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IN THIS ISSUE

FROM THE EDITOR

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The step from research on animals to studies of humans with high blood pressure

Lars H Lindholm, Editor, Hypertension News

Dear member,

Several of us have just returned from the biannual hypertension meeting in Milan, as always well organized by Giuseppe Mancia and his team. This year, the opening ceremony was shorter than usual and it did not end in the usual way by singers from the fabulous Italian opera world. Instead - since the ESH celebrated its 30th anniversary - an enormous birth day cake was rolled in and later shared with the attending delegates. It was quite tasty! ISH wishes it's younger sister society all the best for the future!

The number of attendees in Milan was about 2,400, slightly lower than previous years (about 2,700 in Paris in 2016, 2,600 in Milan 2017, and 2,600 in Barcelona in 2018)[1] and far from the glorious days of the mid-2000s (about 8,000 in Paris in 2004 and 7,200 in Milan in 2005)[1]. The lower number of attendees is a concern for all hypertension societies since many young scientists, working in the high blood pressure field, prefer to attend and present their work at the enormous cardiology meetings in Europe and/or the US. This is a concern for two reasons. First, it makes it more difficult for the hypertension societies to organize good meetings and second, the hypertension sessions for oral presentations during the cardiology meetings are often poorly attended.

The readership for Hypertension News continues to grow with each successive issue and the March 2019 edition (Opus 55) had the highest total number of views so far, with almost 5,000 accessing the Newsletter (page 20). Please note that these are only the readers who opened the Newsletter in such a way that it gets registered. We know that the real figure is much higher.

This issue of the Newsletter has a focus on basic science, where at least half our members are working. In three papers, the "Learning the Ropes" section covers the step from research on animals in hypertension to studies of humans. As stated by Thomas Unger in his lovely Introduction (paper 1 on page 9), *"Why can't we replace animal studies by in vitro experiments?"*. As this is likely to be a very provocative topic that generates much discussion, we have created an online forum to facilitate exchange which can be found at http://ishbp.freeforums.net/. This forum will remain open for discussion on any and all topics related to Hypertension News going forward.

Our “house writer” on “News, Old News, and Fake News”, Stephan Rössner has given us a fabulous text on Elvis Presley – the King - and his eating habits on page 17. Having been a slender and well-trained young man with a particular interest in karate, Elvis continuously put on weight and ended his life grossly obese with hypertension.

In this edition, we also say thanks to Lewis Landsberg who steps down as chairman of the Board of Management of the Journal of Hypertension after more than 25 years (page 2). We also thank our previous Secretariat at Conference Collective in London (page 4) and welcome our New Secretariat at In Conference in Edinburgh (page 4 and 5). Finally, the new President Elect of ISH, Maciej Tomaszewski is presented on page 4. Maciej takes up office in June 2020.

Have a good read!

Reference:
1. Tsioufis K, Kreutz R, Narkiewics K et al. ESH, European Society of Hypertension 30 years (1989-2019). European Society of Hypertension, Athens June 2019 pp 34-35

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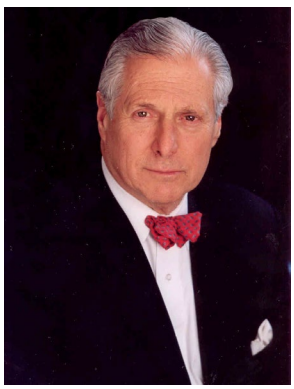
THANKS TO LEWIS LANDSBERG

Lewis Landsberg steps down from chairing the Board of Management of the Journal of Hypertension – Maciej Tomaszewski takes over



Lewis Landsberg has served with great distinction on the Board of Management of the Journal of Hypertension for more than 25 years. He has been Chairman of the Board since here placed John Chalmers in 1995-96, at the time when Alberto Zanchetti took over as Editor from John Reid.

Apart from the Chairman (ISH), the Deputy Chairman (ESH), and the Editor, the Board has four members from the ISH, three from the ESH, and a representative from the Publisher (Wolters Kluwer). The ISH Secretariat assists with writing the Minutes etc. Over these years, Lewis Landsberg has overseen several difficult negotiations of the agreements between the Publisher of the Journal and the ISH and ESH. This has been done together with friends of the Landsberg family skilled in legal matters.

Looking over this long period when the two friends Alberto Zanchetti and Lewis Landsberg worked together, the Journal’ success could be expressed as an increase in Impact Factor from 2.7 in 1996 to 4.1 in 2017, or from below 500 full papers submitted in 1996 to over 1000 in 2018.

Lewis Landsberg graduated ‘Summa Cum Laude’ from Williams College in 1960 and from Yale University School of Medicine in 1964. Following residency training in Internal Medicine at Yale-New-Haven Hospital, he perused a research fellowship at the National Institute of Health (NIH) in the laboratory of Julius Axelrod (Nobel Prize Laureate). Lewis Landsberg was recruited to Harvard Medical School and promoted to Professor of Medicine in 1986. In 1999, he became the Dean of the Northwestern University, Feinberg School of Medicine in Chicago. In honor of Lewis Landsberg’s accomplishments as Dean, the Deanship carries his name after he retired some years ago.

I have had the privilege of working alongside Lewis Landsberg on the Board of Management for more than 25 years, first for the ESH and later for the ISH. With his, polite, gentle and clever ways, his lovely sense of humor, and his “common sense” approach to difficult issues he stands out as an outstanding leader, who I admire immensely and who we owe a lot of thanks! Taking over after Lewis Landsberg will not be an easy task and we wish Maciej Tomaszewski the best of luck!

Lars H Lindholm, Editor- lars.h.lindholm@umu.se

Left to right: Alberto Zanchetti, TBC, Lewis & Jill Landsberg

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Alta Schutte

ISH President 2018-2020

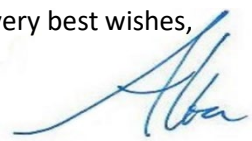
Dear Members of the International Society of Hypertension:

I am delighted to share with you the highlights of the Society's activities over the past months, and to briefly update you on the upcoming initiatives and activities that you should look out for.

- On a practical note, you may have all recently received an email from the ISH Secretariat that from 1 June 2019 onwards the Secretariat services of the ISH will be handled by Margaret Sherry and her team from In Conference. Their team is very familiar with the global community in the field of hypertension and we are greatly looking forward to this partnership. Please note that the ISH website and secretariat email address (secretariat@ish-world.com) will remain unchanged.
- I simply need to mention my delight at the immense efforts from our membership and volunteers all around the world involved in **May Measurement Month (MMM19)**. On all our social media accounts and beyond – the successful global blood pressure screenings have certainly been noticed! Furthermore the findings from MMM2018 has been published in May in the European Heart Journal (http://bit.ly/2RnwuEB), along with the country-specific results from 39 countries (in European Heart Journal Supplements). My sincere congratulations to Neil Poulter as Chair of the MMM-team.
- In the meantime the ISH Guidelines Committee, Chaired by Thomas Unger, is working actively on the development of the **ISH Worldwide Hypertension Guidelines**, also to be released in Glasgow 2020. Of note is that these new guidelines will be a short practical document including information that is clear, relevant and widely applicable – also in lower and middle income countries.
- In less than a year's time I am looking forward to meeting many of you in person again at the **Joint ESH-ISH Meeting** to be held in **Glasgow, Scotland from 29 May to 1 June 2020**. Please save the date! This event will not only be an opportunity to network, meet with old friends and to be updated on the latest science in the field of hypertension and cardiovascular disease, but it will also be the opportune time to recognise our members for excellence in scientific research. We will in the coming months invite you all to submit nominations for the various ISH awards (http://ish-world.com/activities/awards-prizes.htm), recognising new investigators, but also life-time achievers, women and those working in the developing world. **The Women in Hypertension Committee** and **New Investigator Committee** are also actively planning for activities during the meeting in Glasgow. So watch this space!
- For the very 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 awarding **"Fellows of the International Society of Hypertension" (FISH).** FISH status will be a symbol of excellence, and will represent recognition by the ISH of our members' scientific and professional accomplishments in the field of hypertension. Members will be invited during the coming months to apply online.
- Please take note that in 2022 the Scientific Meeting of the Society will be held in Kyoto, Japan. We are now also inviting interested countries to submit bids for the **ISH Scientific Meeting to be held in 2024.**

I would like to thank the many ISH members around the world whom I have met during the past months – electronically, but also during my travels to Indonesia and Korea. I am looking forward to getting in touch with many of you during the coming months. So, please do not hesitate to contact me with any ideas or suggestions (secretariat@ish-world.com).

With my very best wishes,



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Thomas Unger

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Everything flows, the famous πάντα ῥεῖ (panta rhei) of the old Greek philosopher Heraklit. He was right then and even more so today with respect to ISH, our society. We have spent the last months in a transition period from one administrative agency (Conference Collective, London UK) to another (In Conference, Edinburgh/Glasgow, UK), and that we were not "lost in translation" – or rather transition - is due to the fact that several members of the ISH Executive Committee, in particular our President Alta Schutte together with Vice-President Fadi Charchar and Treasurer Markus Schlaich, have spent innumerable hours to allow for a smooth handover.

Over the years, the collaboration with Conference Collective (CC) led by Jacinta Scannell, assisted more recently by Steve Rawson, was quite harmonious and fruitful, especially with the enormous help from Helen Horsfield at CC, who cared about virtually all ISH matters, and also some other members of the group like Charlotte Swindall who helped us very efficiently with our Hypertension Newsletter. However, when both ladies said goodbye to Conference Collective virtually at the same time, they left a certain vacuum. After intensive discussions, the ISH Executive Committee decided to move to a new agency, i.e. In Conference (InC), under the leadership of Margaret Sherry. Within InC, Claire Simpson and Leonie Postma are responsible for the overall management of the society, Juliet Bruce-Dickie will assist our treasurer in financial matters, and they will be supported by Araceli Segreto and Luxor McGowan. After several months of preparation, the final handover took place on June 1st, and, due to the collaborative spirit on all sides, it was a smooth transition without major obstacles. Everyone who was involved in this complex transitional project deserves our deepest gratitude for a great job.

One part of the ISH administration, however, will stay with CC, i.e. May Measurement Month (MMM), which has been run very professionally by Judith Bunn under the leadership of our past President, Neil Poulter, the 'father' of MMM.

Panta rhei: I'm sure that ISH will certainly recover from the strains of transition very quickly and address its multiple tasks with new vigour following our mission to reduce the global burden of raised blood pressure.

Thomas Unger, Secretary - thomas.unger@maastrichtuniversity.nl

PRESIDENT ELECT

Maciej Tomaszewski the New President-Elect of ISH

Maciej Tomaszewski is Professor of Cardiovascular Medicine at the University of Manchester and a member of the ISH Council since 2014. He is now the President-Elect of our Society and will take up the office at the ISH/ESH meeting in 2020 in Glasgow, where his clinical research career commenced in 2000 on an ISH fellowship. Maciej was Secretary of the Scientific Council and of the Society between 2016 and 2018 and many of you have followed his excellent reporting from the Executive meetings in the new column "The Secretary's Voice", which he was first to write.

One of Maciej Tomaszewski's major contributions for the Society was the leadership of New Investigator Committee where he worked very hard indeedrecruiting a new group of young, talented scientists and clinicians with a deep interest in hypertension. Many of them represent the new generation of leaders in the field, and maybe in our Society as well.

So, where does Maciej Tomaszewski want to take the ISH? In his one-pager, sent to the voting members of the Council, he first mentions forming alliances and partnerships between the Society and key hypertension stakeholders in academia, governments, industry, and publishing, in order to promote and strengthen the "ISH Brand" as the leading Hypertension Society. He also wants to strengthen the ISH membership base and create new career opportunities for the next generation of young researchers in the field. Moreover, Maciej wants to increase the engagement of the ISH around the world for better equality of access to blood pressure lowering treatment and better health care to patients in the most under-privileged countries.

The Hypertension News team wishes Maciej Tomaszewski the best of luck! It is indeed a major undertaking.

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We are delighted to be working with ISH, the team dedicated ISH team is led by of Margaret Sherry with Claire Simpson and Leonie Postma responsible for the overall management of the society, Juliet Bruce-Dickie assisting the treasurer in financial matters, and they will be supported by Araceli Segreto and Luxor McGowan.

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Claire Simpson, Leonie Postma, Juliet Bruce-Dickie & the rest of the In Conference team.

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The important relationship between the kidney and the heart

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Opinions diverge about hypertension being a disease belonging to nephrology or cardiology, and I believe the answers are as many as the number of persons you ask. Maybe hypertension is not a single disease but a hemodynamic syndrome, and should be better considered a risk factor for cardiovascular (and other) events [1]. More important, however, is the strong interdependent relationship between the heart and the kidney. In several disorders involving kidneys and the heart, acute or chronic dysfunction in one organ may affect the other organ, which is named the cardiorenal syndrome. A more precise definition of the cardiorenal syndrome than the simplistic view of renal dysfunction secondary to heart disease was advocated more than a decade ago, suggesting five subtypes [2]. A recent very comprehensive review of the cardiorenal syndrome by McCullogh, Rangaswami, and collaborators [3] now adds to our understanding and provides future directions in cardiorenal medicine.

Type 1 cardiorenal syndrome is an acute syndrome of heart failure (e.g. an acute coronary syndrome or acute heart failure) resulting in acute kidney injury, and type 2 is a chronic syndrome of chronic heart failure resulting in chronic kidney disease. Type 3 is an acute renocardiac syndrome with acute kidney injury (e.g. volume overload, inflammatory surge, or uraemia with metabolic disturbances) resulting in acute heart failure, and type 4 is a chronic renocardiac syndrome with chronic kidney disease resulting in chronic heart failure (by e.g. left ventricular hypertrophy or cardiomyopathy associated with chronic kidney disease). Finally, secondary cardiorenal syndrome (type 5) is a systematic condition (e.g. amyloidosis, sepsis, or cirrhosis) resulting in both heart failure and renal failure. These types represent different hemodynamic conditions where the failing heart affects the kidneys or vice versa, and different characteristic patterns of activated neurohormonal and inflammatory pathways.

A diagnosis of cardiorenal syndrome requires signs and symptoms, as well as evidence structural or functional abnormalities in the heart and the kidneys. This review [3] provides a comprehensive overview of available cardiac biomarkers (myocyte death, wall tension, and myocardial fibrosis) and renal biomarkers (glomerular filtration and integrity, and tubular injury), and imaging modalities. Of note, these available common biomarkers also offer prognostic information in acute and chronic cardiorenal syndromes. Specific drug treatment directed to the underlying mechanisms, including diuretics, neurohormonal modulation, vasodilators, and inotropic therapy, with current evidence from clinical trials is presented. Finally, cardiac device based therapy and the treatment of heart failure in kidney transplant patients is reviewed.

Patients with cardiac and renal disease combined have an unacceptable high risk of symptoms, hospitalizations, and fatality rate. A multidisciplinary approach including cardiologists and nephrologists is obviously important in the management of these patients. The target for management of patients a cardiorenal syndrome should be reduction of major cardiovascular (including myocardial infarction, heart failure, and stroke) and renal (including acute kidney injury, progression of chronic kidney disease, renal replacement therapy) events, hospitalizations and death. An increased awareness and understanding of the cardiorenal syndrome is important to all of us.

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A potentially new target for stroke recovery… 'Nox' at the door

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It is well established that hypertension creates a vascular environment ripe for both hemorrhagic and ischemic stroke. Recovery from ischemic stroke is facilitated clinically by interventions that remove vascular occlusions via tissue plasminogen activator-mediated thrombolysis [1]. While patients have largely benefited from this therapy, enjoying leading remarkable recovery rates, a not insignificant proportion of individuals experience vascular complications which include leakage of the blood brain barrier and hemorrhage [2], coupled with reactive oxygen species (ROS) overproduction which can worsen outcomes [1].

The source(s) of such ROS generation have until now remained obscure and therefore beyond the reach of potentially beneficial targeted therapeutic intervention. However, a recent study by Casas and co-workers sheds new light upon the enzymatic source of such deleterious ROS produced during recovery from ischemic stroke[3]. In this novel work, the authors focus upon a relatively unique member of the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (Nox) family – the Nox5 isoform, and show that its expression in the vascular endothelium is sufficient to drive oxidative stress thus rendering the brain susceptible to impaired recovery from post-occlusion-mediated ischemic stroke in a mouse model.

While many sources of ROS contribute to oxidative stress (xanthine oxidases, lipoxygenases and mitochondrial respiratory chain oxidation), Nox enzymes produce physiologically significant $O_2^{-\bullet}$ and H2O2 throughout the body (reviewed in [4]). The Nox family consists of seven members (Nox1-5, Duox1-2). Nox5 is potentially a good target for therapies because it differs from other Nox isoforms in terms of its activation and tissue distribution. Most Nox isoforms are dependent on protein co-factors for their activity (e.g., p22phox), but Nox5 is not[5] . Furthermore, while Nox5 is structurally similar to other Noxes in that it contains conserved C-terminal NADPH and FAD binding domains and 6 transmembrane-spanning regions, its amino terminus harbours multiple EF-hands that regulate its activity in response to intracellular Ca^{2+} [6]. Phosphorylation of amino acid residues alters EF-hand domain conformation to enhance Nox5 sensitivity to physiological Ca^{2+} levels [7].

Research into the precise physiological and pathophysiological roles of Nox5 has been limited by the fact that it is absent from the mouse/rat genomes. While Nox5 is highly expressed during fetal development, its levels are low in healthy adult tissues with the exception of spleen and testis [8,9]. It is upregulated in disease (e.g., in intramyocardial blood vessels and myocytes [10] following infarction and in abdominal aortic aneurysms [11]). Nox5 was detected in glomeruli of individuals with diabetic kidney disease but not in non-diabetic individuals and it was recently reported that Nox5 is found in renal proximal tubules of individuals with hypertension[12]. Transgenic mice with vascular smooth muscle / mesangial cell Nox5 expression are susceptible to diabetic kidney injury, although BP was unaffected[13]. Work in other animal models suggest that NOX5 contributes to the pathophysiology of stroke. Mice with human Nox5 expression in the endothelium exhibit elevated blood pressure along [15]. with enhance stroke risk [14]. Furthermore, Genome wide association studies have suggested a role for NOX5 in hypertension.

Specifically, *NOX5* was identified as a putative blood pressure-associated gene being positively linked to elevated blood pressure [15]. Lastly, SNPs (e.g., T253M) in *Nox5* were identified that alter phosphorylation-dependent Nox5 activity [13]. Interestingly, T253M is a low-frequency SNP (0.37%), suggesting that it is not well tolerated, and it was limited to African Americans – who are at high risk for CKD. These studies imply that interventions that abrogate NOX5 activity could be both vasculoprotective and neurorotective.
Along these line, the studies of Casas and colleagues in the April issue of *The Journal of Clinical Investigation* provide new evidence that Nox5 is sufficient to impair recovery from occlusion-mediated ischemic stroke. They employ both *in vitro* and *in vivo* approaches to support this novel hypothesis.

For *in vivo* studies, since Nox5 is absent from the rodent genome, this group engineered an elegant humanized mouse model wherein Nox5 is knocked into the *Hprt* locus and placed under the endothelium-specific *Tie2* promoter. The result is a mouse line that specifically expresses Nox5 in the vascular endothelium.

These mice were subsequently subjected to a model of stroke by a transient occlusion of the middle cerebral artery. Upon reperfusion, the blood brain barrier typically becomes abnormally permeable (leaky). This impairment is known to be both Ca^{2+} and ROS-dependent which are thought to disrupt tight junction maintenance in the blood brain barrier.

As Nox5 is activated by increased intracellular calcium levels, it was appropriate that Nox5-knockin mice exhibited significantly worsened blood brain barrier leakage as compared to wild type controls. Such blood brain barrier injury was accompanied by excessive poststroke ROS formation, infarct size, and worsened neuromotor performance.
For *in vitro* studies, cultures of human brain microvascular endothelial cells were subjected to hypoxic conditions followed by reoxygenation and cell permeability assessed. A Nox5-specific inhibitor (ML090) was protective in this setting thereby implicating this Nox family member at a cellular level.
While these informative studies suggest a role for Nox5 in limiting recovery of the permeability of the blood brain barrier under conditions of post-ischemic stroke, a number of new questions and avenues for investigation have emerged. Importantly, whether such Nox5-dependent injury occurs in human patients remains to be determined. While the ROS-dependent blood brain injury and infarct sizes were substantial, the question of whether the expression level of Nox5 was reflective of physiological levels remains. Furthermore, the determinants of Nox5 regulation in the brain endothelium– namely at the level of its expression and activity await identification. As for new avenues, this important study opens the door and provides further impetus for the development of novel therapeutic compounds which specifically target the Nox5 isoform. Up until now, most pan-specific antioxidants and non-selective Nox inhibitors have been largely ineffective in reducing disease progression in a number of contexts. Could this be a "Nox at the door" ushering in a new therapy using yet to be developed, highly selective Nox5 inhibitors to improve neuroprotection and recovery from conditions such as stroke?

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Animals in Hypertension Research

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In this issue of "Hypertension News", two articles will deal with animal experiments in hypertension research. This theme has long been controversial in times of animal protection with its activists, and of recent molecular technologies and computer simulation. For years we have heard the outcry from animal protectionists but also from the political side: "Why can't we replace animal studies by in vitro experiments?"

While molecular and cellular experiments as well as computer simulation both have their own realms and merits – they will be dealt with in a later issue of "Hypertension News"– neither of them will be able to fully replace the experiments in animals, be it to augment our physio-pathological knowledge of hypertensive mechanisms or to develop antihypertensive/cardiovascular drugs.

When I started my scientific carrier as a post-doc fellow in Montréal, Canada, my first task was to look into the dopamine metabolism in dogs. My boss had the idea that conjugated dopamine played a physiological role beyond being an inert metabolite for urinary excretion, and to follow his hypothesis, I had to take blood from the renal and adrenal artery of the animals. The outcome of these experiments was rather unspectacular and, in retrospect, I have to admit that I made the unfortunate dogs suffer without adding much of importance to our scientific knowledge. This may serve as an example were the animal protectionists are right: Unnecessary, ill-designed animal experiments are unethical and have to be avoided.

However, the coin has always two sides: When I returned in 1978 to Heidelberg, Germany, to my next post-doc position, Franz Gross, then director of the Institute of Pharmacology at Heidelberg University and a big shot in hypertension research and drug development, showed me a bottle with a white powder which read "SQ 14 225". This was the name of a new drug to be introduced to the market three years later as "Captopril", the first ACE-Inhibitor. Professor Gross handed the bottle over to me with the words: "Try it but no doubt you will see that it does not lower blood pressure in our spontaneously hypertensive rats since they have a suppressed plasma renin-angiotensin system (RAS)". He followed a widespread hypothesis among hypertension scientists of the time, i.e. that inhibition of the RAS could only unfold antihypertensive actions in individuals with a stimulated plasma RAS. I was ignorant enough to feed the animals with this bitter-tasting powder for a period of several weeks and – I could dose-dependently titrate their blood pressure from about 200 mmHg down to normotensive values.[1] This was certainly not the only study showing this effect but together with animal experiments, mostly in rats and dogs, by many other researchers around the globe, it falsified the hypotheses shared by Franz Gross and many others on the antihypertensive action of RAS inhibitors and paved the ground for our understanding of the actions of ACE inhibitors in general and, finally, for their immense therapeutic success.

A further example: At one point my colleague Juraj Culman and I became interested in the role of tachykinin peptides like Substance P in central stress responses, such as the well-known "defense" reaction of the sympathetic nervous system. In a series of experiments in rats, we could indeed demonstrate that Substance P is a central transmitter involved and, moreover, that the 'love hormone' oxytocin plays an additional, critical role in this complex defense reaction to unpleasant stimuli [2]. Such a gain of fundamental knowledge could have never be attained with in vitro-studies or computerized models; for this one needs the whole set of interacting central and peripheral regulatory systems in an intact organism.

And a third example: Frits Prinzen, an internationally recognized physiologist of Maastricht University in the Netherlands, had developed in dog experiments on electro-mechanics of the heart a way to synchronize the cardiac conduction system and thereby improve the cardiac pumping capacity in heart failure.

In 2007 he and colleagues published in the NEJM how left ventricular apex pacing cured a child [3], and this was confirmed five years later in a large clinical trial. A perfect, convincing example of so-called translational medicine, directly from the animal experiment to the bedside.

Without Prinzen's dog studies, this life-saving success wouldn't have been possible. Some years later, when I was still Scientific Director of CARIM - the Cardiovascular Institute of Maastricht University, the animal protectionist had won the battle: Frits Prinzen was forced to stop his experiments in dogs, and I couldn't avert it. His comment: "Experiments in dogs are a sensitive topic in the general public, related to the strokability of these animals. However, there was a considerable literature and experience from the own laboratory that effects on ventricular pacing were significantly different when testing in other large animals like pigs and goats. Therefore, doing these studies in dogs was the only way to reach the goal of a better treatment for pacemaker patients." And: " The question arises whether it is ethically acceptable to take a dog's life to safe a human life". I would say: Yes, it is. But not everyone shares this opinion. In the Netherlands, for instance, there is a political move to ban all animal experiments by 2025.

So, let us open the discussion on animal experiments in hypertension by a number of articles on the issue in this and a further issue of "Hypertension News". You, the readers, are welcome to send us your comments via any media, and we will try to create a dedicated, lively forum in our journal.

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LEARNING THE ROPES (2)

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Role of animal experiments in hypertension research

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From the early times of hypertension research animal models have been instrumental to acquire novel insights in the regulatory principles defining blood pressure. Moreover they have been essential for the discovery of therapeutic targets and the development of corresponding drugs as particularly exemplified in the renin-angiotensin system. Recent technological revolutions in the detailed analysis and in the targeted alteration of genomes will resume and even accelerate this process in the future. In conclusion, animal experiments have been essential and will remain irreplaceable in hypertension research. Animal experiments have been essential for hypertension research from its beginnings. Already 1898, Tigerstedt and Bergmann injected rabbit kidney extracts into recipient rabbits to discover a hypertensinogenic substance, which they called renin [1] (Figure 1). Nearly 40 years later Harry Goldblatt clipped the kidney of a dog, thereby released renin and induced hypertension in the animal [2] (Figure 2).

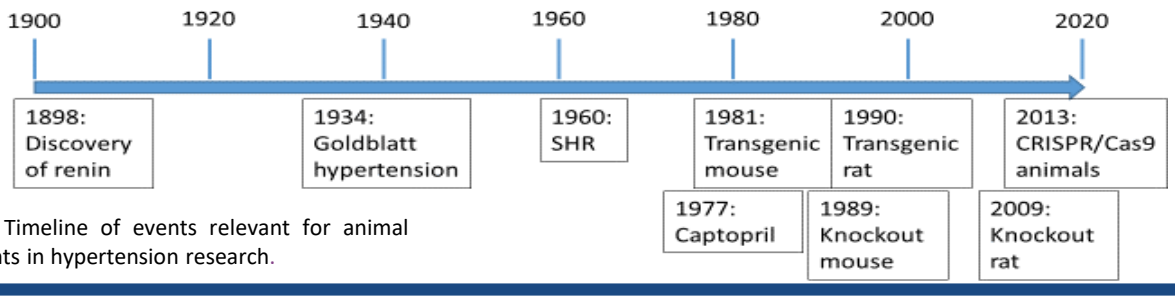

Figure 1: Timeline of events relevant for animal experiments in hypertension research.

This created the classical renovascular model of hypertension (Table 1). It was later mainly applied in the rat which became the most frequently used animal species in hypertension research. In the 1950s and 60s several laboratories intended to generate rat models of human essential hypertension by selecting and inbreeding rats with the highest blood pressures in outbred strains (Table 1). This way the spontaneously hypertensive rats (SHR) were established in Japan, the Dahl salt sensitive rats in the US and several other models all over the world [3]. These experimental and genetic rat models of hypertension helped to discover mechanisms which regulate blood pressure and elicit the hypertensive damage in target organs such as heart, vessels, and kidney. In particular however, they were instrumental in the development of novel antihypertensive drugs. The first inhibitor of the angiotensin-converting enzyme (ACE), captopril, and losartan, the first blocker of the AT1 receptor for angiotensin (Ang) II, were tested in Goldblatt-hypertensive rats [4].

The genetic rat models of hypertension were also used to reveal novel genes involved in the pathogenesis of hypertension by quantitative trait locus (QTL) analysis exploiting polymorphisms between the hypertensive strain and a normotensive control strain. One of the genes discovered by this method codes for ACE2, which turned out to be less expressed in SHR compared to control rats [5]. ACE2 is a major regulator of the renin-angiotensin system since it metabolizes Ang II to Ang-(1-7) and thereby converts a vasoconstrictive peptide into a protective one. We could confirm the importance of this gene for the pathogenesis of hypertension in SHR by reconstituting its expression in vessels of these rats and thereby reducing their blood pressure [6].

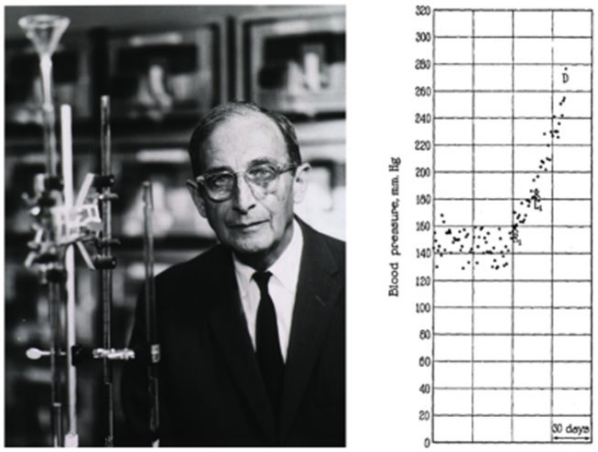

Figure 2: Harry Goldblatt with his blood pressure measuring device (left) and blood pressure response of a dog after clipping of one renal artery (right) [2].

Such experiments became possible in the early 1980s when a new era in animal research begun allowing permanent changes in the genome of animals (Figure 1). First only "transgenes" could be added to the genome by random integration of DNA-constructs but later also targeted alteration of genes was achieved using homologous recombination in embryonic stem (ES) cells, which was mainly used to ablate genes ("knockout technology"). Unfortunately, these techniques were first available only in the mouse, a species which had previously been avoided by hypertension researchers owing to its small size. At least only with a short delay, transgenic technology was also established for the rat in 1990 [7]. Interestingly, the first transgenic rat (TGR(mREN2)27) overexpressed the mouse renin gene Ren-2 and became another classical model of hypertension (Table 1). Other transgenic rats confirmed the importance of the brain and in particular the central Ang II generation in blood pressure control [8].

Table 1: Classical Hypertension Models

Name	Induced by
Goldblatt hypertension	Clipping of one kidney artery
DOCA-salt hypertension	DOCA (mineralocorticoid) pellet implantation, high salt diet
L-NAME hypertension	L-NAME (NO synthase inhibitor) infusion
Ang II hypertension	Angiotensin II infusion
Spontaneously hypertensive rat (SHR)	Selective breeding, polygenic
Milan hypertensive rat	Selective breeding, polygenic
Lyon hypertensive rat	Selective breeding, polygenic
Dahl salt-sensitive (DSS) rat	Selective breeding, polygenic, high salt diet
SABRA hypertensive rat	Selective breeding, polygenic, high salt diet
ISIAH rats	Selective breeding, polygenic, immobilization stress
TGR(mREN2)27 rat	Transgenic expression of the mouse Renin-2 gene
eNOS-knockout mouse	Genetic deletion of endothelial NO synthase

However, knockout technology remained restricted to the mouse for nearly 20 years and forced hypertension researchers to accommodate to the mouse as model species to exploit this powerful method for functional genomics. Cardiovascular phenotyping methods were down-scaled to the mouse, but still remain less reliable as the ones in the rat. For example the state-of-the-art method to measure blood pressure in awake, freely moving animals, the implantation of telemetry transmitters, inevitably alters blood pressure regulation in mice, but not in rats, by blocking blood vessels.

Nevertheless, knockout mouse models were instrumental to discover unpredicted players in blood pressure regulation such as the immune system, by the discovery that Rag2-knockout mice lacking T-cells do not respond to Ang II infusion with increased blood pressure [9]. Surprisingly, mice lacking AT1 specifically in vessels showed that this mechanism was even more important for the hypertensive effect of Ang II than the expected vasoconstriction [10].

Between 2008 and 2013, four new technologies were developed one after the other which finally also allowed targeted genetic alterations in the rat (Figure 1). First rat ES cells and classical knockout technology became available and shortly thereafter zincfinger- and TALE-nucleases were developed. These are restriction enzymes which are guided by specific DNA-binding protein domains to selected sites in the genome. After cutting of the DNA double strand at this site, cellular repair processes religate the DNA, but include small deletions or insertions and thereby often frame-shift mutations in genes. Moreover by offering a repair template, predesigned mutations can be included at the target site. Of note, these powerful techniques were first developed in rats, since there was an urgent need to generate knockout animals in this species mainly driven by cardiovascular researchers. But finally all these techniques were superseded by CRISPR/Cas9 technology, in which the DNase Cas9 is targeted to a specific site in the genome by a homologous guide RNA. When Cas9 cuts, the same options for gene destruction or alteration are available as for zincfinger- and TALE-nucleases. This technique is available in all animal species including the rat and may allow at least a partial renaissance of this species in modern hypertension research.
In parallel to this revolution in transgenic technology, rapid progress in DNA-sequencing methodology allowed the elucidation of whole genomes. By comparing thousands of genomes of hypertensive and normotensive individuals in genome-wide association studies (GWAS) several hundred genes were found to be linked to increased blood pressure. These genes may code for novel targets for antihypertensive therapy. The most straight-forward way to raise this treasure will be to mimic the hypertensive gene variants in suitable animal models using modern transgenic technology and reveal their impact on blood pressure regulation. In the ideal case the same animal models could also be used for the development of drugs interfering with the novel target. This would resume the use of animal models in hypertension research as it started more than a century ago.

In conclusion, hypertension research will stay dependent on experiments in whole mammalian organisms, since cell cultures or organoids can never recapitulate the complex interaction of cardiovascular organs such as heart, vessels and kidney, with different arms of the nervous system, the immune system, and numerous hormones, which set the blood pressure level and thereby determine hypertension in animals including humans.

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Value of animal experiments in drug development for hypertension and associated diseases

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Since the 1960s, more than 150 new drugs for the prevention or treatment of cardiovascular disease (CVD) including blood pressure (BP) lowering drugs have been approved[3]. Nevertheless, recent reports divulge a stagnation in the discovery and development of new cardiovascular therapeutics[3]. This seems problematic against the background that elevated BP remains the leading cause of premature death worldwide and accounts for over 200 million disability-adjusted life years[10]. Recent technological advances for target identification together with the development of novel analytical technologies in animal models for BP phenotypes and hypertension-mediated organ damage (HMOD) could tackle this challenge. Here, we briefly discuss the opportunities provided by animal models to support and improve the discovery and preclinical phase of the drug development process of novel therapeutics in hypertension and HMOD (**Figure 1**).

Recent large genome-wide association studies (GWAS) for BP traits identified >1000 independent genetic loci associated with BP phenotypes and thereby enrich our understanding of the complex, polygenetic nature of BP regulation[4]. This knowledge could potentially impact on risk stratification of patients with genetic risk scores, drug selection by pharmacogenomics, and the discovery of novel molecular entities for drug development (recently reviewed in[7]). So far, however, only a few novel promising candidates emerged among the numerous loci identified. Ironically, UMOD (uromodulin) encoding Tamm-Horsfall protein, that has been known since the 19th century[2] emerged as a valuable new pharmacological target. Subsequent to the identification of a single nucleotide polymorphism (SNP) at the UMOD locus and its association with hypertension in early GWAS, gene targeting of UMOD in mice strongly supported a functional role of UMOD for BP regulation and salt-sensitivity[7]. Thus, the `UMOD example´ represents a case in point by highlighting the importance of experimental animal work in complementing GWAS studies (**Figure 1**).

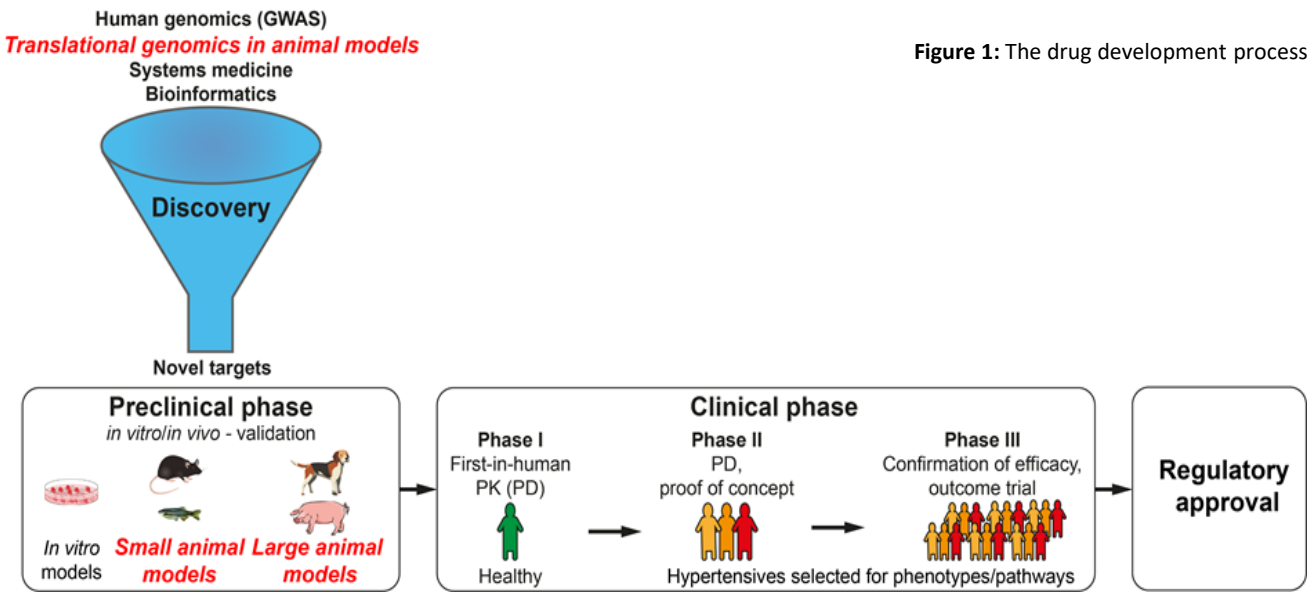

Figure 1: The drug development process

In addition, translational genomic work-up in inbred rodent models of hypertension and HMOD represents another powerful strategy to identify novel targets for therapeutic development[1,7]. These inbred models with their homogeneous genomic background allow tightly controlled experiments to analyze genotype – phenotype relations without the confounding heterogeneous genetic background present in human large – population GWAS[6,8].

A recent study demonstrated that the integrative analysis of the genomic architecture of quantitative trait loci (QTL) identified in inbred hypertensive rat models is a powerful strategy to identify novel targets for HMOD in the kidney (Figure 2)[9]. This particular study focused on the analysis of an albuminuria – QTL identified in the Munich Wistar Frömter (MWF) rat strain as a suitable inbred model for HMOD in the kidney. Congenic substitution mapping of the albuminuria locus combined with next generation sequencing and compartment – specific RNA sequencing analysis in isolated glomeruli tissue led to the identification of Tmem63c as a novel target responsible for the onset of albuminuria in the MWF rat strain. Subsequently, the functional role of Tmem63c was evaluated in zebrafish models as another simple in vivo vertebrate animal model. Reduction of tmem63c levels by targeting an ortholog of the gene with CRISPR–Cas9 or Morpholino gene-editing technologies, respectively in developing zebrafish embryos lead to compromised functionality of the glomerular filtration barrier. The albuminuria - like phenotype could be readily analyzed using transgenic reporter lines; its functional and structural correlates were directly analyzed in the target tissue by imaging analysis using confocal and electron microscopy (**Figure 2**). The potential translational relevance of TMEM63C for kidney damage in humans was confirmed in human biopsies of patients with corresponding kidney disease phenotypes by showing a loss of glomerular TMEM63c in podocytes of patient samples[9].

Taken together, the `UMOD example´ clearly indicates the power of the reverse genetics approach in animals models to validate the functional role of a potential candidate detected in GWAS in humans; in this case UMOD as a candidate for BP regulation and potential target for BP lowering therapy. Conversely, the `Tmem63c example´, supports the power of the forward genetics approach by starting with the analysis of the phenotype in animal model, leading to the discovery of a novel candidate gene for validation in humans studies.

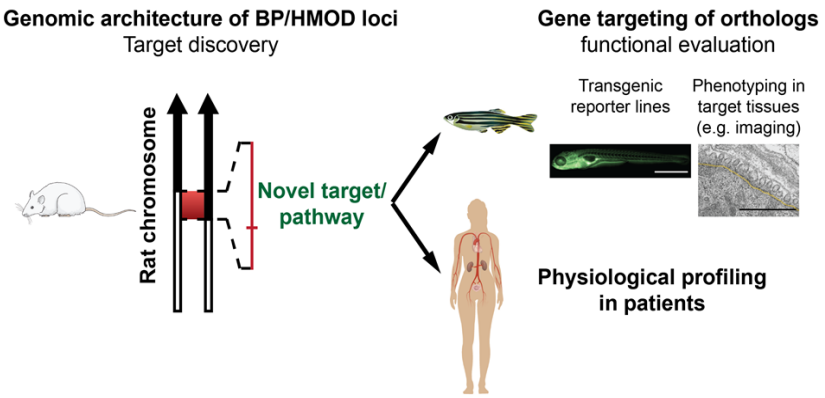

Figure 2: The forward genetics approach: Translational genomics in inbred rodent models as a powerful tool in target identification

Recently, enormous progress has been achieved not only towards the identification of the genetic basis of BP regulation in humans by large-scale GWAS meta-analysis but also by profound advances in systems biology, bioinformatics and computer - aided drug design and development. In addition, major advances in organ–on–a–chip and organoid engineering approaches have been made[5]. Taken together these promising developments led some authors to believe that animal studies can largely be dispensed with in the drug discovery and development process[6].

However, BP and HMOD phenotypes are highly complex traits that depend not only on >1000 genes, but also on environmental conditions with interactions among genes, environment and age. Clearly, the systematic in depth analysis of this complexity in human studies alone has its limitation[6]. Consequently, the combination of observations in humans with the power of experiments in animal models in a virtuous cycle still seems to be an appropriate and promising approach to support drug development in hypertension and associated diseases (Figure 3). In conclusion, despite recent advances in genomics, systems biology, bioinformatics and computer -aided drug design and development, studies in animal models such as rodent models with hypertension and HMOD are still important and indispensable for drug discovery and development.

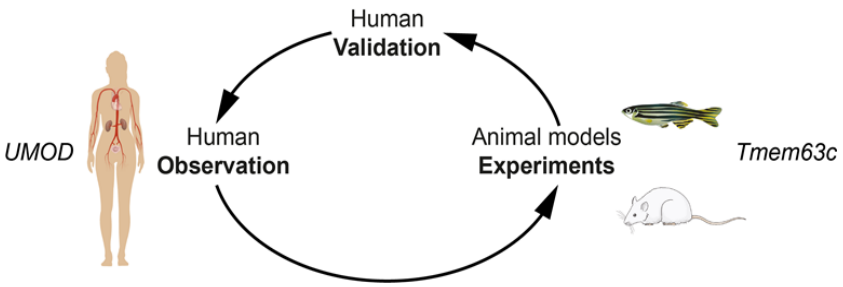

Figure 3: The virtuous cycle of observations in humans and animal models (adapted from (Nadeau & Auwerx, 2019).

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Birth of the 'Women in Hypertension Research Programme'

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The need for the Women in Hypertension Research Programme

During my presidency of ISH, 2014-2016, it became very clear to me that despite women contributing significantly to the hypertension community, they were under-represented in many aspects of ISH. For example, before 2014 there had never been a woman president in the 48 years of the existence of ISH and in 2016, while women constituted 24% of the ISH membership, only 13% were represented on the leadership committees. This was even worse in earlier years. To address this I made it a priority of my Presidency mandate to improve the situation. With the strong support, encouragement and backing of the ISH Executive, this became a reality and the Women in Hypertension Research (WiHR) Programme of ISH was born. Working with an outstanding and committed subcommittee (2015-2018) including Sofie Brouwers (Belgium), Louise Burrell (Australia), Fadi Charchar (Australia), Alta Schutte (South Africa) and Ulrike (Muscha) Steckelings (Denmark), we set out to identify some of the challenges and needs of our women ISH members. Listening to the voices from our male and female members from all regions represented in ISH, we developed a clear mission, in perfect alignment with that of ISH, which is committed to encouraging, supporting and inspiring women in science and medicine in the field of hypertension and related cardiovascular diseases.

The mission and goals

Specifically, the mission of the WiHR programme is to promote women scientists and clinicians so that they can fulfil their career aspirations in hypertension and related cardiovascular diseases.
In addition the WiHR programme aims to:

1. Provide a platform for networking and mentoring.
2. Recognise and promote successes of women in the hypertension community.
3. Involve all ISH members in promoting equal opportunities for women in science and medicine based on merit.
4. Encourage research in the field of 'hypertension and cardiovascular disease in women'

To achieve this mission, our initial goals focused on:

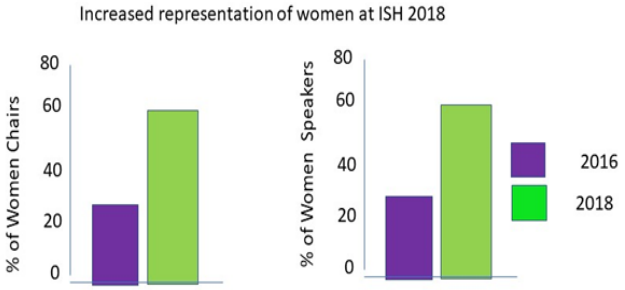
1. Securing better representation of women as key figures in ISH leadership, scientific meetings and activities
2. Having special mentoring and scientific sessions led by the WiHS committee at the biennial ISH Scientific Meetings
3. Ensuring active participation in ISH summer schools
4. Creation of 2 new awards, namely
    - ❖ Mid-Career Award for women researchers
    - ❖ Research Award related to 'hypertension and cardiovascular disease in women'.
5. Establishing a special honour (plaque) for senior women who have given outstanding service to the ISH and/or made exceptionally distinguished contributions to hypertension research.
6. Creation of a global mentoring scheme for women, through networks, seminars, training programmes, discussion groups, travel awards etc.
7. Engagement with the annual MMM by highlighting 'hypertension and cardiovascular disease in women'.
8. Creation of a highlighted section on the ISH website.

Launch of the Women in Hypertension Research Programme

In 2016, the WiHR programme was born at the biennial scientific ISH meeting in Seoul. At a special dedicated session, the programme was launched with special guest speaker Prof Barbara Casadei, BHF Chair of cardiovascular medicine, Oxford University, who gave an inspirational presentation about her journey as a cardiovascular researcher and clinician. At the launch meeting we also honoured our senior members who had provided outstanding service to ISH and/or made exceptionally distinguished contributions to hypertension research.

These included Prof Ann Soenarta (Indonesia, Prof Talma Rosenthal (Israel), Prof Suzanne Oparil (USA), Prof Bonita Falkner (USA) and Prof Lisheng Liu (China).

Over the course of the next 2 years, many of these ambitions were beginning to be realised. By 2018, at the biennial meeting held in Beijing, ISH had secured a second woman president (Alta Schutte, 2018-2020), the number of women in ISH leadership committees had grown and there was a marked increase (from 20% to 50%) in women representation at the Beijing meeting as shown in the graphs.



Moreover, the WiHR group led 3 special sessions at the 2018 Beijing meeting (Special mentoring session 'Women in Hypertension Research- maximising opportunities and research career goals'; Breakfast workshop "Hypertension and cardiovascular disease in women" and Clinical Science Session 'Hypertension in pregnancy/hypertension in women'.

The future of the programme

As I look back over the past few years from when the idea of the WiHR programme was conceived, to its creation and now to see it as a well-established initiative under the umbrella of ISH, it is with tremendous pride and honour that I hand over the leadership to Ulrike (Muscha) Steckelings as the next Chair of the committee. I am truly grateful to Neil Poulter (President 2016-2018) and the ISH Executive, for having being so supportive in the initial idea. It has also been a great privilege working with so many dedicated enthusiastic and hard-working committee members, colleagues and friends, committed to the WiHR mission. There is no doubt in my mind that under the outstanding leadership of Muscha and her committee, the goal to 'promote women scientists and clinicians so that they can fulfil their career aspirations in hypertension and related cardiovascular diseases' will be respected and that the programme and network will continue to grow and strengthen.

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NEWS, OLD NEWS, FAKE NEWS

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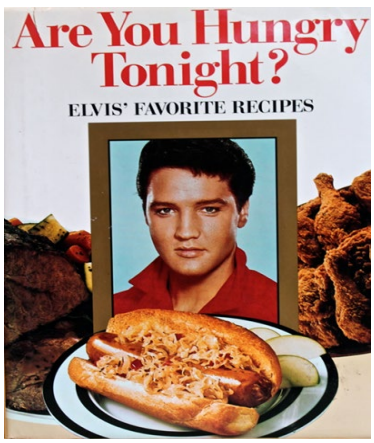
"Are you lonesome tonight?"

Stephan Rössner



Elvis Presley 1935–1977

Elvis Aaron Presley was a cultural icon, widely known simply as Elvis, the king of rock-and-roll. His early musical style was a fusion of country, rhythm and blues and always with a strong backbeat. Elvis has been regarded as one of the most important figures of the popular culture of last century and has sold about one billion records worldwide. He never had any formal musical training and could not read music but played by ear. From the mid fifties onwards Elvis had a spectacular career with admirers all over the world.

Elvis made numerous films, some of which were flops, while others topped the lists. His military service in Germany was followed by thousands of fans but this was also the period in time when Elvis was first introduced to the drugs that would result in ill health and eventually to his premature death. Having been a slender and well-trained young man with a particular interest in karate, Elvis continuously put on weight and ended his life grossly obese.

Elvis's dietary habits were studied and analysed and even described in a television documentary. There was even a cookery book describing what Elvis appreciated eating. It was said that Elvis had a favourite super-sandwich which was flown in especially for him from Denver to Graceland, Tennessee. The recipe is not very appetising: a large baguette, half a kilogram of bacon, a big can of peanut butter plus a jar of grape jelly. Bread is toasted in the oven, the soft dough is removed and filled with fried bacon, peanut butter and jelly. It was said that a "sandwich" of this size would feed ten people – but Elvis had it all by himself. Elvis had extremely simple eating habits and his wife Priscilla, whom he met when she was only 14 years old and married seven years later, described Elvis's dietary habits in her memoirs Elvis and Me. To cook for Elvis was simple, "you just took what there was at home and burnt it".

The king had special demands for what he wanted available around the clock and in his home there was one special chef available just to supply him with what he desired for the moment. There was always minced meat, Pepsi-Cola, orange juice, hamburger bread, potatoes, onions and fresh fruit plus huge amounts of milk, sauerkraut and Vienna sausages, banana pudding, ice cream, cookies and chewing gum.
His favourite night-time snack was a simple sandwich: two slices of white bread covered with mashed banana, peanut butter and fried in a lot of margarine. The recipe suggests that it should be eaten with knife and fork...
Elvis hated strange food. When he once was served snails he refused to eat, arguing that "I don't want to eat anything I can step on when I walk out of my front door". In that respect his aversion is obviously shared by many others.
Pictures showing Elvis together with President Richard Nixon at the White House reveal a 35-year-old man who is already overweight. Elvis wanted Nixon to take action against drugs and saw the Beatles as an example of anti-Americanism and drug abuse in the popular culture. This was obviously ironic since Elvis himself at that time was a manifest abuser.
The outfits in which Elvis is seen on stage became wider and wider to cover his ever-growing body. Elvis became fatter and fatter, was inaudible when he was singing on stage, fell out of cars, hung on to the microphone like a lamppost and shortened his performances but would still draw large audiences. In 1977 he would sit in his rooms almost unable to move and he was suffering from glaucoma, high blood pressure, liver damage, gastrointestinal problems and degenerative arthritis, all potentially related to his weight problem and drug abuse.
Elvis was found dead in his bathroom when his staff came to pick him up to fly out of Memphis for another concert tour. Hundreds of thousands of fans followed the casket. He was buried in Memphis next to his mother but an attempt was made to steal his body 11 days after the funeral and so the remains of both Elvis and his mother were reburied safe inside the Graceland Meditation Garden.

There are several food references in his lyrics: Money honey, blueberry hill, crawfish and others.

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MAY MEASUREMENT MONTH

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May Measurement Month 2019: The global Blood Pressuring Screening Campaign builds momentum across the world

Thanks to the commitment and generous support of many national hypertension and cardiac societies, thousands of volunteers from over 80 countries came together for the third time to run the largest mass synchronised blood pressure screening campaign during May Measurement Month (MMM) 2019.

Once again we have seen a busy MMM across our social media feeds (@maymeasure) with photos of blood pressure screening sites in many diverse locations in both urban and rural areas showing some great imagination. These included hospital waiting rooms, universities, workplaces, pop up events in parks, markets and shopping malls, places of worship and door to door campaigns in remote villages. We also saw some new screening ideas, at yoga centres, world heritage sites and football stadiums. In Sri Lanka the MMM team even incorporated MMM into the medical test required for drivers' licences, National Police in the Philippines had their blood pressure measured and the Nepal MMM team used their social media network to promote their campaign so widely that they received a request to hold an MMM screening site at a wedding banquet! 2019 has been a busy year for publication too, with MMM's first supplement of 39 national papers from MMM17 published in the European Heart Journal Supplement in early April.

This was shortly followed by the publication of the detailed global MMM18 analysis in the European Heart Journal on the 1st May.

In 2018, we reached and measured the blood pressure of over **1.5 million people**. Of these people, 1 in 3 were discovered to have hypertension and of them, only a small proportion (1 in 3) had their condition under control, eitherbecause they were unaware, not on treatment, or both – or their treatment was not working well enough. 2019 has been a busy year for publication too, with MMM's first supplement of 39 national papers from MMM17 published in the European Heart Journal Supplement in early April.

This was shortly followed by the publication of the detailed global MMM18 analysis in the European Heart Journal on the 1st May. In 2018, we reached and measured the blood pressure of over **1.5 million people**. Of these people, 1 in 3 were discovered to have hypertension and of them, only a small proportion (1 in 3) had their condition under control, either because they were unaware, not on treatment, or both – or their treatment was not working well enough. This shows there is still much to do in increasing awareness of the issues surrounding hypertension and in providing more access to blood pressure screening.

Our hope is that MMM19 will continue to build on MMM17 and MMM18, to create further evidence by publishing the analysis to use to influence public health policy. We have already seen many countries engage with health ministers during MMM and the Nepalese government announced this May that budget would be allocated to combatting NCDs including hypertension.

This is a great result and, as part of MMM's goal to increase awareness and influence health policy, we will look to provide guidance on how to use your MMM data in your country to that effect over the coming months.

A Simple Measure to Save Lives
- Be part of it!

www.maymeasure.com

MMM Team - manager@maymeasure.com

"DDD": DYLAN'S DISTRIBUTION DATA

I am happy to report that readership for Hypertension News continues to grow with each successive issue and the March 2019 edition was no exception. Our March 2019 issue had the highest total number of views to date with 4,756 who accessed the Newsletter in a three-month period. By comparison, the first three months of our November 2018 issue was accessed 3 126 times while the first three months of the June 2018 issue was viewed 1 183 times. Please note, that we have previously published four-month data which, of course, were slightly higher than the present ones. Going forward, I will present all data as the first three months after publication.

Dylan's Distribution Data (March-June 2019)	
Total Estimated Readership	**4 756**
Accessed via Twitter	971
Accessed via Facebook	151
Accessed via DOI	2 483
Accessed via Web Site	1 151

Some interesting trends emerged from the readership data this month. CrossRef/DOIs remain the primary method by which our readers access articles, however a large number of people accessed material via twitter in the March issue, possibly due to our feature on social media. A complete summary of the readership data from the most recent issues of Hypertension News is shown in Figure 1.

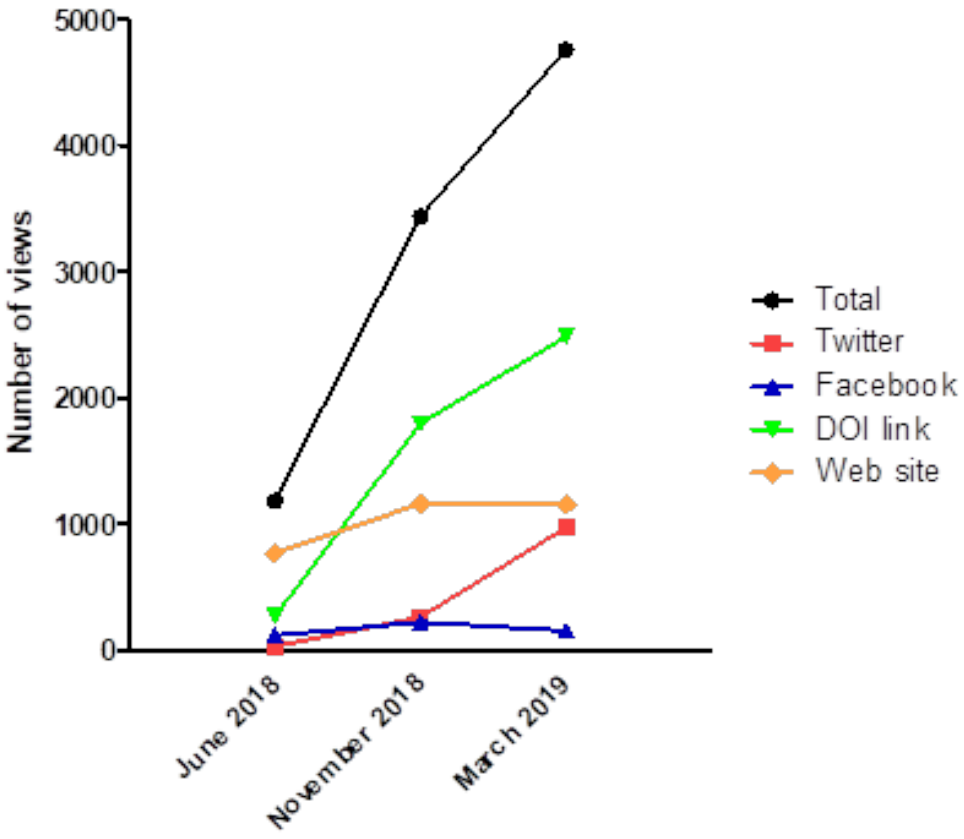

Figure 1: Hypertension News per-issue, readership data by media type. Data are the number of independent hypertension news items accessed over a three-month period.

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Genetic mechanisms of aldosterone related disorders – towards integrative precision medicine

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The Paris Cardiovascular Research Center (PARCC), INSERM-UMR-970, is built upon the substantial strengths and excellence in basic, translational and clinical cardiovascular research of 13 teams, which have been approved by the French National Institute of Health and Medical Research (INSERM) and Université Paris Descartes (now Université de Paris). The center is located at the Georges-Pompidou European Hospital (HEGP), in a single location equipped with laboratories, office space and core facilities, occupying a surface of 4,200 m^2. Teams of the PARCC are conducting projects spanning basic molecular and cellular biology to integrated physiology and pathophysiology, biomarkers, genetics and epidemiology, with the goal of furthering the understanding of major cardiovascular disease, including atherosclerosis, hypertension, heart failure and sudden cardiac death (http://parcc.inserm.fr/).

Translational research is an integral part of the mission of the PARCC, in close connection with clinical laboratories and departments of the HEGP. The HEGP is a new and leading hospital opened in 2000, which comprises 39 services dispatched within 7 health poles and offers 710 beds and 120 daily places. The hospital develops three major areas of activity: cardiovascular diseases, oncology and emergencies.

PARCC team "Genetic mechanisms of aldosterone related disorders – towards integrative precision medicine" is directed by Maria-Christina ZENNARO, MD, PhD, Inserm Research Director, and is composed of three full-time INSERM researchers, two associated clinicians, one engineer, one post-doc, and three PhD students. Our team also hosts 3-4 undergraduate students per year. The team has been appointed FRM team by the "Fondation pour la recherché médicale" in 2014 and 2019.

The overarching aim of our program is to unravel the genetic architecture of blood pressure regulation in relation to aldosterone in order to generate knowledge translatable to clinics. To achieve this goal, we apply the most recent genomic technologies on unique cohorts of patients with primary aldosteronism with access to standardized clinical and biological information, tumor and DNA samples, integrated within national and international networks and programs (COMETE, ENS@T, COST-Admire, ENSAT-HT). An original interdisciplinary approach combines complementary expertise in genetic and clinical investigation with high throughput genomic approaches, molecular, cellular and animal experiments.

This strategy is particularly applied to the development and evaluation of an omics-based stratified health promotion programme for patients with endocrine forms of hypertension in the context of the EU-funded Horizon 2020 research and innovation project ENSAT-HT, which is coordinated by MC Zennaro (www.ensat-ht.eu). The goal of ENSAT-HT is to improve the identification of endocrine causes of hypertension for curative treatment and prevention of cardiovascular and metabolic complications as well as to stratify primary forms of hypertension for effective and cost efficient therapy.

Translational research is performed in close connection with clinical laboratories and departments of the HEGP, where MC Zennaro is associated investigator at the Genetics Department and member of the European Society of Hypertension Centre of Excellence (www.centre-hypertension.org).

The ESH-Centre of Excellence at the HEGP-Paris houses an expert centre for the care of primary and secondary forms of hypertension, and includes the hypertension unit (M. Azizi, L. Amar, G. Bobrie), the clinical investigation center (M. Azizi), the Pharmacology Department (S. Laurent, P. Boutouyrie), and the Genetics department (X. Jeunemaitre), which performs genetic testing and/or genetic counselling. The Centre of Excellence is acknowledged by the French Ministry of Health as a reference clinical centre for rare adrenal diseases. The genetics laboratory of the HEGP (with a ISO 15180 accredited molecular genetics laboratory and a genetics clinic) is reference center for the genetic diagnosis of rare arterial disorders, distal tubulopathies (within the national reference center for rare inherited renal disorders of the child and the adult (MARHEA), adrenal tumors, and for the genetic diagnosis of primary aldosteronism.

Research activities

Detection of secondary forms of hypertension is key to targeted management of the underlying disease and prevention of cardiovascular complications. Primary aldosteronism (PA) is the most common and curable form of secondary arterial hypertension, with an estimated prevalence of ~10% in referred patients and 4% in primary care, but as high as 20% in patients with resistant hypertension [1]. Increased aldosterone levels in PA are associated with increased cardiovascular risk compared to essential hypertension [2]. PA results from autonomous aldosterone production from the adrenal cortex. It is caused in the majority of cases by a unilateral aldosterone producing adenoma (APA) or bilateral adrenal hyperplasia (BAH). Recurrent mutations in genes coding for ion channels (*KCNJ5*, *CACNA1D*, *CACNA1H*, *CLCN2*) and ATPases (*ATP1A1* and *ATP2B3*) regulating intracellular ionic homeostasis and cell membrane potential have been identified in aldosterone producing adenoma and familial forms of PA [3-6]. The current pathophysiological model of APA development involves modifications in intracellular ionic homeostasis and membrane potential, leading to the activation of calcium signaling, the major trigger for aldosterone production. Over the past five years, our team has made major contributions to the identification of genetic abnormalities in PA and the understanding of the mechanistic determinants of increased aldosterone production and nodule formation in the adrenal cortex. In particular, we have identified two new genes involved in inherited forms of PA and deciphered the molecular mechanisms responsible for increased aldosterone production [5, 7]. Our laboratory has also coordinated the largest multicenter study published so far, exploring the genetic, clinical and molecular correlates of somatic mutations in aldosterone producing adenoma [8]. Our laboratory is currently coordinating the EU-funded Horizon 2020 research and innovation project ENSAT-HT (www.ensat-ht.eu). This project will develop and evaluate an omics-based stratified health promotion program for patients with endocrine forms of hypertension. Specific omics profiles will be defined for patients with PA and other forms of endocrine hypertension (pheochromocytoma/functional paraganglioma and Cushing syndrome) by integrating high throughput genetics, genomics and metabolomics data with phenome annotations through bioinformatics modelling

Established profiles will then be validated as stratification biomarkers and applied to the screening of referred hypertensive patients for both stratifying primary forms of hypertension for effective and cost efficient therapy as well as improving identification of endocrine causes for curative treatment and prevention of cardiovascular and metabolic complications. Omics-based profiling should allow identification of patients with preclinical phenotypes along with those hypertensives that cluster into specific endocrine groups who may benefit from personalised treatment. In addition to our translational studies, our laboratory basic research in different model systems, with the aim of identifying molecular pathways of normal and pathological aldosterone production and investigating mechanisms of mineralocorticoid dysfunction in target organs. The results obtained through our program are expected to provide completely novel mechanistic principles on the pathogenesis of blood pressure regulation in relation to aldosterone. This knowledge should pave the way for the development of biomarkers and new and more efficient therapeutic approaches that could benefit a large proportion of the hypertensive population.

Front row (from left to right) : Sheerazed Boulkroun, Fabio Luiz Fernandes-Rosa, Maria-Christina Zennaro
Second row (from left to right) : Rami M El Zein, Isabelle Giscos-Douriez, Kelly de Sousa, Alaa B Abdellatif, Teresa Cosentino, Audrey Soria

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My views on Hypertension

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Not surprisingly, my daily work as a pharmacologist and basic scientist has a major impact on my view on hypertension. As a pharmacologist, my interest is primarily the treatment of hypertension: the major advances in anti-hypertensive treatment over the last ~ 5 decades, the still insufficient treatment options for certain patient groups such as patients with resistant hypertension or women with preeclampsia and, consequently, the identification of novel drug targets. The focus of my own research is the angiotensin AT_2-receptor (AT_2R), which mediates tissue protective actions and which in many instances is a counter player of the AT_1-receptor [1].

Working with this receptor, which is stimulating endogenous protective mechanisms (including lowering of blood pressure), made me aware that the common approach for identifying new drug targets for the treatment of hypertension and other diseases is usually following a certain concept: In most cases, the starting point in drug discovery is the investigation of a pathomechanism, which the new drug is supposed to inhibit or interrupt. All currently approved drugs interfering with the renin-angiotensin-system (RAS) work according to this principle.

However, pharmacological interference in disease can also consist in strengthening endogenous mechanisms, which naturally counteract the disease mechanisms. For example, a new area in cancer therapy, immuno-oncology, is following this principle and has become one of the most promising and fruitful sources of new treatments – a fact that was recognised by the 2018 Nobel Prize in Medicine/Physiology [2].

In the treatment of systemic hypertension, the principle of reinforcing natural mechanisms is only rarely used. In contrast, in pulmonary hypertension, increasing the levels of the endogenous vasodilator nitric oxide (NO) is a common treatment approach, which is achieved by drugs such as phosphodiesterase-5 inhibitors (e.g. sildenafil), soluble guanylate cyclase stimulators or by direct application of NO [3].

Another example of a drug that stimulates an endogenous mechanism for therapeutic use are neprilysin-inhibitors, which are used in fixed combination with the ARB valsartan to prevent degradation and thereby increase levels of the protective natriuretic peptides [4]. These so-called ARNIs are approved for the treatment of chronic heart failure with reduced ejection fraction, but may also have potential for the treatment of hypertension [4]. Drugs for therapeutic use of what is now called "the protective arm of the RAS" are currently in preclinical and clinical development.

Such drugs comprise recombinant human ACE2, the enzyme which is responsible for synthesis of the protective angiotensin fragment angiotensin[1-7], as well as agonists for the AT_2-receptor and the receptor for angiotensin[1-7], MAS[5].

The potential of these drugs for the treatment of systemic hypertension is not clear yet. Preclinical experiments point to the fact that they may only be efficient in certain patient groups such as obese patients or women with preeclampsia, or that only their central effects may be strong enough for a clinically relevant anti-hypertensive effect [6–8]. But the fact that these drugs generally stimulate mechanisms of regeneration and repair seems – according to preclinical evidence - to translate into a significant attenuation of end-organ damage related to hypertension and also diabetes, which may be a significant advantage of these drugs [9].

Therefore, my personal, "pharmacology-flavoured" view on hypertension is that in order to overcome the remaining unmet medical needs such as resistant hypertension, hypertension in preeclampsia or hypertension-related end-organ damage, the approach for finding novel treatments may have to be widened and in addition to inhibition of pathomechanisms also include the search for endogenous systems, which can be used therapeutically by pharmacological reinforcement.

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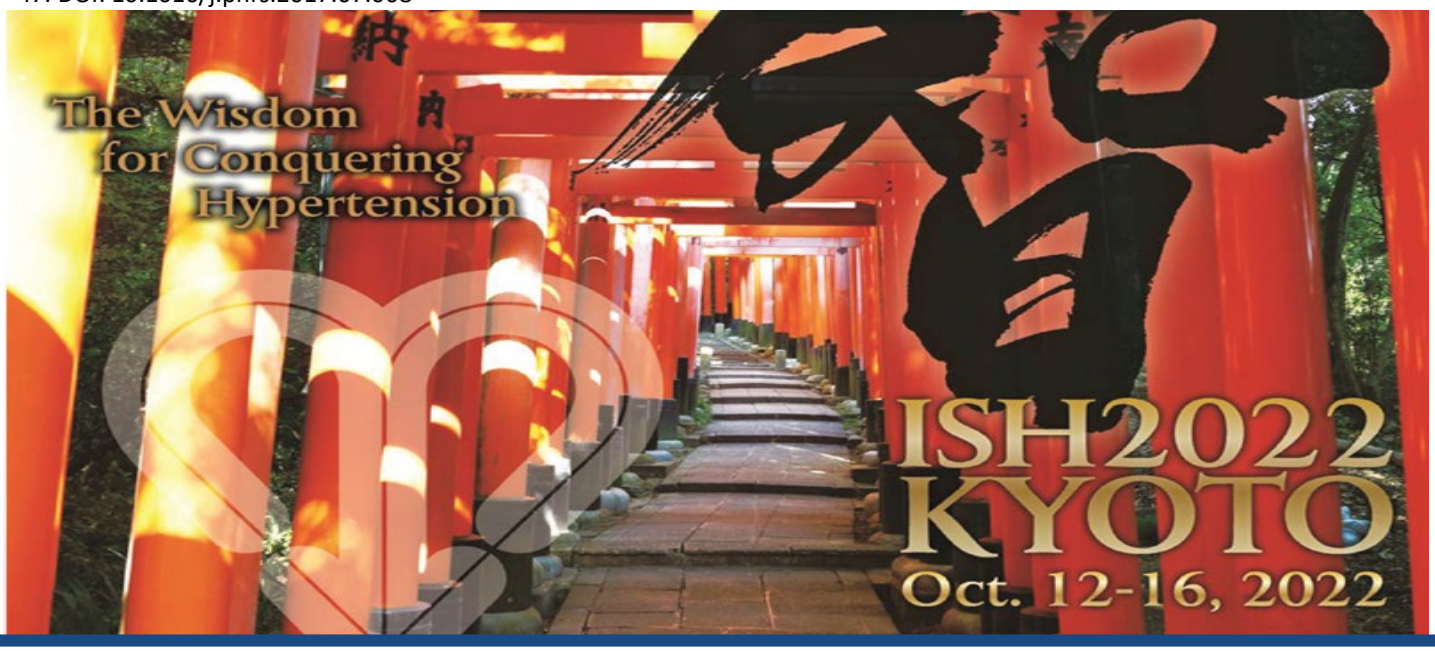

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Argentine Society of Hypertension (SAHA) meeting

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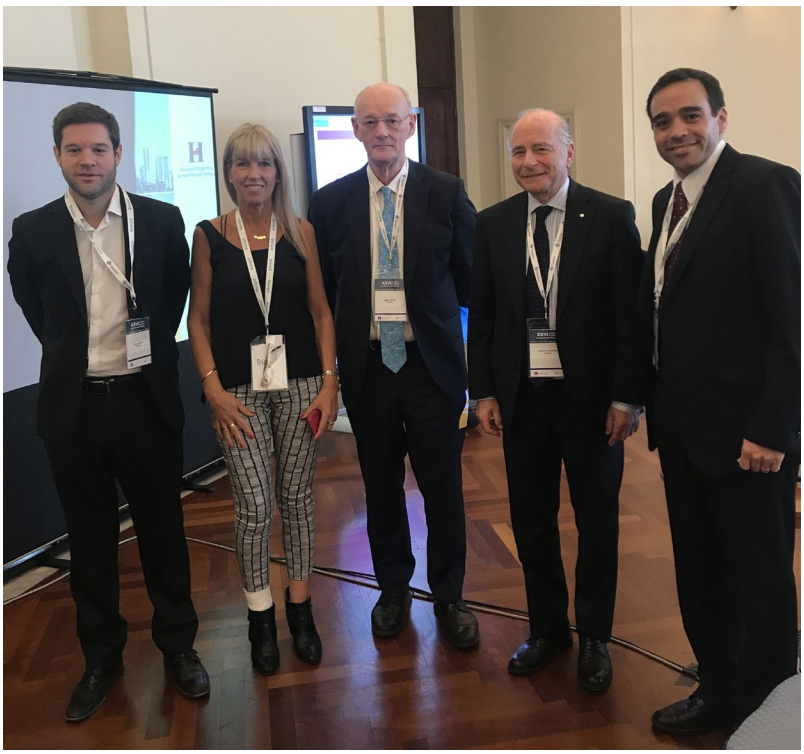
International Society of Hypertension
New investigator Committee

On April 11-13 2019, the XXVI Argentine Society of Hypertension (SAHA) meeting took place in Mar del Plata, Argentina. Organized by Dr. Irene Ennis (organizing committee president) and Dr. Alejandro Aiello (scientific committee president) the meeting was a success with 2049 accredited delegates, and more than 75 original research work presented. International recognized speakers as well as national leaders on hypertension field gave lectures and symposiums showing the latest advances in hypertension. ISH representatives, Ernesto Schiffrin (Canada, ISH past president), Cesar Romero (USA, ISH membership committee and RAG for Americas) and Pablo Kempny (Argentina, ISH-NIC) were attending the meeting. A research course for young investigator between SAHA and ISH was presented on Thursday April 11th.

The course was attended by young investigators and physicians interested to initiates in hypertension research. On Friday 12th, an oral competition between the best 5 original works presented by young investigator was organized.

The competition was coordinated by Pablo Kempny (ISH-SAHA) and Cesar Romero (ISH-SAHA) and was honored with the presence of Ernesto Schiffrin (ISH past president), Irene Ennis (current SAHA president), and James Walker (University of Leeds, UK) who were in charge of judging and selecting the awardees. Maia Aisicovich (ISIM UBA-CONICET, Argentina) won the best oral presentation with “Cardiac-leptin-TRH interaction in left ventricular hypertrophy of the obese mouse”, the runner up was Marina Grand (ICCS-UNICEN, Argentina) who presented “Non-invasive hemodynamic monitoring in children, adolescent and adults based on pulse contour analysis: comparative analysis with echocardiographic derived data and determination of percentile curves”. We thank all the presenters and the general public who attended the oral competition.

The Argentine Meeting of Hypertension was a great opportunity to reinforcing the friendship and collaboration between the ISH and the SAHA.



Young investigators oral competition. From left to right Pablo Kempny (Argentina, ISH-NIC), Irene Ennis (current SAHA president), James Walker (University of Leeds, UK), Ernesto Schiffrin (Canada, ISH past president) and Cesar Romero (USA, ISH membership committee and RAG for Americas).

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CALL FOR BIDS

INTERNATIONAL SOCIETY OF HYPERTENSION 2024 BIENNIAL SCIENTIFIC MEETING

The Council of the International Society of Hypertension (ISH) would like to invite scientists, research groups or national societies with an interest in hypertension to host the **ISH Biennial Scientific Meeting in 2024.**

Bid Deadline 30 September 2019

DELEGATE PROFILE

The congress typically attracts delegates from over **60 countries worldwide** and comprise of hypertension specialists, cardiologists, nephrologists, general practitioners, scientists, nurses, allied health care professionals, patients and patient group representatives.

Financial Liability

All those bidding to host the ISH 2024 Biennial Scientific Meeting must commit to sign a standard contract. All those bidding to host the ISH 2024 Biennial Scientific Meeting must commit to sign a standard contract (which can be modified according to local circumstances). One element of this contract commits the local organiser to pay ISH one half of the income that exceeds agreed expenditures derived from the 2024 Meeting. The ISH does not assume responsibility for any loss associated with the Meeting. The ISH does not assume responsibility for any potential loss associated with the Meeting.

Criteria

1. Quality and quantity of available convention centre space.
2. International air accessibility and cost.
3. Quality, quantity and type of hotel rooms available within close proximity of the convention centre.
4. Incentive appeal of city for international attendees.
5. ISH values innovation and particular credit will be awarded to bids which have new features designed for their programme.
6. Support of national hypertension society hosting the meeting.
7. Support of other national hypertension societies or related organisations in the immediate region of the proposed host country (Mandatory).
8. Commitment from local hypertension experts in the host city (Mandatory)
9. Experience of host organisation with similar types of professional meetings
10. Financial resources available to host the meeting
11. Quality and experience of PCOs (Professional Conference Organisers) and similar organisations in the host city or nation to assist in the organisation and delivery of the conference

Format of Proposals

Please note that only electronic proposals will be accepted and not paper versions. Proposals should be as complete as possible, addressing all items as outlined in this document and indicated in the 'ISH Guidelines for future organisers' document. Bids should be accompanied by at least one set of floor plans of the proposed convention centre indicating the proposed space to be used for the ISH Biennial Scientific Meeting.

For the full guideline document
and any questions regarding this, please contact:

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SUBMISSION TIMETABLE

- Bid Deadline 30 September 2019
- Notification of Shortlisted Candidates Friday 1 Nov 2019
- Presentations of shortlisted bids to ISH Bidding Review Committee in at ESH-ISH Glasgow 2020
- Announcement of 2024 Congress Venue May 2020

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Lumping versus splitting in meta-analysis

Mattias Brunström , Umeå University, Umeå, Sweden

One of the most important aspects in the design of systematic reviews and meta-analyses is the eligibility criteria for individual trials. In the previous issue of Hypertension News, we argued that too broad eligibility criteria leads to inclusion of trials with very different characteristics, and that the combination of such trials in meta-analyses may hide important differences in results.[1] On the other hand, as argued by Professor Nadia Khan, too narrow eligibility criteria may lead to the inclusion of too few trials, impairing the statistical power to make conclusions about treatment effect.[2]

Figure 1a

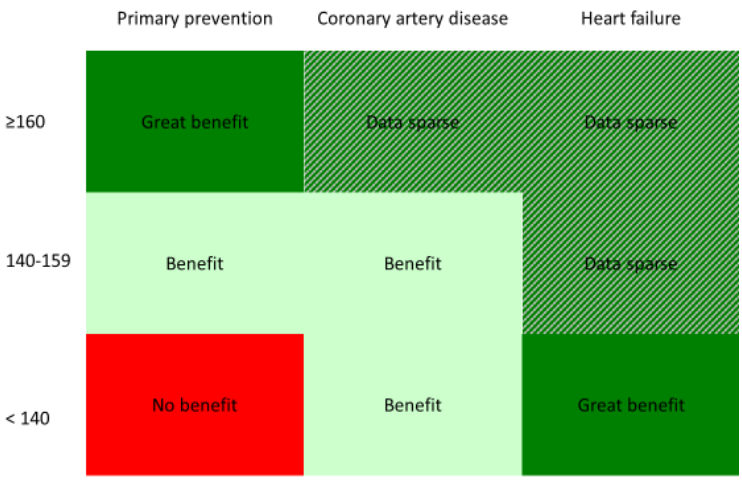
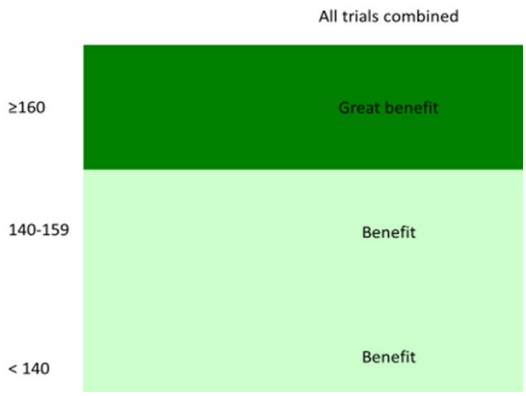


Figure 1 illustrates how lumping versus splitting affects the results of meta-analyses assessing the effect of antihypertensive treatment at different blood pressure levels. If trials are grouped by co-morbidities, separating primary preventive patients from those with established coronary artery disease and heart failure, the primary preventive effect of blood pressure lowering is attenuated at lower blood pressure levels with no effect if systolic blood pressure is below 140 mm Hg (Fig 1a).[3,4] Because treatment is beneficial in coronary artery disease and highly beneficial in heart failure, lumping trials across co-morbidities results in the appearance of an overall beneficial effect in the lowest blood pressure category (Figure 1b).[5-8]

Which one of these analytical approaches is more sensible? That depends on whether one thinks that treatment effects ought to be similar in primary prevention, established coronary artery disease and heart failure. If it is not beyond reasonable doubt that effects may differ, trials with different patient co-morbidities should be analyzed separately. This decision, which should be based on pathophysiological and pharmacological knowledge, cannot be substituted by tests for interaction once trials have been combined.

Figure 1b



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