-lowering effect of an SGLT-2 inhibitor in patients with diabetes and uncontrolled nocturnal hypertension: results from the randomized, placebo-controlled SACRA study. Circulation 2019;139:2089–2097. doi: 10.1161/CIRCULATIONAHA.118.037076

5. Jekell A, Nilsson PM, Kahan T. Treatment of hypertensive left ventricular hypertrophy. Curr Pharm Des 2018;24:4391-4396. doi: 10.2174/1381612825666181203092918

HOT OFF THE PRESS: BASIC

Circulating Extracellular Vesicles in Normotension Restrain Vasodilation in Resistance Arteries

DYLAN BURGER

Ottawa Hospital Research Institute

Ottawa, Canada

DOI: 10.30824/2003-6

Extracellular vesicles (EVs) are particles naturally released from a cell that are surrounded by a lipid bilayer and lack replicative capacity [1]. In recent years they have received significant attention as both biomarkers and mediators of intercellular signaling. In particular, circulating populations of large extracellular vesicles (i.e. microparticles or microvesicles) are elevated in conditions of vascular injury, strongly correlated with measures of vascular health, and predictive of future adverse cardiovascular events [2]. Our laboratory, and others, have also shown that large EVs can serve as vectors for intercellular communication leading to endothelial injury [3].

Interestingly, while there has been considerable interest in the impact of various cardiovascular conditions on circulating EVs, the impact of hypertension has been comparatively understudied. In the January issue of Hypertension work from the laboratory of Dr. Uta Erdbrügger addresses this critical gap in knowledge [4]. Good et al examined levels of circulating EVs in plasma from spontaneously hypertensive rats (SHR) and normotensive Wistar Kyoto Rats (WKY). At 12 weeks of age they observed significant increases in levels of circulating large EVs arising from endothelial cells as well as leukocytes. More importantly, they provided the first functional analysis of the impact of hypertension on the bioactivity of circulating EVs.

First, they observed that large EVs isolated from normotensive rats reduced vasodilation in isolated resistance arteries. This observation was consistent with previous reports from Brodsky et al. [5] and others. Most interestingly however was the observation that this impairment in vasorelaxation is absent in large EVs isolated from hypertensive rats. This was also true for EVs isolated from normotensive vs hypertensive human subjects. The authors also

confirmed that this alteration in EV bioactivity is not seen in SHR prior to blood pressure elevation: EVs from 6 week SHRs (normotensive) are capable of impairing vasorelaxation but EVs from 12 week SHRs (hypertensive) lose this ability. Thus, as the authors state, "alteration of EV function occurs during or after the development of hypertension in SHR animals".

The precise mechanisms responsible for this alteration are unclear, but the authors did report that delipidation of SHR EVs restored their ability to impair vasorelaxation. They speculate that the lack of an effect on vasodilation may be an adaptive response to the hypertension whereby the EVs are rendered less antivasodilatory.

It is interesting to note that this effect is somewhat different than that seen in other systems. Work from Jansen et al. [6] and our group [3] has shown that the antivasodilatory effects of endothelial-derived large EVs is increased when formed under high glucose conditions. Thus these effects appear to be quite disease-specific and further study is clearly needed to understand how EVs are altered by cardiovascular disease and the impact of this on in vivo endothelial function.

There are a number of limitations to this work which are well highlighted in the associated editorial for the article and need not be discussed here [7].

However one pressing question that I think merits investigation is whether antihypertensive treatment has any impact on EV bioactivity and if there differences between antihypertensive agents.

This would appear to be a logical next step for this work. Nevertheless this study represents a critical advance in understanding the impact of hypertension on EVs and the role of EVs in regulating vascular function in health and disease.

Dylan Burger - dburger@uottawa.ca

References:

1 Thery et al (2018) J Extracell Ves https://doi.org/10.1080/20013078.2018.1535750

2 Burger et al (2013) Clin Sci https://doi.org/10.1042/CS20120309

3 Burger et al. (2017) Diabetologia https://doi.org/10.1007/s00125-017-4331-2

4 Good et al (2020) Hypertension https://doi.org/10.1161/HYPERTENSIONAHA.119.13363

5 Brodsky et al. (2004) Am J Physiol Heart Circ Physiol https://doi.org/10.1152/ajpheart.01172.2003

6 Jansen et al. (2013) https://doi.org/10.1093/cvr/cvt013

7 Baher (2020) https://doi.org/10.1161/HYPERTENSIONAHA.119.13549

OBITUARY OF NORMAN K. HOLLENBERG

(1936-2020)

MURRAY EPSTEIN

Professor of Medicine emeritus, Division of Nephrology and Hypertension
University of Miami Miller School of Medicine, Miami, Florida

Norman K Hollenberg

Norman K. Hollenberg, M.D., Ph.D., renowned leader in cardiovascular medicine and hypertension, passed away on January 15th, 2020, after a long illness. Dr. Hollenberg was Professor of Medicine and Radiology and Director Director of the Physiologic Research Division in the Department of Radiology at the Brigham and Women's Hospital and Harvard Medical School. He leaves a remarkable lasting legacy in nephrology, hypertension and in medicine broadly.

Dr. Hollenberg was born in Winnipeg, Manitoba, and was a member of one of the most illustrious medical families in Canada. He earned his undergraduate and medical degrees at the University of Manitoba. His Ph.D. in Pharmacology was obtained under Professor Börje Uvnäs at the Karolinska Institute in Stockholm, Sweden and Professor Mark Nickerson at the University of Manitoba and McGill University in Canada.

After a medical residency in Winnipeg Norm completed his nephrology fellowship in the Cardiorenal Unit of the Peter Bent Brigham Hospital in Boston, under the tutelage of John Merrill, M.D., considered by many to be the renowned founder of modern nephrology as we know it today. Although Uvnäs, Nickerson and Merrill all had an enormous influence on Norm's approach to biology and medicine, his value system, and his dedication to academic pursuits, I believe that Mark Nickerson and the academic environment at the University of Manitoba had the most profound impact in nurturing Norm's scientific discipline and thirst for knowledge.

I first met Norm when I arrived at the Peter Bent Brigham in July of 1966 to start my nephrology fellowship. Our Chief, John Merrill, tasked Norm to "bring me up to speed". I collaborated with Norm in his early studies of intrarenal hemodynamics in both healthy individuals and those with a wide array of diseases[1,2,3]. Our initial studies utilizing the companion modalities of selective renal arteriography and 133 xenon washout curves succeeded in demonstrating that a redistribution of intrarenal perfusion with resultant cortical ischemia mediated acute renal failure[1]. We subsequently succeeded in extending this investigative approach to studies of patients with Hepatorenal Syndrome and demonstrated a preferential reduction in renal cortical perfusion[3]. Subsequently we succeeded in conducting postmortem angiography in the kidneys of 5 patients studied during life. Our findings disclosed a striking normalization of the vascular abnormalities. In concert these studies provided compelling evidence for the functional basis of the renal failure of patients with decompensated cirrhosis.

Norm and I became not only research collaborators, but virtual brothers, frequently traveling worldwide to attend medical congresses, and sharing life cycle events.

From its beginning, Dr. Hollenberg's career focused on the kidney. Over an academic career exceeding 50 years, his extensive and groundbreaking research solidified his position as one of the true giants in the regulation of the renal circulation in both health and disease. Norm's research productivity was enormous

and he authored more than 600 publications. His many accomplishments included documenting the factors (both hormonal and environmental) that control the renal circulation, and delineation of the mechanisms whereby these mediators modulate renal function to subserve both volume and sodium homeostasis. Concomitantly he assessed how dysfunction and dysregulation of these modulators promote the development of a wide array of disease states including hypertension, diabetic nephropathy and congestive heart failure [4]. Much of his research was the product of decades-long collaboration with his close friend, Dr. Gordon Williams, who is Professor of Medicine at Harvard Medical School as well as the Director of the Hormonal Mechanisms of Cardiovascular Injury Laboratory at Harvard's Brigham and Women's Hospital.

Dr. Hollenberg's contributions to the current paradigms for the management and treatment of hypertension were profound. He was a pioneer in the development of new therapeutic agents that modulated the renin-angiotensin system, and their application in the treatment of a wide array of diseases in order to attenuate, abrogate and even reverse many cardiovascular and renal disorders. He was the first investigator to administer an ACE inhibitor to a patient with congestive heart failure, at a time when the prevailing wisdom asserted that this new drug would be fatal. Norm proved the "nay sayers" wrong. The patient was able to ambulate and ultimately be discharged to return home.

Dr. Hollenberg' s groundbreaking research was complemented by concurrent studies by his life-long friend, Professor Mattias Aurell of the Sahlgrenska Hospital and the University of Gothenburg, Sweden who was the first investigator to demonstrate that infusions of subpressor doses of angiotensin II markedly increased sodium reabsorption in the renal tubules in humans.

Dr. Hollenberg's contributions to the world of hypertension were profound. As a consequence of his insights and formidable clinical investigations, Dr. Hollenberg's research catalyzed the development of two important classes of drugs, ACE inhibitors and angiotensin receptor blockers, which constitute the mainstay of our current treatment of hypertension. Today these two major classes of medications are prescribed to millions of patients for the treatment of hypertension, for afterload reduction in the treatment of congestive heart failure and for abrogating and attenuating progression of chronic kidney disease, particularly in patients with diabetes mellitus.

An additional research interest of Dr. Hollenberg, which has mesmerized me and many members of the International society of Hypertension, focused on the vascular effects of flavonoid-rich cocoa. Of note, cocoa is the richest known source of flavanols. Norm's studies married medical anthropology and the important arena of vascular responsiveness [5]. A true medical detective – Dr. Hollenberg was intrigued by initial reports of low to normal blood pressures of the Kuna Amerinds of the San Blas islands of Panama. Norm posed an obvious question; was the absence of hypertension attributable to protective genes or environmental factors. Consequently, Hollenberg and colleagues initiated a series of comprehensive studies of the Kuna Amerinds that provided the link to our understanding of this clinical observation, increased oxidative stress and impaired nitric oxide bioavailability to be the principal features of vascular dysfunction, detectable as abnormal coronary vasomotion[5]. Based on Dr. Hollenberg's seminal research, a large clinical trial is currently underway to determine whether flavanols found in chocolate may confer health benefits, including lowering blood pressure and the risk for cardiovascular disease, the COSMOS study - (The COcoa Supplement and Multivitamin Outcomes Study).

Beyond research, Dr. Hollenberg had a special interest in medical education and teaching. Norm's door was always open in welcome. Over the decades, he mentored countless students and fellows, many of whom became professors and leaders in their communities around the world. He served as one of four Associate Editors at the New England Journal of Medicine for seventeen years. He also served on the editorial boards of a dozen journals, as the Editor of the Atlas of Hypertension and importantly for the members of ISH, the longtime Editor-In-Chief of Current Hypertension Reports.

The world of medicine, especially the Hypertension and Nephrology communities, have lost one of its giants. Norman Hollenberg was truly one of the great leaders in hypertension and renal medicine. The world has lost a kind and caring human being.

His wisdom and deep warmth are legacies that will be treasured by the members of the international Society of Hypertension, and medicine at large. On a personal level, Norm served informally as my longtime consigliore and confidant and we enjoyed a warm and extended friendship, sharing many life cycle events.

Norman Hollenberg is survived by his daughter Ilana Hollenberg, his son David Hollenberg, and his beloved and loving wife of 35 years, Deborah, who stayed close by his side, caring for him with all her love and strength until he left us.

Murray Epstein - murraye@gate.net

Photograph by Christer Andersson, Umeå, Sweden

Acknowledgments:

The author thanks Drs. James R. Oster and David L. Epstein, for their thoughtful assistance and insights in the preparation of this manuscript.

References:

1.Hollenberg NK, Epstein M, Basch RI, Oken DE, Merrill JP. Acute oliguric renal failure in man: evidence for preferential renal cortical ischemia. Medicine 47:455-474, 1968. doi: 10.1097/00005792-196811000-00001

2.Hollenberg NK, Epstein M, Basch RI, Merrill JP. "No man's land" of the renal vasculature: an arteriographic and hemodynamic assessment of the interlobar and arcuate arteries in essential and accelerated hypertension. Am J Med. 47:845-854, 1969. doi: 10.1016/0002-9343(69)90199-5

3.Epstein M, Berk DP, Hollenberg NK, Adams DF, Chalmers TC, Abrams HL, Merrill JP. Renal failure in the patient with cirrhosis; the role of active vasoconstriction. Am J Med. 49:175-184, 1970. doi: 10.1016/s0002-9343(70)80073-0

4.Hollenberg NK, Moore T, Shoback D, Redgrave J Rabinowe S, Williams GH. Abnormal renal sodium handling in essential hypertension: Relation to failure of renal and adrenal modulation of responses to angiotensin II. Amer J Med 81: 412-418, 1986. doi: 10.1016/0002-9343(86)90291-3

5.Fisher ND, Hughes M, Gerhard-Herman M, Hollenberg NK. Flavanol-rich cocoa induces nitric-oxide-dependent vasodilation in healthy humans. J Hypertens. 2003 Dec;21(12):2281-6. doi: 10.1097/00004872-200312000-00016

INVITED PAPER:

Some thoughts about translational research

THOMAS UNGER
CARIM – School for Cardiovascular Research,
Maastricht University, Maastricht, The Netherlands

DOI: 10.30824/2003-7

"Translational research" is a buzzword of the day, but what does it mean? Let's approach the question in two different ways:

Educated in the traditional German ***Bildungssystem*** – the German word ***Bildung*** cannot be literally translated (there is that word again) into the English education; it goes beyond, sometimes defined as "what remains when you have forgotten everything that you have learned" - I would start with the etymological approach. The Latin verb ***transferre*** means that you carry something from one side to the other of, for instance, the Alps (cf. ***Gallia trans-alpina***) or another obstacle. In doing this, there may be an advantage: you may conquer a new territory, you may learn something you have never heard of, you may combine your ancient, traditional knowledge with new insights and reach a higher level of wisdom. In order to achieve this, however, there must be something already in existence to be transferred, "a thing".

The second approach to defining "translation" is, of course, the one that most of us use: Wikipedia. What does the oracle say with respect to translational research?

Translational research (TR) - often used interchangeably with translational medicine - is a highly interdisciplinary field, the primary goal of which is to coalesce assets of various natures within the individual pillars in order to improve the global healthcare system significantly. The goal of translational medicine is to combine disciplines, resources, expertise, and techniques within these pillars to promote enhancements in prevention, diagnosis, and therapies.[1]

The citation refers to a 2014 article by Cohrs et al. "Translational Medicine definition by the European Society for Translational Medicine (EUSTIM)". EUSTIM further defines translational medicine as "***an interdisciplinary branch of the biomedical field supported by three main pillars: benchside, bedside and community***."[2]

This gives us enough material to chew on for a few minutes.

Forget for a moment whether "translational research" is interchangeable with "translational medicine"; this is clearly not always the case, since both (bio)medical research and medicine are still distinct, although sometimes overlapping, areas. Let's concentrate on the interdisciplinarity of translational research. What this means is not only that scientists from different fields of basic research, e.g. a molecular biologist and a pharmacologist working together to develop a new therapeutic molecule, as this needs to be done anyway to be successful these days, but, rather, the interdisciplinary approach refers to the aforementioned pillars: first, from bench to bedside and then, maybe, to the community.

From bench to bedside: something, "a thing" that has been developed, an idea, a technique, a methodological approach, is transferred (here is the word again) to the clinic, is subsequently investigated in patients, and, if successful, further disseminated to the community.

The first step, from bench to bedside, certainly makes sense. Biomedical research draws its justification, to a large extent, from the principle of developing applications in order to help sick people or to prevent disease. We strive to invent; to develop new diagnostic, prognostic and therapeutic approaches; to drive the medical field forward and to benefit patients.

The second step, translating the clinical application of a new drug or a new procedure or method to the community, is less straightforward. Indeed, current members of the "educated" community claim their right to receive all of the information available on biomedical progress, since, in the end, it is they, the taxpayers, who fund most of that research, at least to the extent that academia is involved. In this translational step, the sender and the receiver are often not well attuned to each other, which opens the door for misunderstandings and false expectations, since the community (receiver) cannot be expected to command the same knowledge and expertise as the information–providing scientists (sender), despite Wikipedia and the like. Good examples are the hope-raising monthly reports of novel treatments for Alzheimer's disease that seldom survive the drying of the ink on the paper on which they are printed (if printing is still used for such messages).

Therefore, while I agree that scientists need to open their Pandora's boxes to the scrutiny of the tax-paying community, I acknowledge that this pillar (here translational research has really turned into translational medicine) is quite a delicate issue, requiring serious efforts from both sides to synchronize sender and receiver.

However, there is something else in the world of science, something which is entirely un-translational: the conduct of research driven solely by curiosity.

Curiosity–driven research is not primarily application-oriented. It springs from the zest to discover what is holding the world together, in a first approach, without respecting boundaries or considering consequences. In my view, scientists need to be given the chance to follow their curiosity, sometimes even serendipity, to think the hitherto unthinkable, to bind together thoughts and approaches previously separated, to have never-heard-of, fantastic ideas under the morning shower or while shaving, and try them out.

When the great scientific discoveries and achievements of the past are evaluated, many, if not all, were born out of a combination of the knowledge of the time with one or more unconventional ideas, resulting in the creation of a new paradigm, a new "thing".

One example, in which I participated myself, may serve to illustrate this: the venom of the Brazilian snake ***Bothrops jararaca*** contains certain peptides. Brazilian researchers found out that one or more of these peptides inhibit, among other things, the enzymatic degradation of another peptide present in our body, bradykinin, thus potentiating the actions of the latter. This was an interesting finding, but in and of itself, not sensational. The "living spirit" entered the game when somebody thought of linking the bradykinin degradation to another well-known peptide system, the renin-angiotensin system (RAS), by demonstrating that the bradykinin degrading enzyme, kininase II, was identical to the angiotensin converting enzyme (ACE), which splits off the blood pressure increasing peptide, angiotensin II, from its precursor. With this intellectual bridge to the RAS, the ground was paved for the development of non-peptide small molecules, ACE-inhibitors, which inhibit the formation of angiotensin II (and potentiate kinins). ACE inhibitors were subsequently introduced into the clinic with tremendous success for all kinds of cardiovascular indications and, even, beyond. What is important in this story, however, is this: years of research passed within a curiosity-driven period without translational moves, until the time and the "thing" were ready for drug development, i.e. the translational, application-oriented phase.

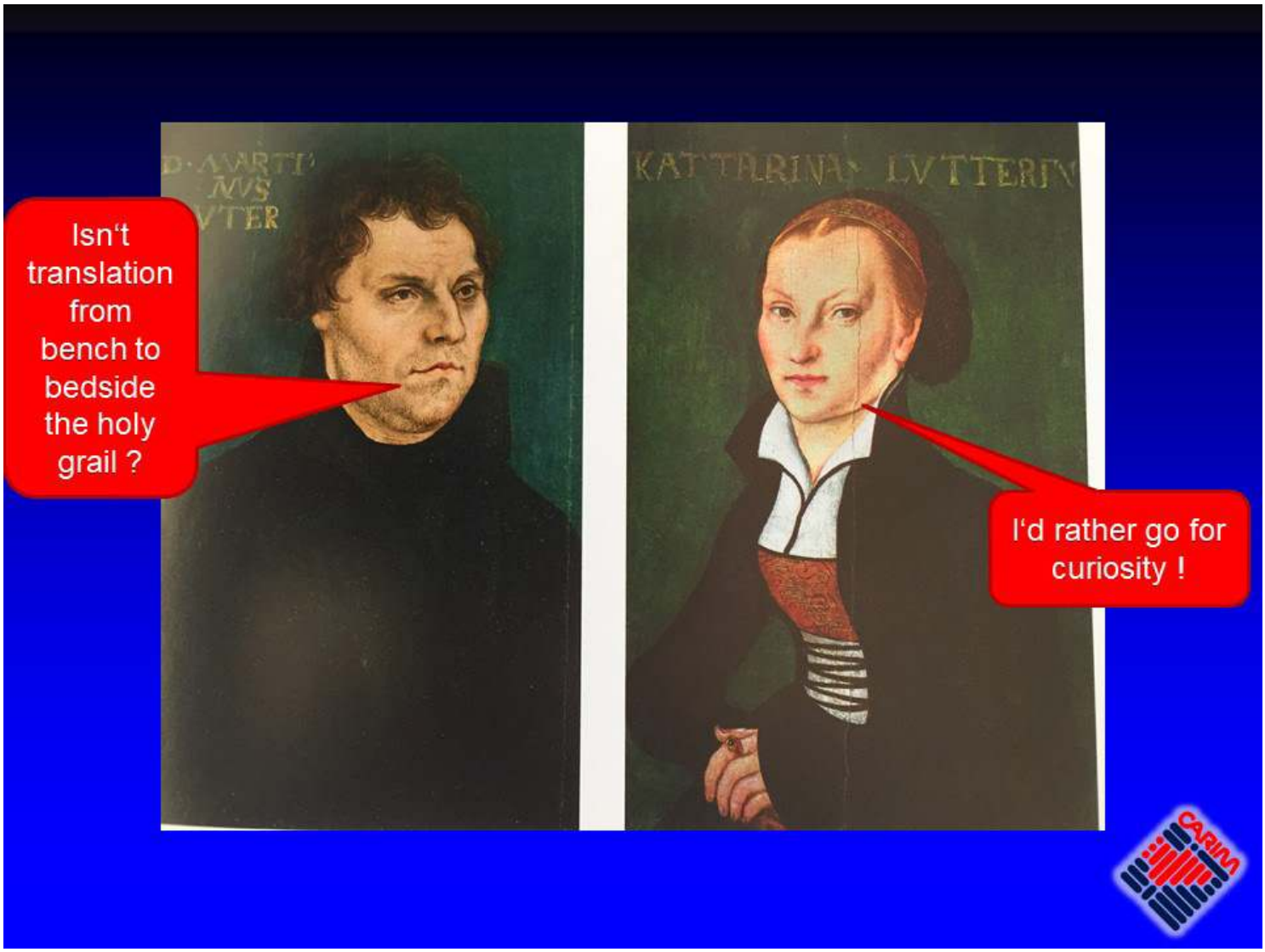
The above example, and many others, tells us that there seems to be a pre-phase driven by curiosity and creativity until the product of this phase finally enters the translational path. Is this curiosity-driven first step a prerequisite for translation? I would say, in most cases, yes: you need to create the "thing", a (drug)target or a novel method or procedure, first and then shape it into an object of translation and render it clinically applicable. On the other hand, does the product of curiosity driven research always end up in translation? Not necessarily, but it happens quite often. To sharpen the argument: does curiosity-driven research inevitably have to end in translation because researchers have a responsibility towards official funding sources or society at large? My answer to this is a definite no.

Curiosity-driven research needs to exist in its own right, not merely because it's the predecessor of the translational. It exists as an expression of the irrepressible human drive to deepen our knowledge about the world, as an expression of the living human spirit. It may even possess an intrinsic aesthetic value. Similarly, the results of our scientific curiosity have their own value, whether or not they will, in the short or long term, engender translational exercises or even give rise to ethical concerns with which scientists and the community will have to deal.

These results serve what is called "gain of knowledge" and are regarded as inherently valuable in our culture. Perhaps not coincidentally, the landmark publications in the leading scientific journals, such as Nature, Science, Cell and the like, usually deal with topics in the "curiosity driven" category.

Thus, the call is out: copiously water all of the flowers growing in the field of creative cardiovascular research; watch them carefully, but let them bloom in their own right; don't be disappointed if not all of them can be picked and bound together, but, simultaneously, help those selected on their way to become part of the rich bouquet of translational medicine.

Thomas Unger - thomas.unger@maastrichtuniversity.nl



[1]Source: https://en.wikipedia.org/wiki/Translational_research

[2]Cohrs, Randall J.; Martin, Tyler; Ghahramani, Parviz; Bidaut, Luc; Higgins, Paul J.; Shahzad, Aamir. "Translational Medicine definition by the European Society for Translational Medicine". New Horizons in Translational Medicine. 2 (3): 86–88. doi:10.1016/j.nhtm.2014.12.002

INVITED PAPER:

A stepwise personalized approach to blood pressure management considering circadian effects and cardiovascular prognosis

KAZUOMI KARIO

Division of Cardiovascular Medicine, Department of Medicine, Jichi Medical University School of Medicine, Tochigi, Japan
The Hypertension Cardiovascular Outcome Prevention and Evidence in Asia (HOPE Asia) Network, Tokyo, Japan

DOI: 10.30824/2003-8

There are significant circadian rhythms in blood pressure (BP). For example, nocturnal BP falls by 10% to 20% of daytime BP (normal dipper pattern). This circadian rhythm is determined partly by the intrinsic rhythm of central and peripheral clock genes, which regulate the neurohumoral factors and cardiovascular systems, but predominantly by the sleep–wake behavioral pattern. Several environmental and behavioral factors and pathological diseases affect this circadian rhythm of BP (Figure 1).[1] Since O'Brian first described the division of nocturnal BP patterns into nondippers (diminished nocturnal BP fall) and dippers,[2] the classification has expanded to include 4 nocturnal BP dipping patterns: the dipper, non-dipper, riser, and extreme dipper patterns.[1] In addition to these circadian patterns, individual 24-hr BP patterns are affected by various shorter-term BP variabilities, such as morning BP surge, physical or psychological stress-induced daytime BP, and night-time BP surges triggered by obstructive sleep apnea (OSA) episodes, arousal, rapid-eye-movement sleep, and nocturnal behaviors (nocturia).

Disrupted circadian patterns, such as non-dipper (reduced nighttime BP fall) and riser (higher nighttime BP than daytime BP) patterns, have been well-established to confer risk for cardiovascular disease (CVD) events and organ damage in both community-dwelling subjects and hypertensive patients.[1] In addition, we first described extreme-dippers with excessive nocturnal BP fall as an additional pathological pattern of disrupted circadian rhythm, with advanced silent cerebral disease (silent cerebral infarct and white matter disease) demonstrated by brain MRI, and with increased prognostic risk of subsequent clinically overt stroke events based on a prospective study of elderly hypertensive patients.[3,4] A recent meta-analysis demonstrated that an extreme-dipper pattern is associated with incidence of CVD risk in very elderly patients.[5]

Antihypertensive medications that affect circadian BP variation might modify the CVD prognosis. A recent clinical trial showed the marked benefit of bedtime dosing of antihypertensive drugs compared with waking dosing on the cardiovascular prognosis in hypertensive patients.[6] In this study, the CVD events were markedly reduced by 56% for CVD death, 34% for myocardial infarction, 42% for heart failure, and 49% for stroke in the bedtime-dosing arm when compared with the wakening-dosing arm, even after controlling for nighttime BP and nighttime BP falls. There are several points worth discussing in regard to this study. First, the degree of risk reduction of CVD events was much higher than expected from the previous evidence. These benefits of CVD event reduction correspond to an office BP reduction of approximately 20 mmHg systolic and 10 mmHg diastolic according to the results of a systematic review of previous randomized controlled trials of antihypertensive drugs.[7] The impact of nocturnal hypertension is greater in medicated hypertensive patients than in the unmedicated patients, suggesting that a significant number of cases of uncontrolled nocturnal hypertension even among patients with well-controlled daytime BP by conventional office BP-guided antihypertensive approach. As estimated from the International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO), a 50% difference of CVD events corresponds to a 40 mmHg difference in nighttime BP in medicated patients.[8] However, in a recent clinical cross-over trial of evening (6 pm-11 pm) vs morning (6 am-11 am) dosing among hypertensive patients with reasonably well-controlled BP, the timing of antihypertensive drug administration (morning or evening) did not affect mean 24-hr or

office BP levels.[9] What mechanisms of non-specific bedtime dosing contribute to such a marked benefit without difference in the nighttime BP level or nocturnal dipping status? In consideration of these disparate results, any standardized change in the dosing of all antihypertensive drugs from morning to bedtime for all hypertensive patients should wait until the results of future clinical trials.

Instead, I would like propose a STEpwise-Personalized 24-hr approach (STEP24 approach) for the management of hypertension, targeting morning BP first and nighttime BP second (***Figure 2***) to achieve perfect 24-hr BP control than the standardized bedtime dosing to achieve perfect 24-hr BP control in clinical practice. To reduce morning BP effectively, long-acting antihypertensive drugs should be considered a first step, and if morning BP is not controlled, then bedtime-dosing or twice-daily dosing of antihypertensive medication might be a second step. After controlling morning BP, uncontrolled nocturnal hypertension would seem to be the next logical target. Conventionally, nighttime BP has been measured by ambulatory BP monitoring in clinical practice. Recently, we demonstrated that nocturnal hypertension evaluated by home BP monitoring was associated with poor prognosis of stroke and coronary artery disease events in the J-HOP (Japan Morning Surge-Home Blood Pressure) Nocturnal BP study.[10] Thus, nocturnal home BP measurement could be useful for the STEP24 approach in clinical practice.

Theoretically, several different approaches involving pressor mechanisms could be used to control nocturnal BP effectively (***Figure 2***).[1] The effectiveness of these approaches should be tested in future clinical studies. For example, for salt-sensitive non-dippers with increased circulating volume, salt restriction, diuretics, and new drugs such as a sodium-glucose cotransporter 2 inhibitor (SGLT2i) and angiotensin receptor neprilysin inhibitor (ARNi)seem to be effective. Calcium channel blockers would be preferable for patients with structural nocturnal hypertension with vascular remodeling of the small and large arteries. For patients with sympathetic hyperactivity exhibiting nocturnal and morning hypertension, renal denervation and bedtime dosing of sympatholytic drugs such as doxazosin and carvedilol are effective to suppress the nighttime BP and morning and sleep BP surges.

To achieve perfect BP control in consideration of the different circadian BP variabilities, a personalized approach would essentially be the best method on the top of guideline-driven standardized approach, to minimize the CVD event risk. Given the marked and continuing advances in information and communication technology, a personalized approach based on the 24-hr BP profile accurately and frequently measured by a wearable BP-monitoring device could be expected to dramatically change the quality of hypertension management in the near future.

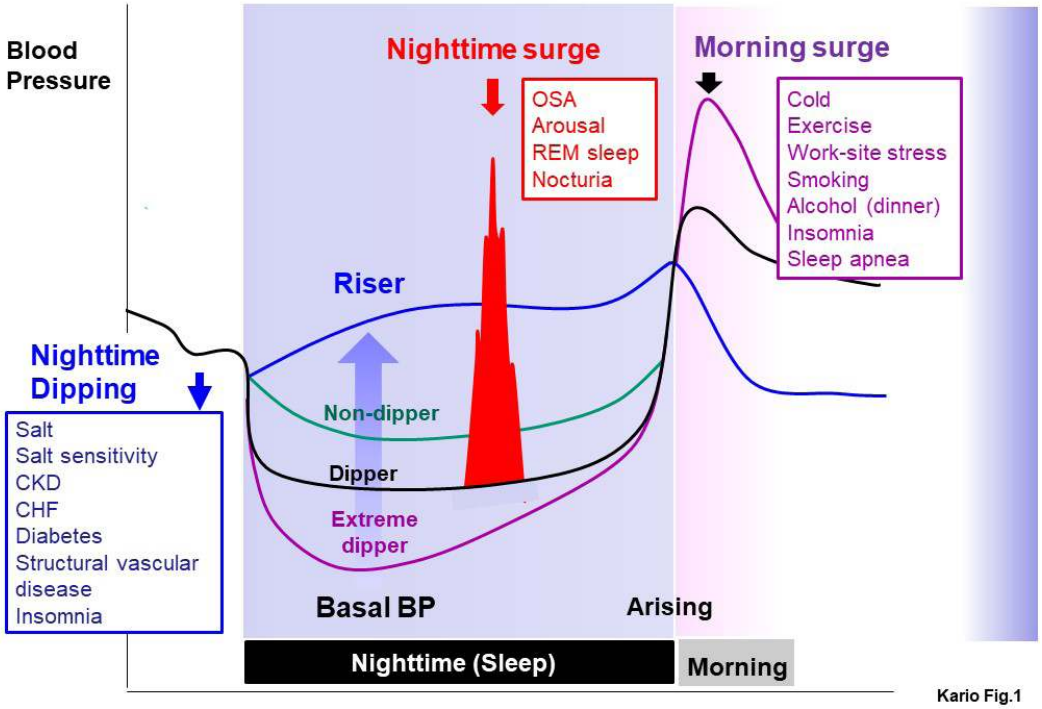


Figure 1. Components of nocturnal hypertension and determinants – nighttime dipping status and surge in blood pressure. CKD, chronic kidney disease; CHF, chronic heart failure; BP, blood pressure; REM, rapid eye movement. [1]

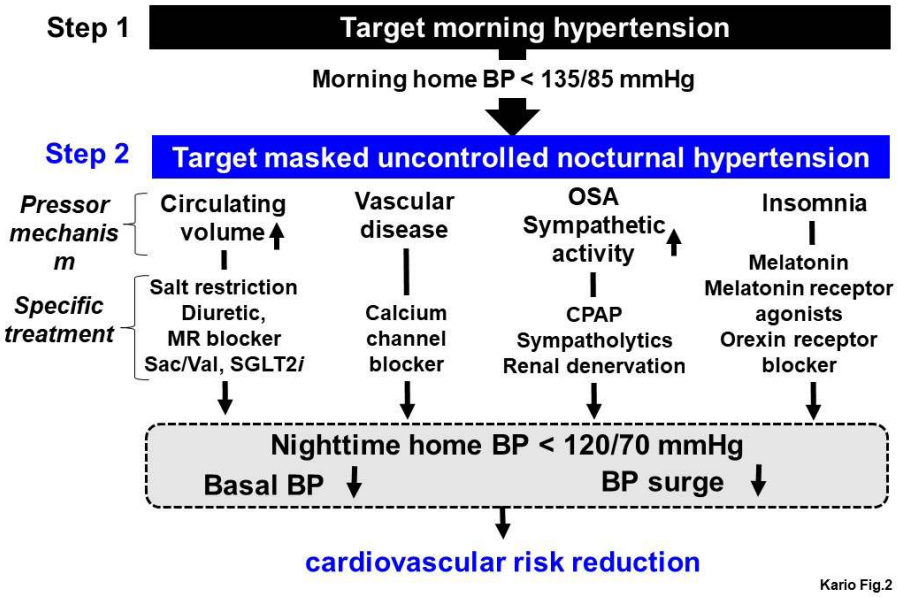


Figure 2. STEpwise-Personalized 24-hr blood pressure control approach (STEP24 approach) BP, blood pressure; MR, mineralocorticoid receptor; Sac/val, sacubitril/valsartan; SGLT2i, sodium glucose cotransporter 2 inhibitor; OSA, obstructive sleep apnea; CPAP, continuous positive airway pressure. [1]

Kario Fig.2

Kazuomi Kario - kkario@jichi.ac.jp

Reference

[1]Kario K. Nocturnal Hypertension: New Technology and Evidence. Hypertension. 2018;71:997–1009. doi: 10.1161/HYPERTENSIONAHA.118.10971

[2]O'Brien E, Sheridan J, O'Malley K. Dippers and non-dippers. Lancet. 1988;8607:397. doi:10.1016/s0140-6736(88)92867-x

[3]Kario K, Matsuo T, Kobayashi H, Imiya M, Matsuo M, Shimada K. Nocturnal fall of blood pressure and silent cerebrovascular damage in elderly hypertensive patients. Advanced silent cerebrovascular damage in extreme dippers. Hypertension 1996;27:130–135. doi: 10.1161/01.hyp.27.1.130

[4]Kario K, Pickering TG, Matsuo T, Hoshide S, Schwartz JE, Shimada K. Stroke prognosis and abnormal nocturnal blood pressure falls in older hypertensives. Hypertension 2001;38:852–827. doi: 10.1161/hy1001.092640

[5]Palatini P, Verdecchia P, Beilin LJ, Eguchi K, Imai Y, Kario K, Ohkubo T, Pierdomenico SD, Saladini F, Schwartz JE, Wing L, Signorotti S, Reboldi G. Association of Extreme Nocturnal Dipping With Cardiovascular Events Strongly Depends on Age. Hypertension. 2020;75:324-330. doi: 10.1161/HYPERTENSIONAHA.119.14085

[6]Hermida RC, Crespo JJ, Domínguez-Sardiña M, Otero A, Moyá A, Ríos MT, Sineiro E, Castiñeira MC, Callejas PA, Pousa L, Salgado JL, Durán C, Sánchez JJ, Fernández JR, Mojón A, Ayala DE; Hygia Project Investigators. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J. 2019 Oct 22. pii: ehz754. doi: 0.1093/eurheartj/ehz754.

[7] Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K.Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet. 2016;387:957-967. doi: 10.1016/S0140-6736(15)01225-8

[8]Boggia J, Li Y, Thijs L, Hansen TW, Kikuya M, Björklund-Bodegård K, Richart T, Ohkubo T, Kuznetsova T, Torp-Pedersen C, Lind L, Ibsen H, Imai Y, Wang J, Sandoya E, O'Brien E, Staessen JA; International Database on Ambulatory blood pressure monitoring in relation to Cardiovascular Outcomes (IDACO) investigators. Prognostic accuracy of day versus night ambulatory blood pressure: a cohort study. Lancet. 2007;370:1219-1229. doi: 10.1016/S0140-6736(07)61538-4

[9]Poulter NR, Savopoulos C, Anjum A, Apostolopoulou M, Chapman N, Cross M, Falaschetti E, Fotiadis S, James RM, Kanellos I, Szigeti M, Thom S, Sever P, Thompson D, Hatzitolios AI. Randomized Crossover Trial of the Impact of Morning or Evening Dosing of Antihypertensive Agents on 24-Hour Ambulatory Blood Pressure. Hypertension. 2018;72:870-873. doi: 10.1161/HYPERTENSIONAHA.118.11101

[10]Kario K, Kanegae H, Tomitani N, Okawara Y, Fujiwara T, Yano Y, Hoshide S, on behalf of the J-HOP study group. Nighttime blood pressure measured by home blood pressure monitoring as an independent predictor of cardiovascular events in general practice: The J-HOP Nocturnal BP Study. Hyperetnsion 2019;73:1240-1248. doi: 10.1161/HYPERTENSIONAHA.118.12740

INVITED COMMENT:

Is Bedtime the best time of the day?

BO CARLBERG

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

MATTIAS BRUNSTRÖM

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

DOI: 10.30824/2003-9

In October 2019, European Heart Journal published the Hygia Chronotherapy Trial online before print [1]. The results have been widely discussed among researchers, on internet forums, in lay press, and among patients. Here, we argue why the findings should be interpreted with caution, and future studies awaited before changing clinical practice.

The Hygia Chronotherapy Trial, including 19 084 participants with high blood pressure, compared intake of all antihypertensive drugs in the morning with intake of at least one drug at bedtime. All participants underwent 48-hour ambulatory blood pressure monitoring at baseline and repeatedly during the study. The median follow-up time was 6.3 years.

At the end of the study, the morning group were treated with on average 1.80 antihypertensive drugs whereas the bedtime group were treated with 1.71 drugs (p<0001). The mean blood pressures at the end of the study were:

	Morning group	Bedtime group
Office Blood Pressure	143.2/82.4 mm Hg	140.0/81.4 mm Hg
Daytime ABPM	129.5/76.7 mm Hg	129.2/76.3 mm Hg
Nighttime ABPM	118.0/66.1 mm Hg	114.7/64.5 mm Hg

Taking at least one antihypertensive drug at bedtime was associated with a very pronounced decrease of cardiovascular morbidity and mortality. Also, the effect on total mortality was extraordinary. Below are some selected individual outcomes:

Selected oucome events

All-Cause Mortality (Adjusted Hazard Ratio, 95% CI)	0.55 (0.48-0.63)
Cardiovascular mortality (Adjusted Hazard Ratio, 95% CI)	0.44 (0.34-0.56)
Ischemic Stroke (Adjusted Hazard Ratio, 95% CI)	0.54 (0.42-0.69)
Hemorrhagic Stroke (Adjusted Hazard Ratio, 95% CI)	0.39 (0.23-0.65)
Myocardial infarction (Adjusted Hazard Ratio, 95% CI)	0.66 (0.52-0.84)
Heart Failure (Adjusted Hazard Ratio, 95% CI)	0.58 (0.49-0.70)
Angina Pectoris (Adjusted Hazard Ratio, 95% CI)	0.65 (0.51-0.83)

Selected composite outcome events

Total events (Adjusted Hazard Ratio, 95% CI):	0.58 (0.54-0.62)
CVD-outcome events* (Adjusted Hazard Ratio, 95% CI):	0.55 (0.50-0.61)
Stroke (Adjusted Hazard Ratio, 95% CI):	0.51 (0.41-0.63)
Coronary events (Adjusted Hazard Ratio, 95% CI):	0.56 (0.49-0.64)

*CVD Outcome (CV Mortality, Myocardial infarction, Coronary revascularization, heart failure and stroke)

If the results are valid, they imply that there could be very important pathophysiological mechanism in

hypertension treatment that has been less known until now. This may be true, but several important questions need to be answered before such conclusions can be drawn.

It is difficult to assess the methods and results presented in the article, mainly because it is not reported transparently according to common standards (CONSORT) [2]. Therefore, some questions are still unanswered.

Is this a randomized controlled trial?

Most people read the paper as if it was a randomized controlled trial, but the word "randomization" appear only once, in the context of the PROBE abbreviation. Instead, words like "assigned" and "allocated" are used throughout the text; in the abstract, the study is defined as a "multicenter, controlled, prospective endpoint trial". Whether randomization was adequately performed is not clear in the methods paper. Here, the randomization procedure is described as if there are several short-term trials testing different agents separately. A random code has been generated at the coordinating center, but it is not clear if allocation was concealed to physicians at participating centers.

How were losses to follow up handled?

There are no data presenting the number of participants lost to follow-up. In the flow diagram, 84 out of 19 168 participants were excluded as they had less than 1 year follow-up duration. Does this mean no one were lost with more than 1 year follow-up? It is not obvious why the 84 participants with less than 1 year follow-up were excluded; the conventional approach would be to include them and censor at last follow-up.

Were there non-protocol differences between treatment groups?

There is no obvious difference in non-study treatments between the two groups as far as reported, with one exception. Participants in the morning group were given more ACE-inhibitors, betablockers and diuretics and the bedtime group received more calcium antagonists compared with the other group. If this has any impact on the outcome is unknown, but it is not reasonable that this minor difference could account for such huge difference in cardiovascular outcomes between the groups.

Statistical issues

The results are presented as hazard ratios derived through a Cox-model adjusted for nine different covariates, including asleep SBP and sleep-time SBP decrease. Firstly, presenting adjusted hazard ratios, without crude numbers and unadjusted estimates, is not transparent and therefore difficult to appraise. Some of these data have been added in a letter published online, but mortality data are still lacking. Secondly the number of participants with composite outcomes are the same as the sum of the individual outcomes included in each composite outcome analysis. This could not be the case in time-to-first event analyses, because one participant can only contribute with one event. If the number of events for individual outcomes equate the number in the composite outcome, it implicitly means that no one died after a cardiovascular event. Thirdly, by hand counting, it looks like the risk for non-cardiovascular deaths would be approximately 40 % lower in the evening group. What other deadly outcomes did the intervention have impact on?

Ethical issues

Why was the study expanded? In randomized controlled trials with important patient-related outcomes, like cardiovascular disease and mortality, an Independent Data and Safety monitoring Board (DSMB) should monitor the outcomes at regular intervals. A DSMB assures that unnecessary harm is not caused by the intervention, or from not receiving the intervention, by stopping the trial once differences between groups are established. Different studies have different rules for early termination. The most conservative outcome used in cardiovascular outcome trials is all-cause mortality. As the effect on all-cause mortality in the Hygia Chronotherapy trial was very large, with a narrow confidence interval (see above), the study should have been stopped years before it actually was stopped. Instead, comparing the number of participants reported in the article with the number of participants in the methods paper and previous records on clinicaltrials.gov, it seems as if the study

was expanded almost four-fold from an original estimated 5000 participants.

To conclude, it is difficult to draw conclusions from this very interesting study as it is not transparently reported. With many unanswered questions, it is too early to change clinical practice. There are two ongoing studies testing similar hypotheses, the BedMed and TIME study. It will be very important to follow the outcome of these trials.

Bo Carlberg - bo.carlberg@umu.se

References

1. Hermida RC, Crespo JJ, Domínguez-Sardina M et al. Bedtime hypertension treatment improves cardiovascular risk reduction: the Hygia Chronotherapy Trial. Eur Heart J 2019; doi: 10.1093/eurheartj/ehz754

2. Schulz KF, Altman DG, Moher D et al. CONSORT 2010 Statement: Updated Guidelines for Reporting Parallel Group Randomized Trials. Ann Intern Med 2010;152:726-32. doi: 10.1097/AOG.0b013e3181d9d421

INVITED COMMENT:

New NICE Guideline opts for stability

JOHN CHALMERS

The George Institute for Global Health
The University of NSW, Sydney
Australia

DOI: 10.30824/2003-10

Following the publication of the SPRINT study in the New Engl J Med in 2015[1], a number of the major international guidelines have gradually been revised, beginning with those of the American College of Cardiology and American Heart Association (AHA) in 2017[2]. These were followed by the guidelines of the European Societies of Cardiology and of Hypertension (ESC/ESH) in 2018[3] and then by the British guidelines for "Hypertension in Adults: diagnosis and management" from the National Institute for Health and Care Excellence ('NICE')[4].

One of the attractive features of NICE is that these guidelines are written in plain and simple English and are aimed as much at patients and their families and carers, as they are at hypertension specialists, general practitioners or other health care professionals[4]. Another attractive feature is their relative brevity and simplicity, though that is achieved in part by referring the reader to a variety of separate NICE guidelines such as those on "chronic kidney disease in adults", or "cardiovascular disease" or "alcohol-use disorders" or on "stop smoking interventions and services". On the other hand, these new NICE guidelines do apply to people with type 2 diabetes[4].

Opportunities for change that were resisted

These are no major dramatic changes in the updated NICE guidelines though they do refer to the relevant literature, albeit with a conservative bent. The major areas where possible change has been resisted include the following:

Measurement of Blood Pressure

The 2019 NICE guideline does not consider the possible use of "Unattended Automated Office Blood Pressure Measurement", (AOBPM) the method used in SPRINT & recommended in the ACC/AHA 2017 guidelines as well as in the 2016 Canadian Guidelines[5], on the grounds that this method of measuring BP would be difficult to translate into UK clinical practice. They prefer the more traditional use of automated devices or of manual measurement using direct auscultation over the brachial artery[4]. That may well be true but a recommendation from NICE in 2019 encouraging the use of AOBPM might have provided valuable leadership. It is interesting to note that in a recent survey of patients with

resistant hypertension across 76 specialist centres from 6 major regions, completed in August 2016, the preferred method of BP measurement reported was AOBPM in 97% of patients in Australia and 87% in North America (USA & Canada)[6].

Setting of BP thresholds and targets for treatment

The 2019 NICE guideline retains a BP of 140/90 mmHg as the threshold for the diagnosis of hypertension or high BP and as the target for the treatment of high BP. For out-of-office BP these readings are reduced to 135/85 mmHg, for both daytime Ambulatory Blood Pressure Monitoring (ABPM) and Home Blood Pressure Monitoring (HBPM).

While the authors recognise that there is evidence from the SPRINT trial that lower BP thresholds and targets do confer significant benefits, they point out that this is accompanied by significant harms. They also have concerns that many aspects of the trial, which was conducted in the USA, including the patient populations, and the method for measurement of BP (AOBPM) "made the evidence difficult to interpret and use to inform the recommendations".[4] In part this might be because the focus of the NICE Guideline on Hypertension in Adults is primarily on primary prevention and treatment, which also may explain how they can quite readily ignore or outweigh the evidence of meta-analyses such as that by Ettehad et al[7] which may be more relevant to one of the other NICE Guidelines, such as the one on "cardiovascular disease".

Starting antihypertensive drug treatment with monotherapy

NICE 2019 continues to recommend starting with monotherapy in part because the results of the Pathway-1 trial, suggesting dual therapy could help achieve BP control more rapidly, were excluded, because the outcome was a surrogate outcome, and in part because the other evidence in favour of dual therapy is based on improved adherence, not on improved efficacy.[8,9]

Changes recommended by the 2019 Guideline

A bouquet for Including Diabetes

The new NICE Guideline is the first to include people with diabetes, and furthermore their threshold and target BPs are the same as those for people without diabetes. This helps to simplify many issues for the practicing doctor.

New cardiovascular risk threshold of 10% for treatment in stage 1 hypertension

Having resisted any temptation to lower the BP threshold for treatment, the authors of the 2019 NICE Guideline do lower the 10-year cardiovascular risk threshold for initiation of treatment in people with stage 1 hypertension below 80 years, from the previous 20%, to the new level of 10%! This recommendation was supported by a health economic analysis which confirmed that treatment was cost effective at the 10% threshold in people aged 60 years. Given the increasing emphasis on total cardiovascular risk, in preference to blood pressure alone, this makes good sense.

New recommendations for taking BP in the two arms

The 2019 NICE Guideline continues to recommend BP should be measured in both arms at the time of diagnosis, but recommends a difference of 15 rather than the previous 20mmHg should be regarded as significant, and subsequent readings should be taken from the arm with the highest reading, with the patient informed which that is. This was in line with recent evidence that quite small differences in arm BP are associated with increased risk of cardiovascular events.

Conclusions

I have long been a believer in the benefits of lowering blood pressure, and was a little disappointed that NICE 2019 chose not to act on the evidence of the SPRINT trial and of numerous meta-analyses to lower the BP threshold and target for various groups, but I did appreciate the consolation prize, in that the 10 year cardiovascular risk threshold for treatment in people below 80 with stage 1 hypertension was lowered to 10% from the previous 20%. As a long-time advocate of combination therapy for the treatment of hypertension, and a firm believer in the merits of using single pill combinations for the initiation of therapy, I was again disappointed. I was however delighted to see people with type 2 diabetes included in the NICE 2019 Hypertension Guideline, with the same threshold and target BP as people without diabetes. And I did appreciate the way NICE spoke to the reader, and explained its point of view – a real lesson for all the other guidelines which are strictly written for the expert and require that person at their sharpest and fit enough to run a marathon! Finally, it seems likely

that for many doctors and their patients in the UK – and that is for whom these guidelines are meant – they will be welcomed as "steady as she goes", with a few sensible changes and a simple regime to follow, with a common threshold and target BP, but nothing too radical. Let's hope that significantly more people with high blood pressure will actually take their medication and achieve that target clinic blood pressure of <140 mmHg. That would be progress!

Cartoon by Jordi Carreras - Sydney, Australia

John Chalmers - chalmers@georgeinstitute.org.au

References

1. Wright JT, Williamson JD, Whelton PK et al for the SPRINT Research Group. A randomised trial of intensive versus standard blood pressure control. N Engl J Med 2015;373:2103-2116 doi: 10.1056/NEJMoa1511939

2. Whelton PK, Carey RM, Aronow WS et al (2017) ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guidelines for the prevention, detection, evaluation and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e127-e248 doi: 10.1016/j.jacc.2017.11.006 [published Online First 2017/11/18]

3. Williams B, Mancia G, Spiering W et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Journal of Hypertension 2018; 36:1953-2041 doi: 10.1097/HJH.0000000000001940

4. The National Institute for Health and Care Excellence. Hypertension in Adults: diagnosis and management. NICE guideline 136.London.National Institute for Health and Care Excellence 2019. https//www.nice.org.uk.guidance/ng136

5. Leung A, Nerenberg K, Daskalopoulou SS et al, Hypertension Canada's 2016 Canadian Hypertension Education Program Guidelines for Blood Pressure Measurement, Diagnosis, assessment of Risk, Prevention, and Treatment of Hypertension. Canadian Journal of Cardiology 2016; 32:569-588 doi: 10.1016/j.cjca.2016.02.066

6. Carcel C, Neal B, Oparil S et al. Clinical characteristics, antihypertensive medication use and blood pressure control among patients with treatment-resistant hypertension: the Survey of Patlents with treatment Reslstant hyperTension study. J Hypertens 2019;37:2216-2224 doi: 10.1097/HJH.0000000000002184

7. Ettehad D, Emdin C, Kiran A et al. Blood Pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. The Lancet 2016; 387:957-67 doi: 10.1016/S0140-6736(15)01225-8

8. Gupta P, Patel P, Strauch B et al. Biochemical screening for non-adherence is associated with blood pressure reduction and improvement in adherence. Hypertension 2017; 701:1042-48 doi: 10.1161/HYPERTENSIONAHA.117.09631

9. Corrao P, Parodi A, Nicotra F et al. Better compliance to antihypertensive medications reduces cardiovascular risk. J Hypertension 2011; 29:610-618 doi: 10.1097/HJH.0b013e328342ca97

INSTITUTE FOCUS:
Medical University of Gdansk, Poland

KRZYSZTOF NARKIEWICZ
Department of Hypertension and Diabetology
Medical University of Gdansk
Gdansk, Poland

DOI: 10.30824/2003-11

Founded in 1945, the Medical University of Gdansk is the largest medical academic institution in Northern Poland. It continues the tradition of the Atheneum Gedanense with its Chair of Anatomy and Medicine, established in 1580.

The Department of Hypertension and Diabetology is located in a newly-opened University Clinical Centre complex.

The department is recognized as an ESH-Centre of Excellence, and includes state-of-the art in-patient and out-patient clinics serving Gdansk region as a reference centre for both primary and secondary hypertension.

Our centre organized several national and international hypertension events including a first satellite ESH symposium in Central Europe (1995), ESH Summer School in 2001, four congresses of the Polish Society of Hypertension, four editions of the European Forum on Hypertension (2016-2019) and the Nordic-Baltic Regional University Research Course (September 2019), which was generously supported by the ISH.

University Clinical Centre in 2007 and 2019.

Ongoing research activities

First, we continue our efforts to better understand mechanisms underlying the link between sympathetic overactivity and cardiovascular risk. Our studies coordinated by Dagmara Hering are focused not only on hypertension[1], but also on chronic kidney disease[2], coronary artery disease and cardiovascular risk factors including smoking and alcohol abuse[3]. We have recently initiated functional magnetic resonance imaging studies. Our findings indicate that compensatory functional reorganization may precede hypertension-related brain damage and cognitive decline[4].

Second, our centre is involved in search of new approaches for treating difficult-to-manage hypertension. In collaboration with the group of Julian F. R. Paton, we performed the first prospective proof-of-concept, safety and feasibility study of unilateral carotid body excision from a cohort of patients with drug-resistant hypertension[5]. We have shown that the carotid body may be a novel target for treating an identifiable subpopulation of humans with hypertension.

Third, sleep medicine remains our research priority. We have completed several mechanistic and clinical studies assessing impact of obstructive sleep apnea on cardiovascular structure and function, with special emphasis on cerebral flow and intracranial pressure [6].

Prof. Alberto Zanchetti and Prof. Peter Sleight attending the ESH satellite symposium "Metabolic disturbances in hypertension" in Gdansk (May 1995).

Fourth, we have gained expertise in the assessment of both large vessels (collaboration with Stephane Laurent, Pierre Boutouyrie and Peter Nilsson) and microcirculation (collaboration with the group of Roland E. Schmieder). Our group contributed to the development of the early vascular aging (EVA) concept. We have shown that pulse wave velocity is independently associated with both short-term and long-term outcome after acute ischemic stroke[7].

Inaugural meeting of the Translational Medicine Centre initiative.

Fifth, our recent projects incorporate genetics (collaboration with the group of Olle Melander) and metabolomics. We have recently demonstrated that the genetic risk score composed of 13 SNPs related to cardiovascular phenotypes is associated with an increased arterial stiffness in hypertensive patients[8].

Finally, our centre is involved in population-based studies coordinated by Jan A. Staessen. This collaboration resulted in numerous publications including a recent study published in JAMA[9]. Furthermore, Tomasz Zdrojewski and Piotr Bandosz have initiated several epidemiological studies and contributed to NCD Risk Factor Collaboration[10].

Our University has recently decided to accelerate innovative interdisciplinary projects focused on personalised medicine. MUG has established the Translational Medicine Centre serving as the platform linking several research groups.

As a first step, we opened a cardiovascular imaging core facility gathering the best high-tech equipment in one place, which clearly boosted the scattered potential of individual research groups. The more effective transfer of knowledge is to be fostered through the proximity of the Technology Transfer Office of MUG in the same location.

The efforts of Translational Medicine Centre will be supported by the Early Clinical Trials Unit, a new structure established by MUG in 2019. The Unit assesses the safety and efficacy of therapies at an early development phase. Phase I/II studies include dose escalation, drug interactions, interactions with food, cardiologic safety, and proof-of-concept. In the close future, the functionalities of the unit will be extended with research that require close monitoring of pharmacokinetics and pharmacodynamics as well as first-in-human research. Our hospital implemented a modern electronic record system in 2016 enabling fast and easy search for suitable patients in a database including records of more than 900 thousand subjects, which should allow fulfilling restrictive admission criteria for trials including those with a molecular or immunological focus.

The Polish Ministry of Science and Higher Education has recently launched the Excellence Program to stimulate a small number of Poland's universities to become on a par with Europe's best research universities. The international panel selected MUG as one of the top 10 Polish universities and awarded the higher level of additional subvention research funding, which should result in further strengthening of Gdansk cardiovascular centre.

Opening of the Translational Medicine Centre (from left: Prof. Edyta Szurowska, Prof. Anna Dominiczak and Prof. Krzysztof Narkiewicz)

Krzysztof Narkiewicz - krzysztof.narkiewicz@icloud.com

References

[1.] Hering D, Kucharska W, Kara T, Somers VK, Parati G, Narkiewicz K. Effects of acute and long-term slow breathing exercise on muscle sympathetic nerve activity in untreated male patients with hypertension. J Hypertens. 2013; 31: 739-46. doi: 10.1097/HJH.0b013e32835eb2cf

[2.] Hering D, Zdrojewski Z, Król E, Kara T, Kucharska W, Somers VK, Rutkowski B, Narkiewicz K. Tonic chemoreflex activation contributes to the elevated muscle sympathetic nerve activity in patients with chronic renal failure. J Hypertens. 2007; 25: 157-61. doi: 10.1097/HJH.0b013e3280102d92

[3.]Hering D, Kucharska W, Kara T, Somers VK, Narkiewicz K. Potentiated sympathetic and hemodynamic responses to alcohol in hypertensive vs. normotensive individuals. J Hypertens. 2011; 29:537-41. doi: 10.1097/HJH.0b013e328342b2a9.

[4.]Naumczyk P, Sabisz A, Witkowska M, Graff B, Jodzio K, Gąsecki D, Szurowska E, Narkiewicz K. Compensatory functional reorganization may precede hypertension-related brain damage and cognitive decline: a functional magnetic resonance imaging study. J Hypertens. 2017; 35:1252-1262. doi: 10.1097/HJH.0000000000001293

[5.]Winklewski PJ, Wolf J, Gruszecki M, Wszedybyl-Winklewska M, Narkiewicz K. Current understanding of the effects of inspiratory resistance on the interactions between systemic blood pressure, cerebral perfusion, intracranial pressure, and cerebrospinal fluid dynamics. J Appl Physiol (1985). 2019; 127: 1206-1214. doi: 10.1152/japplphysiol.00058.2019

[6.]Narkiewicz K, Ratcliffe LE, Hart EC, Briant LJ, Chrostowska M, Wolf J, Szyndler A, Hering D, Abdala AP, Manghat N, Burchell AE, Durant C, Lobo MD, Sobotka PA, Patel NK, Leiter JC, Engelman ZJ, Nightingale AK, Paton JF. Unilateral Carotid Body Resection in Resistant Hypertension: A Safety and Feasibility Trial. JACC Basic Transl Sci. 2016 Aug 29;1(5):313-324. doi: 10.1016/j.jacbts.2016.06.004

[7.]Gasecki D, Rojek A, Kwarciany M, Kubach M, Boutouyrie P, Nyka W, Laurent S, Narkiewicz K. Aortic stiffness predicts functional outcome in patients after ischemic stroke. Stroke. 2012; 43:543-4. doi: 10.1161/STROKEAHA.111.633487

[8.]Polonis K, Hoffmann M, Szyndler A, Wolf J, Nowak R, Becari C, Laurent S, Boutouyrie P, Melander O, Narkiewicz K. A multilocus genetic risk score is associated with arterial stiffness in hypertensive patients: the CARE NORTH study. J Hypertens. 2018; 36:1882-1888. doi: 10.1097/HJH.0000000000001773

[9.]Yang WY, Melgarejo JD, Thijs L, Zhang ZY, Boggia J, Wei FF, Hansen TW, Asayama K, Ohkubo T, Jeppesen J, Dolan E, Stolarz-Skrzypek K, Malyutina S, Casiglia E, Lind L, Filipovský J, Maestre GE, Li Y, Wang JG, Imai Y, Kawecka-Jaszcz K, Sandoya E, Narkiewicz K, O'Brien E, Verhamme P, Staessen JA; International Database on Ambulatory Blood Pressure in Relation to Cardiovascular Outcomes (IDACO) Investigators. Association of Office and Ambulatory Blood Pressure With Mortality and Cardiovascular Outcomes. JAMA. 2019; 322:409-420. doi: 10.1001/jama.2019.9811

[10.]NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in body-mass index, underweight, overweight, and obesity from 1975 to 2016: a pooled analysis of 2416 population-based measurement studies in 128·9 million children, adolescents, and adults. Lancet. 2017; 390:2627-2642. doi: 10.1016/S0140-6736(17)32129-3

"DDD" DYLAN'S DISTRIBUTION DATA

DYLAN BURGER
Ottawa Hospital Research Institute
Ottawa, Canada

I am pleased to report that the November 2019 issue was far and away our most accessed issue to date with over 11,000 views. This represents a major increase from our summer issue as well as our previous peak in readership (the March 2019 issue). While such an increase in readership is likely multifactorial, the Hypertension News editorial board did make distribution of the issue a major focus in November. In addition, this issue featured multiple high quality contributions including a timely discussion on the inclusion of heart failure as an endpoint in clinical trials.

It is worth noting that the vast majority of readership (>90%) is accessing the newsletter through digital object identifiers. In part this is due to the fact that distribution through ISH channels has linked via DOIs, but it also suggests that readers may be accessing Hypertension News in other ways (possibly search engines or linked references).

Dylan's Distribution Data (November 2019-February 2020)

Total Estimated Readership	11,579
Accessed via Twitter	133
Accessed via Facebook	344
Accessed via DOI	10,615
Accessed via Web Site	487

Ultimately the November issue continuing a long-term trend towards increased readership of Hypertension News. This is no doubt a result of the high quality contributions that Hypertension News regularly receives as well as the efforts of our members to showcase the flagship newsletter of the ISH. Going forward the editorial board is committed to ensuring the continued quality of material published in Hypertension News and to extending the global reach of the International Society of Hypertension.

Dylan Burger - dburger@uottawa.ca

a CATching Photo of Social Media Training

Photo by Li Winther, Stockholm (from the Lindholm family)

YOUNG INVESTIGATORS:

Why should we care about hypertension in children?

RUAN KRUGER

Hypertension in Africa Research Team (HART) and the Medical Research Council: Research Unit for Hypertension and Cardiovascular Disease, North-West University, Potchefstroom, South Africa

DOI: 10.30824/2003-12

A recent analysis reported a 2-4% prevalence of hypertension in American children and an increase from 14.8% to 16.3% in elevated blood pressure among children[1]. Yet these estimations seem very different in countries with large inequalities such as South Africa. A systematic review indicated that childhood hypertension prevalence ranged between 7.5% and 22.3%, dependent on location, region and culture[2]. With the current global population of children (under 15 years) estimated at approximately 2 billion and a median prevalence of hypertension at 6.75%, almost 134 million children suffer from hypertension. Of these, the majority of children are from developing countries.

Perhaps the most common contributing factor of paediatric hypertension is obesity. According to the recent UNICEF report on "The state of the world's children", at least 340 million adolescents worldwide between ages 5-19 years are overweight[3]. With the global increasing availability and cheap cost of processed foods and beverages, along with the increasing lack of physical activity, the prevalence of overweight children increased from 19% to 75.8% in the last 10 years in low-income countries[3]. This in itself is a global emergency with major economic implications, especially for low-, lower middle- and upper middle-income countries.

Although we cannot ignore the major impact of overweight and obesity on the development of high blood pressure, many other conditions may accompany the onset and development of childhood hypertension. Among these are diabetes mellitus (both types 1 and 2) including other metabolic syndrome risk factors[4], as well as chronic kidney disease and renal insufficiency[5]. In addition, secondary hypertension is more common in children and not proportional to age. These conditions may include complications such as hypertensive encephalopathy, cranial nerve palsy, resistant hypertension and heart failure, as well as a clinical history of urinary infections, gross haematuria or oedema, sleep problems and an unavoidable family history of hypertension[6]. Children with congenital heart disease including aortic coarctation are also subjected to an increased risk to develop hypertension[7]. Other (perhaps less common) conditions contributing to hypertension in children include renal parenchymal disease[8], Cushing's syndrome[9], pheochromocytoma[10] and primary aldosteronism[11].

More importantly, the increasing prevalence of primary hypertension in children remains a global health concern, especially with certain risk factors in rural regions and developing countries often overlooked.

Among these risk factors are less clinical and more sociocultural contributors including poverty, infectious diseases, violence and injury, child abuse and sanitation[12]. These factors are often listed when describing the socioeconomic burden and ethnic inequalities that still exist in many countries. These adversities directly affect a child's development since they are often not educated, malnourished and under huge amounts of psychosocial stress[13] due to poverty and the reality of ethnic inequalities. High impact studies have shown that childhood blood pressure tracks into adulthood from as early as 4 years of age[14,15], making children and adolescents

the most appropriate population to promote healthy lifestyle and prevent the early onset of elevated blood pressure.

So, should we care about childhood hypertension? Indeed, we have to. With recent evidence highlighting early life exposures to risk factors that may determine the origin and trajectories of disease across the lifecourse[16], monitoring blood pressure in children and adolescents should become a priority area for clinician and research scientists as well as in mainstream scientific programmes of hypertension related conferences.

Ruan Kruger - Ruan.Kruger@g.nwu.ac.za

References

1.Bell CS, Samuel JP, Samuels JA. Prevalence of Hypertension in Children. Hypertension 2019; 73(1): 148-52. doi: 10.1161/HYPERTENSIONAHA.118.11673

2.Kagura J, Ong KK, Adair LS, Pettifor JM, Norris SA. Paediatric hypertension in South Africa: An underestimated problem calling for action. SAMJ: South African Medical Journal 2018; 108: 708-9. doi: 10.7196/SAMJ.2018.v108i9.13317

3.UNICEF. The State of the World's Children 2019. Children, Food and Nutrition: Growing well in a changing world. UNICEF, New York 2019.

4.Juonala M, Magnussen CG, Berenson GS, et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. N Engl J Med 2011; 365: 1876-85. doi: 10.1056/NEJMoa1010112

5.Flynn JT, Mitsnefes M, Pierce C, et al. Blood pressure in children with chronic kidney disease: a report from the Chronic Kidney Disease in Children study. Hypertension 2008; 52(4): 631-7. doi: 10.1161/HYPERTENSIONAHA.108.110635

6.Lurbe E, Agabiti-Rosei E, Cruickshank JK, et al. 2016 European Society of Hypertension guidelines for the management of high blood pressure in children and adolescents. J Hypertens 2016; 34(10): 1887-920. doi: 10.1097/HJH.0000000000001039

7.Morgan GJ, Lee KJ, Chaturvedi R, Bradley TJ, Mertens L, Benson L. Systemic blood pressure after stent management for arch coarctation implications for clinical care. JACC: Cardiovascular Interventions 2013; 6(2): 192-201. doi: 10.1016/j.jcin.2012.10.009

8.Flynn JT. Evaluation and management of hypertension in childhood. Progress in pediatric cardiology 2001; 12(2): 177-88. doi: 10.1016/s1058-9813(00)00071-0

9.Lodish MB, Sinaii N, Patronas N, et al. Blood pressure in pediatric patients with Cushing syndrome. The Journal of Clinical Endocrinology & Metabolism 2009; 94(6): 2002-8. doi: 10.1210/jc.2008-2694

10.Garnier S, Réguerre Y, Orbach D, Brugieres L, Kalfa N. Pediatric pheochromocytoma and paraganglioma: an update. Bulletin du cancer 2014; 101(10): 966-75. doi: 10.1684/bdc.2014.2031

11.Zennaro M-C, Jeunemaitre X. SFE/SFHTA/AFCE consensus on primary aldosteronism, part 5: Genetic diagnosis of primary aldosteronism. Annales d'Endocrinologie 2016; 77(3): 214-9. doi: 10.1016/j.ando.2016.02.006

12.Rosengren A, Smyth A, Rangarajan S, et al. Socioeconomic status and risk of cardiovascular disease in 20 low-income, middle-income, and high-income countries: the Prospective Urban Rural Epidemiologic (PURE) study. The Lancet Global Health 2019; 7(6): e748-e60. doi: 10.1016/S2214-109X(19)30045-2

13.Nilsson P. Premature ageing: the link between psychosocial risk factors and disease. Medical hypotheses 1996; 47(1): 39-42. doi: 10.1016/s0306-9877(96)90041-9

14.Chen X, Wang Y, Mi J. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-analysis. Federation of American Societies for Experimental Biology; 2007.

15.Chen X, Wang Y. Tracking of blood pressure from childhood to adulthood: a systematic review and meta-regression analysis. Circulation 2008; 117(25): 3171. doi: 10.1161/CIRCULATIONAHA.107.730366

16.Olsen MH, Angell SY, Asma S, et al. A call to action and a lifecourse strategy to address the global burden of raised blood pressure on current and future generations: the Lancet Commission on hypertension. The Lancet 2016; 388(10060): 2665-712. doi: 10.1016/S0140-6736(16)31134-5

MAY MEASUREMENT MONTH GETS SET FOR ITS FOURTH YEAR OF SUCCESS

JUDITH BUNN
MMM Project Manager

LISA WOODWARD
MMM Communications Manager

We would like to thank the ISH members and the many organisations around the world, including national hypertension and other cardiovascular societies, who have driven May Measurement Month (MMM) over the past 3 years. MMM Chief Investigator, Professor Neil Poulter explains:

"**MMM19 was our largest campaign to date, which means we have now screened over 4.2 million people across more than 100 countries. In total we have identified almost 1million people with untreated or inadequately treated hypertension**."

Following the many MMM papers that have been published over the last 2 years (in the Lancet Global Health, European Heart Journal (EHJ) and EHJ Supplements) we are pleased that 41 national papers for MMM18 are currently in press for a publication as another EHJ Supplement. The global analysis for MMM19 has also been submitted and is under review by a major journal, with the aim of publication before May 2020 and therefore in advance of MMM20. Thanks to the data we have collected, we are now building a bank of scientific evidence that can be used to promote the need for more widespread and accessible global blood pressure screening.

Professor Alta Schutte, President of the International Society of Hypertension, stated:

"We are delighted to see MMM go from strength to strength, going a long way to meet our objective to raise global awareness of the issues surrounding raised blood pressure. But with over 10 million people still dying each year from raised blood pressure, there is clearly more work to be done and we hope our generous volunteers will continue to support this campaign in its fourth year."

If you have not already signed up for MMM20, it's not too late! We have a huge pool of resources ready to help you in setting up your national MMM campaign, from the MMM20 protocol for ethical approval, to training and recruitment videos, branding guidelines and printed artwork for posters and leaflets. All of these, and more, are available to download from the MMM website. Even if you are only able to run a small campaign you will be contributing important data to help improve and save lives. If you would like to learn more about how to get involved as a country leader or site leader, please contact the MMM Project Team: admin@maymeasure.com

Judith Bunn and Lisa Woodward - manager@maymeasure.com

YOUNG INVESTIGATORS REPORT FROM THE ASIAN-PACIFIC SOCIETY OF HYPERTENSION MEETING

Enabling regional and global engagement through the Asian-Pacific Congress of Hypertension

FRANCINE Z. MARQUES

Hypertension Research Laboratory, School of Biological Sciences, Faculty of Science, Monash University, Melbourne, Australia;
Baker Heart and Diabetes Institute, Melbourne, Australia;

RACHEL E CLIMIE

Baker Heart and Diabetes Institute, Melbourne, Australia;
Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

The High Blood Pressure Research Council of Australia (HBPRCA) hosted the 15th Asian-Pacific Congress of Hypertension (APCH) in Brisbane, Australia, on November 24-27th, 2019. The congress was organised by Michael Stowasser, Karen Moritz, Bradley Broughton, Louise Burrell, Kate Denton, Francine Marques, Anastasia Mihailidou, Trefor Morgan, Markus Schlaich, James Sharman and Martin Wolley (all from Australia), and was attended by 347 delegates from 29 countries with 165 original oral and poster presentations.

The meeting commenced with four satellite symposia: Aldosterone and Hypertension, Role of the Sympathetic Nervous System in Hypertension and Target Organ Damage, Gut Microbiome and Hypertension, and Central Blood Pressure (BP): What's New? We (FZM, RC) attended the latter two symposia.

During the "Gut Microbiome and Hypertension" symposium, we learned about what the gut microbiome is, culturing microbes previously deemed 'unculturable', and designing robust microbiome studies. Work on hypertension, its complications and risk factors was also presented. The key take home messages were: 1) the gut microbiota is complex and dynamic; 2) recent technological advances make it easy to study the gut microbiota, but data is equally easy to be over-interpreted;[1] 3) the microbiome has a great potential to be used as therapy for human disease, however, appropriate study design is essential to minimise confounding factors;[1] 4) the gut microbiota and epithelial barrier are altered in cardiovascular disease models (hypertension, stroke, myocardial infarction);[2] 5) the interaction between the gut microbiome and the immune system is likely to be an important driver for cardiovascular disease, where microbial effects are likely indirect and driven by gut metabolites activating immune cells;[3] 6) age and sex are important factors, but they are not always considered in experimental studies;[1] 7) a diet that is relevant to cardiovascular disease such as fibre, fat and salt, are typically associated with changes in the gut microbiome, and some of these affect the immune system that is likely to drive the cardiovascular phenotype and;[3] 8) there is a potential for use of gut metabolites such as short-chain fatty acids to treat cardiovascular disease.[4-6]

Discussions during the "Central BP" symposium ranged from pressure waveforms and waveform models, cuffless BP technology, the importance of measuring central BP in young populations to the BP clinic of the future. The key take home messages from the symposia were: 1) that deeper BP phenotyping is required to truly understand the risks related to elevated BP, and; 2) that cuffless BP technology is likely to be more and more utilized in future.

The congress included 17 keynote and 12 plenary speakers from a diverse background covering discovery, public health and clinical cardiovascular disease research. The main meeting commenced with the plenary session on hypertension, heart failure and diabetes, and followed with free communication sessions on hypertension management in diabetes. Recent research on the novel diabetes medications, SGLT2 inhibitors, was presented including their

APCH_Brisbane photo by Anastasia Mihailidou

effects on sympathetic nervous activity. A multi-omics session had talks on the use of gut microbiome analyses for stroke therapy, regulation of the renin gene, and mechanisms associated with type 2 diabetes and cardiac hypertrophy. The APSH Invited Lectureship presentation delivered by Professor Markus Schlaich discussed device based approaches for the treatment of hypertension including an update on renal denervation for lowering BP.[7] The APSH Presidential Lecture was delivered by Professor Michael Stowasser who presented on advances in diagnosis and the genetics of primary aldosteronism.[8] Professor Alta Schutte delivered the HBPRCA RD Wright Lecture, in recognition of

Anastasia Mihailidou, Alta Schutte & Francine Marques

outstanding contribution to hypertension research, and discussed why the burden of high BP is higher in lower income countries and touched on the social determinants of disease.[9] The HBPRCA Austin Doyle Lecture, in recognition of research excellence outside of the field of hypertension, was delivered by Professor Ingrid Scheffer who presented on the life of a clinician scientist and the work she has done in the genetics of epilepsy as a paediatric neurologist.[10] Professor Grant Drummond delivered the HBPRCA Colin Johnston Lecture, in recognition of excellence in hypertension research by a young but established investigator, on the immune mechanisms of hypertension which included seminal findings on the role of B cells, inflammasomes and interleukin-18 in hypertension.[11] The HBPRCA Judith Whitworth Award, for the highest ranked abstract for which the first named author is a woman, was awarded to Dr Jordyn Thomas, the HBPRCA Jaye Chin-Dusting Award, highest ranked abstract for which the first author is a mid-career scientist, was awarded to Dr Sheila Patel, and the HBPRCA Paul Korner Medal, for an active researcher who has made a significant contribution to high BP research, was awarded to Professor Louise Burrell.

A consistent theme throughout the meeting was lifestyle approaches for the management of hypertension with presentations focused on the polypharmacy failing to control BP, reducing salt intake, nutrition and physical activity. Recent work from China showed that educating children to be health ambassadors is effective in lowering salt intake and the first reference values for submaximal exercise BP were presented by local researchers. Australian data on the lack of research funding for cardiovascular researchers in Australia was also presented. This work, now under peer-review, highlighted that stagnation of funding in

cardiovascular research, combined with a lack of long-term job security, threatens to have profound effects on cardiovascular researcher retention in Australia, particularly for women.

In the junior researchers' corner, a highlight was the more than 10 oral and poster awards from the ISH, the HBPRCA and the Asian-Pacific Society of Hypertension awarded for high quality research presented by PhD students and early career researchers.[12] A joint New Investigator Symposium between the HBPRCA and the ISH included discussions on research impact, how to maintain a work-life balance in academia, and how make and maintain international collaborations, followed by a networking event with support from senior HBPRCA and ISH members, was extremely successful and well-attended.

A combination of high calibre and innovative invited speakers, excellent original research presented by the attendees and engagement at all career levels made the APCH a successful meeting.

Prof Michael Stowasser and Prof Narsingh Verma

Francine Z. Marques & Rachel E Climie - francine.marques@monash.edu

References

1. Marques FZ, Jama HA, Tsyganov K, Gill PA, Rhys-Jones D, Muralitharan RR, Muir JG, Holmes AJ, Mackay CR. Guidelines for transparency on gut microbiome studies in essential and experimental hypertension. ***Hypertension***. 2019;74:1279-1293 doi: 10.1161/HYPERTENSIONAHA.119.13079

2. Marques FZ, Mackay CR, Kaye DM. Beyond gut feelings: How the gut microbiota regulates blood pressure. ***Nat Rev Cardiol***. 2018;15:20-32 doi: 10.1038/nrcardio.2017.120

3. Jama H, Beale A, Shihata WA, Marques FZ. The effect of diet on hypertensive pathology: Is there a link via gut microbiota-driven immune-metabolism? ***Cardiovasc Res***. 2019;115:1435-1447 doi: 10.1093/cvr/cvz091

4. Marques FZ, Nelson E, Chu PY, Horlock D, Fiedler A, Ziemann M, Tan JK, Kuruppu S, Rajapakse NW, El-Osta A, Mackay CR, Kaye DM. High-fiber diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in hypertensive mice. ***Circulation***. 2017;135:964-977 doi: 10.1161/CIRCULATIONAHA.116.024545

5. Bartolomaeus H, Balogh A, Yakoub M, Homann S, Marko L, Hoges S, Tsvetkov D, Krannich A, Wundersitz S, Avery EG, Haase N, Kraker K, Hering L, Maase M, Kusche-Vihrog K, Grandoch M, Fielitz J, Kempa S, Gollasch M, Zhumadilov Z, Kozhakhmetov S, Kushugulova A, Eckardt KU, Dechend R, Rump LC, Forslund SK, Muller DN, Stegbauer J, Wilck N. The short-chain fatty acid propionate protects from hypertensive cardiovascular damage. ***Circulation***. 2019;139:1407-1421 doi: 10.1161/CIRCULATIONAHA.118.036652

6. Kim S, Goel R, Kumar A, Qi Y, Lobaton G, Hosaka K, Mohammed M, Handberg EM, Richards EM, Pepine CJ, Raizada MK. Imbalance of gut microbiome and intestinal epithelial barrier dysfunction in patients with high blood pressure. ***Clin Sci (Lond)***. 2018;132:701-718 doi: 10.1042/CS20180087

MENTORING:

A powerful tool to improve diversity and inclusion in hypertension

FRANCINE Z. MARQUES

Hypertension Research Laboratory, School of Biological Sciences, Faculty of Science, Monash University, Melbourne, Australia;
Baker Heart and Diabetes Institute, Melbourne, Australia;

I am honoured to have been recently appointed as the new chair of the ISH Mentoring and Training Committee (MTC). The MTC is particularly close to my heart as one of its early versions paired me with Professor Gavin Lambert, from Swinburne University, Australia, back in 2012. Gavin's guidance over the years has been fundamental not only for my career progression, but without his support (and the support from my other mentors and sponsors) I would have probably left hypertension research by now. This should not come as a surprise considering we know that women drop out of science around my career stage[1]. Adding to being female, I came from a developing country where research is far from being a national priority and I was diagnosed with cancer 5 years ago, right during the 'make it or break it' PhD to post-doc transition. Individually, all of these are reasons that make people leave science, academia and even medicine[2-4]. Over the years, Gavin has given me critical feedback on fellowship and grant applications, nominated me for awards, prepared me for job interviews, discussed career opportunities and directions, and set me up for collaborations. His friendship, however, was essential during chemotherapy. I was very fortunate to have such a wonderful mentor, and in my new role as chair of the MTC I aim to ensure others are given a similar opportunity.

Mentoring is also important to me because of my personal value of fairness. The same way that I believe every person has the right to age healthily (and, thus, my passion about hypertension research), mentoring improves opportunities leading to better equity and inclusion to all [4, 5]. Investing in mentoring should not only equip our junior members to become better scientists and leaders, but also help ensure that our field has a bright future. While mentoring benefits all, it is particularly important for women[4,6], who are under-represented in our community.

We are actively working to address some of the barriers junior researchers and women in hypertension face from a mentoring perspective. In partnership with the Women in Hypertension Research Committee, we have developed the New Parent in Hypertension Travel Award to support three ISH members with primary care responsibilities for a child/children to attend the 2020 ISH conference. What is new about this award is that it can be used in anyway the awardee sees fit to support their attendance: these awards could be used to support local child care, a babysitter or to bring someone else with them to look after their children. Similarly, we are also launching a new Developing Countries Travel Award to support the attendance of two ISH members that come from a developing country. The awardees of both travel grants will be appointed ISH mentors, who they will have the opportunity to meet face-to-face at the conference in Glasgow in May 2020. Applications for both awards are open until the 15th of March, and more information can be seen here.

We understand it can be nerve-racking to ask someone to be your mentor (believe me, I have been there!), but that's something the ISH-MTC can help you with. ***If you are looking for an International Society of Hypertension mentor, please fill in*** this form ***(it will take you less than 10 min and, believe me, it might change your life).*** Any age, gender and career stage ISH members are welcome

to apply. We have also developed a new package you will receive to make the most out of your mentoring relationship.

We are very fortunate to have amazing examples of leadership and research excellence at several career levels, research areas, and countries as part of our ISH community. For those more experienced, engaging with junior peers can be very rewarding[7] – if ***you would like to become a mentor, please fill in*** this form ***(it will take you less than 5 min).*** As the ISH mentoring scheme now completes nearly a decade of successfully matching mentors and mentees, we welcome those who have transitioned from PhD students and post-doctoral researchers to also transition from mentees to mentors. In recognition of the wonderful mentors we have in our society, we also welcome applications for the ***ISH Distinguished Mentor Award*** until the 15th of March – more information can be found **here**.

Finally, we look forward to hosting you for a mentoring and networking event in Glasgow! This is a unique opportunity to meet and greet some of our senior members (including the ISH Council), learn more about mentoring and the awardees, and network with our wonderful ISH researchers. Registrations to this event will open soon – it is one not to miss!

I look forward to seeing you in Glasgow!

Francine Marques - francine.marques@monash.edu

References

1. Martinez ED, Botos J, Dohoney KM, Geiman TM, Kolla SS, Olivera A, et al. Falling off the academic bandwagon. Women are more likely to quit at the postdoc to principal investigator transition. EMBO Rep. 2007;8(11):977-81. doi: 10.1038/sj.embor.7401110

2. Ciocca DR, Delgado G. The reality of scientific research in Latin America; an insider's perspective. Cell Stress Chaperones. 2017;22(6):847-52. doi: 10.1007/s12192-017-0815-8

3. Sohn E. When sickness interrupts science. Nature. 2018;553(7687):239-41. doi: 10.1038/d41586-018-00112-7

4. Pope JE. Mentoring women in medicine: a personal perspective. Lancet. 2018;391(10120):520-1. doi: 10.1016/S0140-6736(18)30243-5

5. Sharma GV, Freeman AM. Mentoring: why it matters even after training. J Am Coll Cardiol. 2014;64(18):1964-5. doi: 10.1016/j.jacc.2014.09.015

6. Kuehn BM. Flexibility and Mentoring Key to Boosting the Ranks of Women in Cardiology. Circulation. 2017;135(6):614-5. doi: 10.1161/CIRCULATIONAHA.116.027035

7. [Available from: https://hbr.org/2019/03/stressed-at-work-mentoring-a-colleague-could-help.

British and Irish Hypertension Society

Annual Scientific Meeting

Glasgow

We are delighted to invite you to Glasgow for the **2020 BIHS Annual Scientific Meeting.** The BIHS meeting will be held *immediately before* the joint ESH/ISH 2020 meeting 28-29 May at the Queen Elizabeth Teaching & Learning Centre, University of Glasgow. This is a stand-alone meeting and is not part of the ESH/ISH congress although a discount is available for delegates who wish to attend both. Please visit the registration page on our website for details.

In Glasgow, we will be celebrating 40 years of the BIHS, with an exciting programme open to all healthcare professionals with an interest in **cardiovascular disease and high blood pressure**. There will be ample opportunities for young investigators to showcase their work and compete for awards, and for all attendees to participate in the exchange of new ideas and lively debate, all within a friendly, convivial atmosphere.

Programme Highlights:

- Sir George Pickering Lecture
- Three Young Investigator awards based on submitted abstracts, with opportunities to present your work in Australia, the USA and Italy in our reciprocal exchange programmes
- The Dr Robert Grayson Award - presented to the best research into diseases of the aorta and blood vessels
- Prizes for the best Poster and best Nurse & Allied Health Professional presentation
- Clinical sessions on guidelines, complex cases and co-morbidities

Visit our website for more information, venue details and programme updates

We look forward to welcoming you to Glasgow!

UNA MARTIN

President, British and Irish Hypertension Society

the global hypertension hub

JOINT MEETING
ESH-ISH
2020
Glasgow

May 29 - June 1, 2020
Scottish Event Campus
Glasgow, United Kingdom
www.hypertension2020.org

European Society of Hypertension

International Society of Hypertension

BIHS
British and Irish Hypertension Society
Committed to preventing cardiovascular disease

#hypertension2020

@ESH_Annual / @ISHBP / @BIHSoc_Events

@ESHAnnualMeetings / @ISHBP / @bihsocevents

LET'S PARTNER IN THE BATTLE AGAINST HYPERTENSION

High blood pressure remains one of the largest unmet needs in healthcare. Let's try to do something about it.

Taking healthcare Further, Together.

Medtronic.com/hypertension

Medtronic
3576 Unocal Place
Santa Rosa, CA 95403
USA
Tel: 707.525.0111

LifeLine Customer Support
Tel: 877.526.7890
Tel: 763.526.7890

Product Services
Tel: 888.283.7868
Fax: 800.838.3103

Europe
Medtronic Intl. Trading SARL
Route du Molliau 31
Case Postale
CH-1131 Tolochenaz
Switzerland
Tel: 41.21.802.7000
Fax: 41.21.802.7900

Canada
Medtronic of Canada Ltd.
99 Hereford Street
Brampton, Ontario L6Y 0R3
Canada
Tel: 905.460.3800
Fax: 905.460.3998
Toll-free: 800.268.5346

Asia Pacific
Medtronic Intl. Ltd.
49 Changi South Avenue 2
Nasaco Tech Centre
Singapore 486056
Singapore
Tel: 65.6436.5000
Fax: 65.6776.6335

Latin America
Medtronic USA, Inc.
Doral Corporate Center II
3750 NW 87th Avenue
Suite 700
Miami, FL 33178
USA
Tel: 305.500.9328
Fax: 786.709.4244

medtronic.com

Medtronic

ISH HYPERTENSION NEWS TEAM

MEMBERS

Lars H. Lindholm
Editor of Hypertension, News Sweden

Dylan Burger
Deputy Editor of Hypertension News, Canada

Thomas Unger
ISH Secretary, The Netherlands

Thomas Kahan
Sweden

Maria-Christina Zennaro
France

ISH CORPORATE MEMBERS

SERVIER

Medtronic

OMRON

Otsuka Medical Devices

ISH Secretariat

Contact:
c/o In Conference Ltd
Unit 1 Q Court, Quality Street,
Edinburgh, UK, EH4 5BP

Tel (UK):
+44 (0)131 336 4203

Email:
secretariat@ish-world.com

ISH Registered Charity No: 1122135