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IN THIS ISSUE

FROM THE EDITOR

ISH Kyoto 2022 - We are coming soon!

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Editor

Dear ISH member,

There are 1,600 Buddhist temples, 400 Shinto shrines, 200 listed gardens in Kyoto, and about 20 per cent of Japan's national treasures, including 20 World Heritage Sites. To this, you can add many universities capable of fostering Nobel laureates. Kyoto served as Japan's capital for eleven centuries and has been spared earthquakes and bombings, but not urbanisation (population about 1.5 million). To me, it is indeed an exceptional city well worth visiting, where the 29th scientific meeting of the International Society of Hypertension will take place on 12 -16 October 2022. I am convinced that many of you have already planned to attend this meeting, but if you haven't, I strongly recommend you to do so and to set aside funds to cover the travel costs. It may also be a good idea to check the need of a visa to enter Japan and, if a visa is needed, start the process of getting one, which may take some time.

On page 33 of this Newsletter, Professor Hiroshi Itoh from The Keio University School of Medicine in Tokyo, who is the President of the 2022 ISH meeting, gives us an update on the planning of the meeting which will be held under the banner "The Wisdom of Conquering Hypertension". The number of delegates at this face-to-face meeting is estimated to be 4,500 and there will be travel grants for 300 young scientists.

The number of patients with Covid-19 in Japan has decreased steeply this autumn, and the latest (10 December 2021) two-week figure from Johns Hopkins for the cumulative incidence per 100,000 population was a low 1.2 in Japan compared with 288 in Sweden, 972 in the UK, 881 in France, and 469 in the US. Moreover, in Japan, about 78 per cent of the population (all age groups included) have already been fully vaccinated (i.e. have received two jabs). These are difficult times, however, and the rules for entering Japan may change rapidly, as we have seen recently. The best and latest information can be found on the website of the Ministry of Foreign Affairs of Japan (https://www.mofa.go.jp/ca/fna/page4e_001053.html), which I recommend you look at when you make your plans.

This issue of Hypertension News has a focus on basic science, and rightly so since more than half of our ISH members are basic scientists. On page 24, you will find an outstanding and elegant "Institute Focus" from the University of Mississippi Medical Centre (UMMC) written by John Hall, which I strongly recommend you to read. The UMMC was established in 1955 to "educate tomorrow's health care professionals by conducting health sciences research and by providing cutting-edge patient care".

The "Learning the Ropes" section in this issue (pages 9-23), is entitled "RAAS: Measuring its Components and New Therapeutic Strategies". The renin-angiotensin-aldosterone System (RAAS) has inspired cardiovascular research since the discovery of renin by Tigerstedt and Bergmann in 1898. However, despite huge progress in our knowledge of the RAAS and its manipulation on a molecular and clinical level, it appears that with each step of advancement new questions arise and new therapeutic options are unveiled. A good example of this is the discovery of the ACE2-angiotensin (1-7) branch of the RAS or the angiotensin AT2 receptor whose tissue-protecting actions may become therapeutic tools in the future. In this Newsletter, there are four papers on RAAS measurement methodology and novel therapeutic perspectives, written by prominent experts in the field and elegantly introduced by Thomas Unger, who also edited this section.

We would normally have provided our readers with an update on the distribution numbers for the October issue of the Newsletter. This is not possible, however, since we will not have the three-month data until early February 2022. Instead, we have revisited our four publications published in 2021 (96 articles, including the December issue) to see how well our texts represent the ISH membership. As you can see on page 37, we had a fairly good global representation, with all continents represented. Moreover, there was also a reasonable split between male and female authors as well as between senior and early-career researchers. There were, however, more contributions from high-income countries than from low- and middle-income countries.

Therefore, in the next issue, we plan to introduce a new section entitled "African Voices", with papers written by scientists from different parts of Africa, introduced by Lebo Gafane-Matemane.

Finally, sincere thanks to the deputy editor Dylan Burger and the lovely Hypertension News team. We plan the publication of the next issue of the Newsletter (Opus 69) for March 2022.

Enjoy a good read!

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Update from the Executive Committee

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It has only been 2 months since my last update from the executive, but that does not mean that I am short on information for our members. First and foremost, the ISH report to the UK Charity Commission for the 2020 calendar year was filed and is now available here. The report summarizes our annual returns and key activities/ initiatives.

Many readers will also be aware that the 2021 edition of May Measurement Month has now come to a close. As a reminder, "May" Measurement Month was extended until November for the 2021 campaign. This was to allow for screening at the safest times in line with local public health recommendations. All data has now been submitted and we look forward to the result of the 2021 campaign as well as an update on the soon to launch 2022 campaign from Professor Neil Poulter and the MMM team in the near future.

There has also been significant activity on the research and education front with several key opinion/position papers now in development. Most immediately, several ISH members, led by Prof Alta Schutte, have been working on a global review of the epidemiology of hypertension that highlights regional-specific challenges and seeks to identify strategies to improve hypertension awareness and control. This work is expected to be submitted in early 2022. In addition, professors George Stergiou and Nadia Khan from the Research and Education Committee are overseeing a number of ISH position papers in development and we hope to have an update on progress in the new year. Finally, ISH President Maciej Tomaszewski, Dr. Erika Jones, and myself recently contributed to a statement from the Global Coalition for Circulatory Health titled "Preventing the next pandemic: The case for investing in circulatory health". This statement served as the foundation for lobbying efforts at the recent WHO World Health Assembly. Going forward the ISH is presently working to establish status as a "non-state actor" which would give the ISH a platform to more effectively advocate for hypertension in global health policy. If you are interested in details on these and other ISH activities be sure to check out the President's blog" which can be found here.

As 2021 comes to a close I think that it is worth taking a moment to appreciate all that the ISH has accomplished in the past year. One year ago the New Blood campaign had just concluded and 70 new leaders from more than 40 different countries had just joined ISH committees. The impact of this injection of talent, energy, and fresh perspectives has been felt throughout the society. New initiatives abound: notably the #ISHLive series from the New Investigators, Workshops organized by the Mentorship and Training Committee, and the many partnered seminars from the Women in Hypertension Research Committee. The Regional Advisory Groups have also been reinvigorated and new partnerships are emerging such as our involvement in the Global Coalition for Circulatory Health. As chair of the Communications Committee I have been particularly pleased with our new website, the growth of the monthly E-bulletin, and the launch of the Café ISH video series. These are just a handful of significant advances that ISH has made in the

last 12 months and they build upon existing strengths such as Hypertension News which had its highest readership to date in 2021.

It is incredible to think that all of this growth and expansion has happened in spite of the fact that our society has not had an opportunity to meet in person in more than 3 years. Certainly, the very successful joint ISH/ESH virtual meeting in April provided an opportunity to reconnect, but I think we all are looking forward to the Kyoto 2022 meeting and the possibility of an in person program. I have recently seen a very preliminary draft program and have to say that it looks truly outstanding and innovative.

Best,

Dylan

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Merry Christmas and Happy New 2022

FROM ALL ON THE HYPERTENSION NEWS EDITORIAL BOARD

HOT OFF THE PRESS

Blood pressure and outcome in primary and secondary prevention is all about risk

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There is strong evidence from epidemiological studies for an association between blood pressure and fatal cardiovascular complications, and interventional studies have demonstrated antihypertensive treatment to reduce cardiovascular events and all-cause mortality. Whereas recommended target blood pressure for treated hypertensive patients according to recent American guidelines is <130/80 mm Hg, and European recommendations now indicate 120-129/70-79 mm Hg for people below 65 years old or 130-139/70-79 mm Hg for those 65 years or older[1,2], the threshold blood pressure levels for initiating antihypertensive therapy are still a matter of discussion [1,2]. Furthermore, whether a given initial blood pressure for starting treatment provides similar benefit across different age groups and for patients treated for primary prevention or secondary prevention has not been settled.

Two recent publications from the Blood pressure Lowering Treatment Trialists' Collaboration by Rahimi et al add new information to these questions. First, the authors performed a meta-analysis [3] based on individual patient data from 48 major clinical trials (>1000 patient years per treatment arm, assessing drug vs placebo, drug vs drug, or more vs less intensive treatment) comprising 348 854 patients to assess 1) the effect when blood pressure before treatment is below typical threshold values for detecting or treating hypertension; and 2) to compare the effects of antihypertensive treatment in patients with and without concomitant cardiovascular comorbidity [3]. Participants were divided into those with a prior diagnosis of cardiovascular disease and those without cardiovascular comorbidity, and further divided into groups according to systolic blood pressure at study entry: <120, 120-129, 130-139, 140-149, 150-159, 160-169, and ≥170 mm Hg. In patients with cardiovascular comorbidity, 76% had a history of ischemic heart disease, 36% stroke, 12% peripheral artery disease, and 27 % diabetes. Major outcome was a composite of stroke, myocardial infarction, heart failure hospitalizations, and cardiovascular death. Mean age was 65 years, median follow up four years, and mean blood pressure at study entry 146/84 mm Hg (secondary prevention) and 157/89 (primary prevention).

A second similar meta-analysis[4] including 358 707 patients from 51 major clinical trials evaluated the risk of major cardiovascular events (as defined above) stratified by age (<55, 55-64, 65-74, 75-84, and >85 years) and baseline systolic (<120, 120-129, 130-139, 140-149, 150-159, 160-169, and ≥170 mm Hg) and diastolic (<70, 70-79, 80-89, 90-99, 100-109, and ≥110 mm Hg) blood pressure. Compared to patients <55 years, those >85 years were more often women (61 vs 35%), had higher systolic and lower diastolic blood pressures (157/82 vs 150/95 mm Hg), and a shorter follow up (2.8 vs 4.5 years).

The results[3] show similar treatment effects on cardiovascular events in patients with (secondary prevention) and without (primary prevention) prevalent cardiovascular comorbidity. Thus, overall hazard ratios (and 95% confidence intervals; adjusted to a 5 mm Hg reduction in systolic blood pressure) for the composite primary outcome were 0.89 [0.86–0.92] vs 0.91 [0.89–0.94] in patients with and without cardiovascular comorbidity, respectively, and 0.89 [0.85–0.94] vs 0.85 [0.81–0.90] for stroke, 0.90 [0.86–0.94] vs 0.95 [0.91–0.99] for ischemic heart disease, 0.88 [0.82–0.94] vs 0.83 [0.78–0.89] for heart failure, and 0.97 [0.92–1.03] vs 0.93 [0.88–0.98] for cardiovascular death, respectively. The benefit

of treatment was similar across all strata of entry blood pressure, with no difference between patients with and without cardiovascular comorbidity.

Furthermore, hazard ratios (and 95% confidence intervals; adjusted to a 5 mm Hg reduction in systolic blood pressure) for a major cardiovascular event in age groups < 55, 55-64, 65-74, 75-84, and >85 years were 0.82 [0.76–0.88], 0.91 [0.88–0.95], 0.91 [0.88–0.95], 0.91 [0.87–0.96], and 0.99 [0.87–1.12], respectively, suggesting a smaller risk reduction with advancing age [4]. However, absolute risk reductions appeared to be largest in the oldest age group; with similar findings also for all-cause mortality. The results for diastolic blood pressure strata were similar. The results did not suggest the relative risk reductions to vary by baseline systolic or diastolic blood pressures.

In my view, these results may have major implications for clinical practice. First, the results show that a relative benefit of antihypertensive treatment is proportional to the intensity of blood pressure reduction, and the magnitude of relative risk reduction is similar across baseline blood pressure levels from below 120 to above 170 mm Hg systolic. There is a benefit also at low entry systolic blood pressure in patients with a high (76%) proportion of ischemic heart disease. This favours a more intensive blood pressure lowering strategy[5,6], and suggests that the risk with blood pressure lowering (i.e. the J-curve) may not be a major problem in most patients. Second, a similar relative benefit of treatment in primary and secondary prevention indicates that cardiovascular risk will be a major determinant of the absolute benefit of treatment. Also, the results show that antihypertensive treatment is effective into old age, where absolute risk is higher. This suggests that antihypertensive treatment should be considered regardless of age. Finally, as the absolute benefits of antihypertensive medications seem to be proportional to the predicted cardiovascular risk before treatment, the two studies underscore the importance of risk assessment in the individual patient when deciding on who to offer antihypertensive treatment[7].

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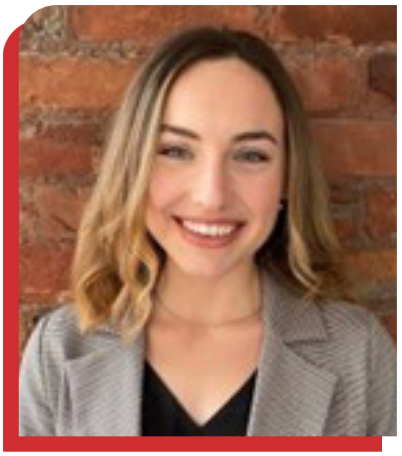
Neutrophil extracellular traps as potention mediators of reparative vascular regeneration



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Neutrophils mediate immune responses and inflammation via three distinct mechanisms: phagocytosis, degranulation, and neutrophil extracellular trap (NET) formation. The latter is a tightly regulated process mediated by the citrullinating enzyme peptidylarginine deiminase 4 (PAD4), wherein neutrophils release intricate webs of unraveled DNA, histones, and granular protein capable of trapping pathogens[1]. Their immunomodulatory capacities, although critical to proper innate immune function, have been shown to contribute to sterile inflammation and consequent NET-associated host damage in disease. NET-induced vascular damage, resulting from increased endothelial cell (EC) apoptosis and activation, has been reported in cardiovascular and inflammatory autoimmune diseases[2]. Contrastingly, Binet et al. report that, by promoting EC apoptosis, NETs could prove to be critical in the regression of pathological vessels in retinopathy, allowing for proper vascular remodeling[3]. This study showed that neutrophil infiltration and sterile inflammation (characteristic of the late stages of retinopathy) allow for NET release at sites of neovascularization and is facilitated by the senescence-associated secretory phenotype (SASP) of ECs.

Mouse pups were exposed to 75% oxygen from postnatal day 7 to 12 to induce vaso-obliteration, after which hypoxia-driven neovascularization occurs (Oxygen-Induced Retinopathy, OIR). Retinas were collected for transcriptome analysis by bulk and droplet-based single cell RNA sequencing. Gene-set variation analysis (GSVA) revealed enrichment in transcripts related to innate immune system activation, more specifically for neutrophil-associated genes, at time of maximal pathological angiogenesis. Neutrophil presence was further validated using fluorescent-activated cell sorting (FACS) and found adjacent to neovascular tufts, as observed by ex-vivo live confocal-imaging microscopy. Immunostaining of retinas for citrullinated histone H3 (CitH3) and myeloperoxidase (MPO) was used to detect NETs, which were observed at neovascular tufts but absent in normoxic controls. Similar neutrophil infiltration and NET release was observed in retinas from proliferative diabetic retinopathy (PDR) patients. To identify potential NETosis stimuli, GSVA was used on single-cell transcriptomic data for gene sets related to cellular senescence and secretory processes. Transcripts related to cellular senescence, namely RAS signaling-associated genes, were found to be up-regulated in ECs and triggered SASP. Human Umbilical Vein Endothelial Cells (HUVECs) were rendered senescent through sustained RAS activation by transduction with a RAS-expressing plasmid retrovirus. Exposing neutrophils to senescent HUVECs and/or their conditioned media triggered significant DNA release. Stable isotope labeling using amino acids in cell culture (SILAC) was used to identify senescent EC secretome, which was primarily enriched in proteins related to immune pathways, namely IL-1b and CXCL1. Downregulation of both proteins through lentiviral transduction of short hairpin RNAs lead to significant reduction in NET release. In OIR mice, DNAse I injection at time of maximal neovascularization and deficiency in myeloid-resident PAD4 both stalled clearance of senescent ECs, which allowed for persistence of pathological vessels, and restricted vascular regeneration.

This study thoroughly investigated the role of NETs at all stages of OIR, leading into functional impacts on vascular regeneration. Murine OIR presents three distinct stages (i.e. neovascularization, vascular remodeling, and vascular regression), characteristic of the pathology in humans, and thus serves as an appropriate model for investigating mechanisms of reparative vascular regeneration. SASP induction is observed in various cell types in PDR patients, leading to SASP-associated

cytokine release in the vitreous humour[4]. Binet et al. highlighted the role of SASP-associated cytokines (i.e. IL-1B and CXCL1) in neutrophil recruitment and NETosis and, more specifically, the contribution of EC SASP. Reciprocally, EC activation, brought on by NET-induced cytokine signalling, leads to expression of leukocyte adhesion molecules and increased EC-immune cell interactions[5]. Through induction of EC apoptosis, NETs were shown to be vital in vascular remodeling, as to allow for vascular regression of pathological vessels. Such clearance of senescent vessels and enhanced vascular repair has not been achieved with currently used anti-VEGF treatment, which only shows inhibition of pathological neovascularization[4]. Despite the therapeutic promise of NETs in retinopathy, the impact of sustained NETosis on retinal health and its potential to exacerbate vascular damage through microvascular occlusions has yet to be investigated. Still, this paper established a novel intrinsic reparative mechanism of NETs and contributes to further understanding on their dichotomous role in disease.

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International Society of Hypertension

CALL FOR BIDS

INTERNATIONAL SOCIETY OF HYPERTENSION 2026 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 2026.**

Bid Deadline is Wednesday 1st March 2022

ISH particularly encourages submissions from regions that have not hosted ISH Biennial Scientific Meetings before.

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. Innovative / new programme features.
6. Support of national hypertension related society.
7. Support of related national hypertension societies /organisations in the region.
8. Commitment from local hypertension experts.
9. Experience of host organisation with similar meetings.
10. Financial resources available to host the meeting.
11. Quality and experience of PCOs (Professional Conference Organisers) and similar organisations to assist in the organisation and delivery of the conference.
12. Meetings should ideally be hybrid to allow remote participation and offer a number of free to view lectures.

DELEGATE PROFILE

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

Financial Liability

Local organisers must sign a contract committing to pay ISH one half of the surplus income. The ISH does not assume responsibility for any loss associated with the event.

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:

ISH Secretariat
Email: helen@ish-world.com
Web: www.ish-world.com

SUBMISSION TIMETABLE

- **Bid Deadline 1st March 2022**
- Notification of Shortlisted Candidates Wednesday 1st June 2022
- Presentations of shortlisted bids to ISH Bidding Review Committee at ISH Kyoto 2022 in October 2022
- Announcement of 2026 Congress host November 2022

LEARNING THE ROPES: RAAS: MEASURING ITS COMPONENTS AND NEW THERAPEUTIC STRATEGIES

Introduction

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The renin-angiotensin-aldosterone system (RAAS) has inspired cardiovascular research since the discovery of renin by Tigerstedt and Bergmann in 1898[1]. They reported that an extract from rabbit kidney would raise blood pressure when injected into a recipient rabbit. In the decades to follow, the individual RAAS components: the precursor protein angiotensinogen, the enzyme renin, the converting enzymes ACE and ACE2, the various angiotensin peptides, notably the octapeptide, angiotensin II (Ang II), as well as the adrenal steroid aldosterone with their different receptors were stepwise identified, and methods to analyze, measure and monitor all these components were developed over the years around the world. Today, we can fill libraries with literature, not only about presence, regulation, and concentration of the individual proteins, peptides and of aldosterone in blood and various tissues of many species, but also about their interplay with other relevant hormonal systems and many aspects of their physiological and pathophysiological functions.

Concerning hypertension, an inadequately regulated RAAS has been identified as a major player contributing to the induction and maintenance of the disease: Ang II, a prominent effector peptide of the renin-angiotensin system (RAS), raises via its AT1 receptor blood pressure by a direct vasopressor effect. In addition, it can also exert a plethora of further actions in the kidney and other organs contributing not only to the increase of blood pressure but also, among others, to vascular and cardiac hypertrophy, fibrosis, inflammation, or a decrease of insulin sensitivity. Similar actions have been ascribed to aldosterone, which is to a certain part under the control of Ang II.

In view of these unwanted pathological features of the RAAS, it is quite understandable that laboratories in the pharmaceutical industry as well as in academia, often in close collaboration, were driven by the idea that an inhibition of the system could be beneficial in lowering elevated blood pressure and by this preventing or reducing the sequelae of hypertension such as stroke, renal and cardiac failure. The first aldosterone antagonist, spironolactone, was brought to the market in the sixties of the last century, followed by the converting enzyme inhibitors in the eighties and the angiotensin AT1 receptor antagonists in the nineties. These newly established drug classes had a tremendous impact on the management of cardio-metabolic diseases reaching far beyond the mere reduction of blood pressure, and today's drug armamentarium is unthinkable without compounds inhibiting the RAAS.

However, despite this unquestionably huge progress in our knowledge of the RAAS and its manipulation on a molecular and clinical level, it appears that with each step of advancement new questions arise and new therapeutic options are unveiled. A good example for this is the discovery of the ACE2-angiotensin (1-7) branch of the RAS or the angiotensin AT2 receptor whose tissue-protecting actions may become therapeutic tools in the future[2,3].

In the current 'Learning the Ropes' section you will find four articles on RAAS measurement methodology and novel therapeutic perspectives written by prominent experts in the field.

Joel Ménard, a pioneer and doyen of RAAS research, opens the section with an article of how to measure renin and where renin measurements can be used clinically. For quite a time, renin was the only measurable compound of the RAS in the blood, and classifications of hypertension (low-, normal-, high renin hypertension) were based on this information. In a historical perspective, Joel Ménard describes the long

and cumbersome way of how these measurements were begun with a relative crude bioassay methodology and were then continuously refined over the years towards the laboratory routine of our days.

Jumping right into our current days, Marko Poglitsch describes a novel method he and his colleagues have developed to simultaneously measure various angiotensin peptides and aldosterone in the blood together with angiotensin-based calculation of RAS proteins like renin and ACE. For the first time, this methodology provides an exact pattern of RAAS components under different clinical and therapeutical circumstances. It allows not only for the identification of hypertension subtypes but also for the demonstration of possible causes of therapeutic failure i.e. uncontrolled hypertension. This approach may open up new perspectives towards an individualized, more successful, drug therapy.

Reure Lopez, Edward Sturrock and Rhian Touyz present us with a new therapeutic option, the ACE-C-domain-neprilysin inhibitor. The idea to combine ACE inhibition with neprilysin inhibition in one molecule was first entertained by the development of the compound omapatrilat. However, due to a doubling of angioedemea, a well-known, potentially dangerous, side effect of ACE inhibitors, this compound never entered the market. More recently, another pharmaceutical company has developed a supramolecular salt complex of an AT1-blocker and a neprilysin inhibitor (ARNI). This compound has proven to be very successful, mainly in the treatment of heart failure with low ejection fraction. Rhian Touyz and colleagues have chosen a different approach: They inhibit the C-domain of ACE with a compound called lisW-S and combine it with the neprilysin inhibitor sacubitril. By this, they only lower the production of Ang II with no effects on bradykinin and other peptides, thus avoiding the ACE inhibitor-induced bradykinin accumulation which is thought to be a mechanism of cough and angioedema formation. The authors demonstrate that, in animal experiments, the combination of lisW-S+sacubitril lowers blood pressure like omapatrilat but does not lead to a bradykinin accumulation.

Finally, Liwei Ren and Jan Danser surprise us with a completely new molecular approach to inhibit the RAAS by targeting angiotensinogen, the precursor of all angiotensin peptides, via interfering RNA or antisense oligonucleotides (ASO). They describe experiments with a siRNA in genetically hypertensive rats (SHR) or in a low renin model of chronic kidney disease (CKD). In SHR, they could decrease blood pressure to the same extent as with classical RAS inhibitors with the advantage of a much lower dosing frequency. Combination with an AT1 receptor blocker augmented the blood pressure lowering effects. In CKD, they observed tissue protecting effects with a moderate reduction of blood pressure.

These four examples may suffice to demonstrate that the venerable RAAS still represents a rich source of inspiration to creative minds if they are ready to learn their ropes.

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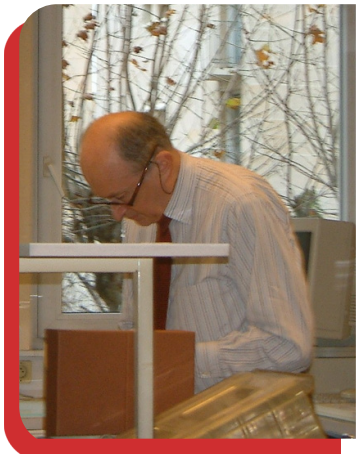
LEARNING THE ROPES:

Measuring Renin: a long way from bioassasys to current standardization



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Measuring renin in plasma has been a long-term dream, as soon as it was known that renin was liberated from the kidneys in proportion to the decrease in perfusion pressure. To achieve this goal, plasma renin measurements were established through measurement of renin's enzymatic activity to produce angiotensin I (Ang I) from plasma angiotensinogen in vitro (PRA) and to investigate its variations under different physiological and pathological conditions[1,2]. The detailed molecular mechanism underlying this step is better known since the crystal structures of glycosylated human angiotensinogen and renin and their interaction have been revealed.

At a late stage of 50 years of methodological research, investigators directly involved in laboratory measurements have collectively written a general review on all technical matters[3]. They discussed the difference between the enzymatic assay, PRA, and plasma renin concentration (PRC), and the so-called ponderal assay. i.e., the quantification of the active and total renin molecules circulating in plasma by a sandwich assay using pairs of monoclonal antibodies directed towards different epitopes of the protein.

Different methods of in vitro activation of the enzymatic activity of renin and some specific monoclonal antibodies which recognize total renin make it possible to investigate plasma active renin, total renin, and, by difference, prorenin. This inactive precursor of renin biosynthesis in the juxtaglomerular apparatus of the kidney and in other organs outside the kidney, such as the eye, is present in plasma at much higher concentration. Because of the possibility of an artificial ex-vivo activation or an interference with renin inhibitors, the exact conditions of blood sampling and plasma storage are of utmost importance[3,4].

The main methodological issues are the following:

1) The in vitro production of Ang I by renin is dependent on renin's unique substrate species specificity (with an advantage of sheep substrate for human renin). It is proportional to active plasma renin and is influenced by the level of angiotensinogen of hepatic origin present in the plasma with a concentration near the Km (Michaelis Constant) of the enzymatic reaction and is modestly influenced by the genotype. Angiotensinogen is high during pregnancy and synthetic estrogen therapy and low during congestive heart failure or renin-angiotensin system (RAS) inhibition in conjunction with diuretics.

2) Ang I has to be protected from its in vitro destruction by angiotensinases in proportion to the incubation time selected for the enzymatic reaction. Up to 1970, Ang I was measured by a pressor assay in anesthetized binephrectomized rats. From 1970 to 1985, radioimmunoassays with high specificity and sensitivity were developed followed by immuno-enzymatic assays in different systems which eliminate the use of radioactivity and allow to perform large series of determinations at the same time with the appropriate internal standards. Separation of angiotensin peptides was later-on performed by high performance liquid chromatography and further by liquid chromatography-tandem mass spectrometry. Multiple degradation peptides of angiotensins were separately measured in vivo and in vitro[5].

A complementary and necessary information was given by the appropriate measurement of a main final product of the system, angiotensin II (Ang II) after immediate inhibition of its production and degradation during blood sampling[6]. PRA levels are always highly correlated with plasma Ang II levels. The slope of correlation is influenced by any decrease (flatter slope) or increase (steeper slope) of plasma angiotensinogen and, in a practical way, renin assays are easier to perform than Ang II assays.

The first period of PRA measurements between 1960 and 1975, based on bioassays, provided important information on the influence of age, day-night cycle, posture, sodium content of the diet, menstrual cycle, specific effects of antihypertensive drugs and other conditions which can influence renin levels. Individuals

have been defined as having low, normal or high levels of plasma renin within a continuous distribution of values[1,2]. Micromethods of renin activity measurement were established in many animal species to study renin release in experimental hypertension. They detected renin outside the juxtaglomerular apparatus of the kidney, in the central nervous system, blood vessels, or the adrenal gland. The sensitivity and specificity of the methodology has a major influence on the results and their interpretation as it happens to be also for other techniques of renin measurement (western, northern and Southern blots for proteins, RNA and DNA)[7]. The putative presence and function of local RAS is still controversial, especially at the level of the brain. Similar controversies have concerned the extrarenal actions of aldosterone and the possibilities of its extra-adrenal production at the vicinity of its receptors.

Two original examples of the use of some poorly known advantages of enzymatic and other renin measurements are selected. A first example is given when total plasma renin is captured by a monoclonal antibody which immobilizes renin (prorenin and active renin) and allows for quantification by polyclonal antibodies linked to another epitope, located against the active site to measure active renin or, at another site, to measure at the same time active renin and prorenin (total renin)[8]. A group from Glasgow has measured the reactive rise in plasma renin concentration during the first-to-man administration of their H142 renin inhibitor in accordance with previous experimental results[9,10]. Inhibition of the enzymatic property of renin precisely correlated with the rise in active renin from renal origin, followed by a liberation of its intracellular precursor, prorenin.

A useful example of the species specificity of the renin-angiotensin system was given by first investigations in transgenic hypertensive rats. This experimental model was initially considered a low renin model aiming to decipher the potential role of extra-renal renin in the pathogenesis of hypertension. By selecting different pHs for in vitro renin measurements, it was possible to separate in the Ang II excess, which characterizes the model, the predominant role of the transgenic mouse renin (optimal enzymatic reaction at pH 8.5), from its feed-back to lower the native rat renin (pH 6.5). By this, it was demonstrated that the model, initially described as low-renin, was indeed a high-mouse renin and a low rat-renin model with an equilibrium between the two systems[11,12].

In 2020, the time of home-made renin assays was gone. Today, various chemoluminiscence assays with high output are used for multiple hormonal systems. Their intra-assay and inter-assay coefficient of variations are below 10 %. It is desirable to have renin results within three hours for the diagnosis of secondary hypertension and to monitor plasma renin during treatment, especially to monitor the sodium balance when diuretics and anti-aldosterone drugs are used as a monotherapy. By different mechanisms, beta-blockers decrease plasma renin, and blockers of the RAS increase it. Dihydropyridine type calcium channel blockers are rather neutral on plasma renin.

The optimal clinical information of plasma active renin can be obtained either by an Ang I enzymatic assay or an immunoenzymatic assay. Less frequently, both active renin and prorenin are measured, but the extra-renal origin of prorenin makes it difficult to interpret values, for instance when they are increased in diabetic patients. It is useful, and even mandatory, to detect secondary hypertension in the check-up of every individual with newly discovered permanent hypertension, who will have a follow-up of several decades. It is logical to simultaneously measure plasma aldosterone but the popular renin/aldosterone ratio, which has been widely promoted, is more a mnemotechnic than a reasonable tool.

The demonstration of unilateral disease by plasma renin measurements in the renal veins has been, and still should be, a major indication to investigate renal artery stenosis, renal infarctions, renin-secreting tumors and some renal and extrarenal cancers[13]. The results of the Cardiovascular Outcomes in Renal Athero-sclerotic Lesions (CORAL) study result did not encourage an agressive attitude on renal arteries to improve the global cardiovascular prognosis[14] but the renal problem persists, and a case by case analysis aiming to retard renal insuficiency includes renin measurements in renal veins in conjunction with other hemodynamic and isotopic investigations.

Suggestions

Any person, who has a recently discovered permanent high blood pressure, could benefit once in life from a renin- and aldosterone measurement measured under optimal conditions, before being labelled as hypertensive and treated for several decades. The shorter the time to obtain and analyze the results between clinic, laboratory and clinic, the easier will be the practical use of plasma

renin and aldosterone measurements[15]. Evaluating each parameter separately is more informative than the simplified memorization of an aldosterone/ renin ratio with an arbitrary threshold within a continuous distribution.

The use of fixed-dose combination therapies, as recommended today by hypertension guidelines, minimizes the advantage of the «low and high renin « classification, initially proposed by John Laragh, to make the choice of a full-dose of monotherapy between diuretics (low renin) or beta-blockers and renin-angiotensin inhibitors (high renin). Plasma renin measurements are already used to follow the magnitude of sodium depletion during the medical treatment of primary aldosteronism by an anti-aldosterone drug. Information on the results, which could be expected from a systematic monitoring of renin and aldosterone measurements at the different dosages of these fixed-dose combinations, could be useful to interpret treatment results at different sodium intakes in conjunction with blood pressure changes. The renin methodology requires to be well controlled at the clinic during blood sampling and in the laboratory. Proper use as a routine will certainly confirm previous research contributions to clinical care.

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Renin form measured	Activity assays	Immunoassays	Units
Plasma Renin Activity (PRA)	**Ang I production by plasma renin activity (both renin and prorenin in open conformation acting on endogenous plasma angiotensinogen**		**Nmol/L per hour**
Plasma Renin Concentration (PRC)	Ac-PRC Ang 1 production by plasma renin activity(both renin and prorenin in open conformation)acting on exogenous angiotensinogen	Ir-PRC: renin radioimmunometric or enzymo-immunometric assay of untreated plasma (measures both renin and prorenin with open conformation)	IU/l or ng/L or pmol/L
Total Renin Concentration (TRC)	Ac-TRC Ang 1 production by total renin activity(after trypsin activation of prorenin)acting on exogenous angiotensinogen	Ir-Total renin radioimmunomtric or enzymo-immunoradiometric assay of untreated plasma (measures renin and all prorenin with closed and open conformation	IU/L or ng/L or pmol/L
Prorenin Concentration	Ac-Prorenin: calculated from the difference between ac-TRC and Ac -PRC	Ir-prorenin Calculated from difference betwwen ir-TRC and Ir-PRC	IU/L or ng/L or pmol/L

Activity assays (ac-PRC, ac-TRC, ac-prorenin) can be calibrated against the International Reference Preparation of human renin, and results are expressed in international units per liter [Bangham et al. Clin Sci Mol Med Suppl 1975;2:135s–159s]. ir-TRC can be measured by 2 methods :by immunoassay with a pair of antibodies that recognize both renin and pro-renin, or by renin immunoassay after trypsin activation of prorenin or after conversion of prorenin to an open conformation by incubation with a renin inhibitor. Modified from DJ Campbell et al. Clinical Chemistry 55:5 867–877 (2009)

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LEARNING THE ROPES:

Angiotensin Metabolites in the diagnostic workup of hypertension

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More than 50% of patients on antihypertensive therapy remain hypertensive. Identifying the individual cause for uncontrolled hypertension remains a major challenge for physicians. Underdosing, lack of treatment adherence, whitecoat and resistant hypertension but also secondary forms of hypertension are among the most common causes of uncontrolled hypertension. Identification of these subtypes and therefore enabling individualized therapeutic approaches is key to improve hypertension control. Simple and reliable diagnostic tools for molecular profiling of hypertension are desperately needed to bring light into the black box of uncontrolled hypertension.

The renin angiotensin aldosterone system (RAAS) is the central pharmacologic target in the treatment of hypertension. Angiotensin-converting-enzyme (ACE) inhibitors (ACEi) and angiotensin receptor blockers (ARBs) are part of every first-line therapy recommended by clinical guidelines[1]. The key effector hormone of RAAS is angiotensin II (Ang II). Ang II binds to Ang II type-1 receptors (AT1R) resulting in direct vasoconstriction. In adrenals, AT1R stimulation by Ang II results in upregulation of aldosterone synthesis and secretion. The RAAS is a humoral peptide hormone cascade that is abundantly fueled with the pro-hormone angiotensinogen (AGT) secreted by the liver. AGT is cleaved by renin, the secretion of which is tightly regulated in the kidneys. Renin mediated cleavage of AGT results in the release of angiotensin I (Ang I). Endothelial and circulating ACE convert Ang I to Ang II, which then can act through its vascular and adrenal receptors. With its key functions within the RAAS, either blocking Ang II formation or signaling became key strategies in the pharmacologic treatment of hypertension using ACEi and ARBs.

Molecular diagnostics in hypertension is currently limited to the measurement of renin and aldosterone using different technologies. Of note, antihypertensive medications strongly interfere with these readouts[2], which can be problematic when interpreting test results. Consequently, the use of aldosterone and renin, especially in the context of using the aldosterone-to-renin ratio (ARR) in screening for primary aldosteronism (PA) requires drug withdrawal to maintain screening sensitivity, which is a major barrier for broad clinical implementation of PA screening. Moreover, the lack of certified reference standards for active renin as well as methodological caveats of antibody-based methods for detection of renin and aldosterone[3] result in poor comparability of cut-off values between different methods and even clinical centers, resulting in low screening rates and severe underdiagnosis of PA. In PA, adrenal aldosterone secretion becomes independent of Ang II. The underlying pathology involves aldosterone producing cell clusters (APCCs), bilateral adrenal hyperplasia and aldosterone producing adenomas, which in total are thought to affect 5-10% of all hypertensive patients. In PA, the aldosterone excess leads to sodium and water retention and a subsequent volume increase culminating in angiotensin independent hypertension. Consequently, first-line therapies using ACEi and ARBs are inefficient in treating PA, as the molecular cause for hypertension is downstream of ACE and AT1R. ACEi and ARBs strongly interfere with the current screening strategy for PA, which leads to the requirement of drug withdrawal before PA screening using the ARR[2]. Although renin concentration is widely used as a surrogate marker for RAAS activation in PA screening, the effector hormone Ang II is only partially reflected by the renin concentration. Patient specific variations in ACE activity, especially in the presence of ACEi therapy result in a loss of the correlation between renin concentration and Ang II levels, which is one of the reasons why screening for PA is prone to drug interference artifacts if using renin based diagnostic ratios like the ARR. Compensatory up-regulation of renin results in a suppression of the ARR,

which is used as a screening test for PA. Recently, Ang II has been introduced as an alternative denominator to be used in PA screening[4]. By using Ang II instead of the surrogate marker renin as a measure for RAAS activation, the direct link between the Ang II and adrenal aldosterone secretion seems to provide a more solid diagnostic ratio for PA screening. The Aldosterone-to-Ang II-ratio (AA2-Ratio) remained elevated while the ARR was significantly suppressed in PA patients treated with ACE inhibitors[5].

With the availability of LC-MS/MS based RAAS equilibrium analysis, angiotensin levels became available for applications in clinical routine. In contrast to immunoassay-based approaches, LC-MS/MS is a direct quantification method allowing for easy internal standardization and analyte multiplexing, which reduces costs and increases accuracy of the test results. Recently, the RAAS Triple-A test has been introduced for molecular hypertension profiling. The assay simultaneously determines Ang I, Ang II and aldosterone in serum samples and is available as an LC-MS/MS kit (Attoquant Diagnostics, Vienna), that is compatible with clinical LC-MS/MS systems. Obtained angiotensin levels are used to calculate angiotensin-based markers for renin activity (PRA-S), ACE activity (ACE-S) and adrenal AT1R function (AA2-Ratio). Measured analytes and derived enzyme markers are obtained from a single analytic run and are interpreted in the context of the existing drug prescription. Both, ACEi and ARBs induce specific changes in angiotensin profiles and derived biomarkers, which can be used to evaluate the pharmacologic efficacy of RAAS blockers in clinical samples. In contrast to measuring drug molecules in serum during therapeutic drug monitoring, RAAS Triple-A parameters are used to evaluate the physiological responses induced by antihypertensive drugs. Therefore, drug efficacy monitoring using angiotensin levels remains independent of the type of drug molecule. The approach is currently being validated in a large population-based cohort and for the first time offers drug efficacy monitoring and screening for secondary hypertension in a single diagnostic approach.

In summary, the utilization of angiotensin metabolites in hypertension profiling moves clinical diagnostic approaches away from surrogate markers and introduces the actual effector hormones of the RAAS into clinical diagnostics. Selected angiotensin metabolite ratios can be utilized as markers for pharmacologic efficacy of ACE inhibitors and ARBs while simultaneously screening for secondary forms of hypertension. With the broad availability of the RAAS Triple-A test for clinical mass spectrometry laboratories, multiple causes of uncontrolled hypertension can be simultaneously addressed in a single diagnostic workup that only requires a simple blood collection on standard antihypertensive therapy. The interpretation of a patient's angiotensin metabolite levels and derived biomarkers in the context of the existing drug prescription could be a gamechanger in hypertension management, allowing for individualized and effective therapeutic approaches.

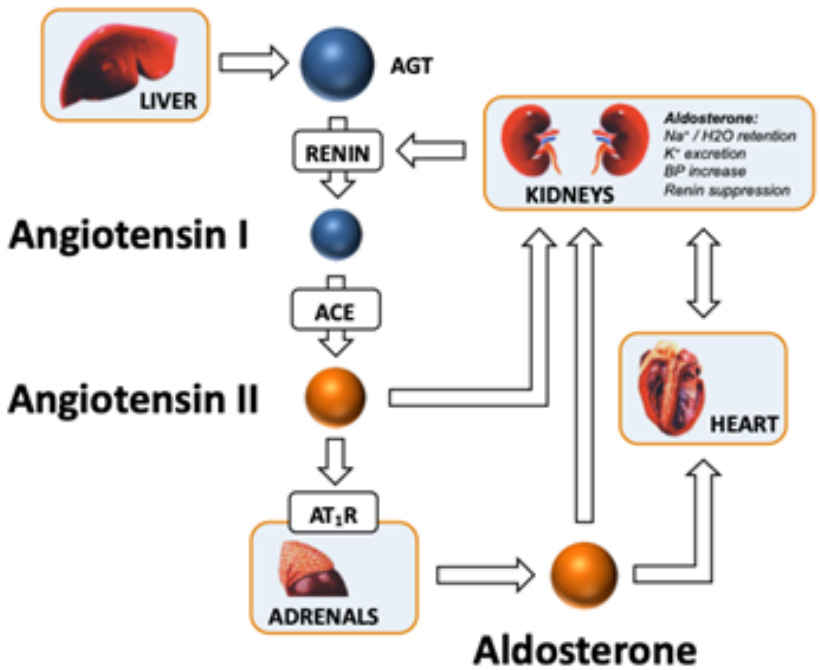

Figure 1: Schematic representation of the RAAS.

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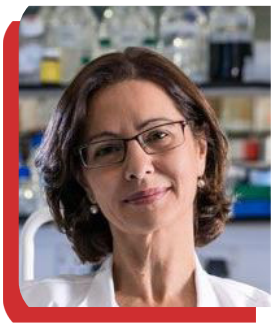
LEARNING THE ROPES:

Targeting C-domain of Angiotensin Converting Enzyme and Nerprilysin as a Potential New Therapeutic Strategy in Hypertension



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More than 30% of all deaths worldwide are due to cardiovascular disease, where overactivity of the renin-angiotensin-aldosterone system (RAAS) plays a key role. Activation of the RAAS leads to fibrosis, excessive vasoconstriction, reduced vasodilation, increased sodium and water retention, and cardiac hypertrophy. This has led to the development of drugs that inhibit key components of the RAAS to treat conditions including hypertension, where angiotensin-converting enzyme inhibitors (ACEi) are among the first-line treatments. Reduction of blood pressure induced by ACEi is mostly via reduction of angiotensin II (Ang II) levels, and reduction in bradykinin (BK) degradation. The anti-hypertensive effects of ACEi and angiotensin receptor blockers (ARB) are well established. However, some patients are non-responsive to these drugs, hence, there is a growing need for novel antihypertensive drugs[1,2].

Drugs targeting diverse components of the RAAS are used to treat cardiovascular diseases, where most of them are predominantly designed to antagonize Ang II effects. Increasing evidence indicates that in addition to Ang II, other components play an important role in the system, including neprilysin (NEP). NEP also controls BK degradation and inhibition of NEP causes an increase in BK levels. However, NEP inhibition alone is not able to sustain a reduction in blood pressure, probably because NEP also regulates other peptides involved in vascular control, including natriuretic peptides, Ang I, Ang II, ET-1, enkephalins, substance P, insulin, amyloid-β peptide, and gastrin[1,2]. NEP inhibitors also have a short half-life.

There is similarity between the three-dimensional structures of ACE and NEP, which enabled the development of a single molecule able to target both enzymes. Clinical trial data comparing antihypertensive effects of dual inhibition of ACE and NEP (omapatrilat) versus ACEi alone showed greater efficacy for omapatrilat. However, a large phase III clinical trial, demonstrated unwanted side effects, specifically angioedema with omapatrilat and accordingly the drug failed to obtain U.S. Food and Drug Administration (FDA) approval. Increased risk of angioedema induced by omapatrilat is associated with high levels of BK, probably because this drug inhibits NEP, aminopeptidase P, and ACE, all of which are involved in BK degradation. ACE has two distinct catalytic domains, N- and C-domains. The C-domain hydrolyzes angiotensin I (Ang I) and is primarily responsible for Ang II production. On the other hand, both domains contribute to the degradation of BK, and nonspecific inhibition of C- and N-domains, leads to excess BK formation, leading to adverse effects[3].

To better explore the inhibition of NEP, it was thought that this class of drug could be combined with endothelin-converting enzyme-1 (ECE-1) inhibitors to treat cardiovascular conditions. This was based on the fact that the accumulation of ET-1, induced by NEP inhibition, would be prevented if ECE-1 was also inhibited. However, systemic blood pressure, heart rate, and cardiac output were unaffected by dual ECE-1/NEP inhibition, further highlighting the important role of the RAAS in blood pressure control[4].

A third strategy was to combine a drug that simultaneously inhibits ACE, NEP and ECE-1. However, similar to what was observed with omapatrilat, pre-clinical data showed a significant accumulation of BK, and once again safety issues were a concern[5]. The complexity of this approach may cause many off-target

actions, and possibly serious undesired effects, and needs careful evaluation before testing this combination in humans.

Recognition of serious adverse effects associated with BK accumulation led to the development of sacubitril/valsartan (previously known as LCZ696). This combination reduces NEP activity via sacubitril while inhibiting the detrimental effects of Ang II via valsartan, with no effect on ACE, and therefore less impact on BK levels. Despite this drug having demonstrated clinical efficacy in the reduction of blood pressure in patients, this medication is approved for the treatment of heart failure only, and it is estimated that thousands of deaths could be prevented each year with the implementation of sacubitril/valsartan therapy to treat hypertension[6]. Despite its effective blood pressure-lowering effects, the drug is licensed primarily for heart failure and not for arterial hypertension.

Since the N- and C-domains of ACE have different functions, it was thought that targeting the domain only involved in Ang II production may be an interesting approach to regulate blood pressure without undesired effects induced by N-domain inhibition including BK accumulation. With the development of a C-domain-selective ACEi, a derivative of lisinopril [lisW-S (lisinopril-tryptophan)], by substituting a tryptophan for the P2' proline [7-9], a potential new strategy to treat hypertension was launched. The combination of lisW-S with a NEP inhibitor (sacubitril) in an animal model of hypertension reduced systolic blood pressure (SBP) similar to that of omapatrilat. However, unlike omapatrilat, which improved endothelial function, this was not observed for lisW-S + sacubitril. In addition, omapatrilat but not lisW-S + sacubitril caused plasma extravasation and vascular leakage, important processes that play a role in angioedema. Of significance, lisW-S + sacubitril, but not omapatrilat, increased plasma levels of BK inactive metabolites, suggesting that N-domain activity of ACE is preserved in animals treated with lisW-S. Together these findings indicate that lisW-S combined with sacubitril has the same beneficial effects as omapatrilat, but without the undesirable properties attributed to BK accumulation[10]. This combination provides potential new approaches in the treatment of hypertension and opens new avenues for development of novel anti-hypertensive drugs.

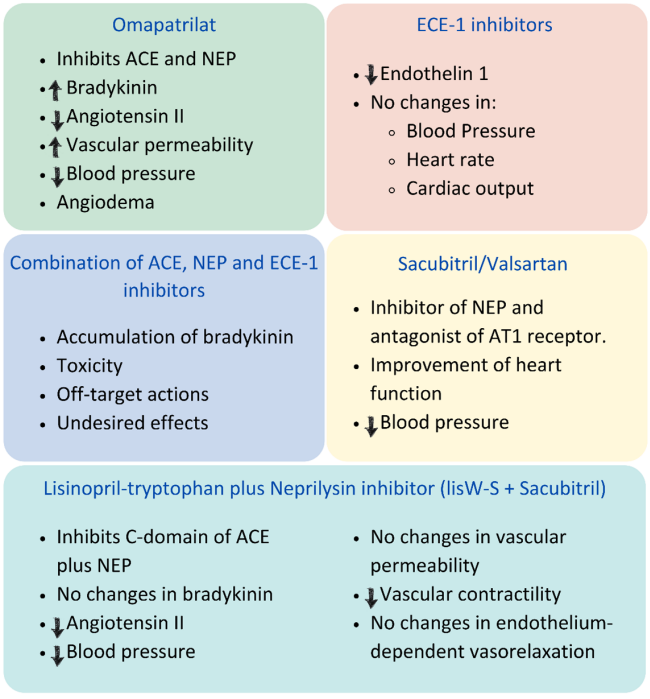

Figure 1. Pharmacological targets involving RAAS system and ECE in the treatment of hypertension. Evidence indicates that in addition to Ang II, other components play an important role in blood pressure control, including neprilysin (NEP) and ECE. All of them, somehow negatively modulates pro-hypertensive signalling pathway, however, undesired effects such as BK accumulation and angioedema, make it impossible for most of these drugs to be used therapeutically. With the development of a C-domain-selective ACEi (tryptophan), a potential new strategy to treat hypertension was launched: tryptophan combined with NEP inhibitor Sacubitril. ACE: Angiotensin Converting Enzyme; NEP: Neprilysin; ECE-1: Endothelin converting enzyme 1; AT1: angiotensin II type 1; LisW-S: Lisinopril-tryptophan.

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LEARNING THE ROPES:

Angiotensinogen suppression: a promising approach

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Hypertension remains the leading cause of death worldwide[1], despite the fact that more than 100 commercial drugs and drug combinations are available for its treatment. Blood pressure is often non-optimally controlled, either due to non-adherence or mechanisms that counteract the antihypertensive effect. For instance, in the case of angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II type 1 (AT1) receptor blockers (ARBs), a renin rise will occur, due to interference with the negative feedback loop that normally allows angiotensin II to suppress renin. Here it is important to realize that, at 90% ACE inhibition, a 10-fold rise in renin is sufficient to restore the original angiotensin II levels. Such rises are easily achievable, and even renin rises of up to several 100-fold may occur. Hence, the idea has come up to combine multiple renin-angiotensin system (RAS) blockers at the same time to achieve better blockade. Unfortunately, this also resulted in more side effects. Another option is to target angiotensinogen, i.e., the ultimate source of all angiotensins. Normally, its levels are in the order of 1200 nmol/L, or almost 1 million times the level of angiotensin II. This allows angiotensin generation to rise in parallel with renin, even if renin increases 100-fold. Obviously, in the absence of sufficient angiotensinogen, renin will still rise substantially, but now it cannot generate angiotensins. Thus, this approach should prevent the normal counterbalancing consequences of the renin rise[2].

Circulating angiotensinogen is predominantly liver-derived, although several studies suggest that angiotensinogen is also generated at extrahepatic sites, like the kidney and adipose tissue. An elegant way of suppressing angiotensinogen is to make use of antisense oligonucleotides (ASO)[3] or small interfering RNA (siRNA) [4], particularly when conjugated to the hepatocyte-targeting ligand N-acetylgalactosamine (GalNAc). This ligand recognizes the asialoglycoprotein receptor, which is primary expressed on hepatocytes. Upon binding it will be rapidly endocytosed, and once intracellular both ASO and siRNA ultimately result in the destruction of angiotensinogen mRNA, thereby preventing de novo synthesis of angiotensinogen. Due to their liver-specificity, low doses of GalNAc-conjugated siRNA or ASO are sufficient to suppress angiotensinogen[5]. It is worth noting that several liver-targeted siRNA drugs (e.g., patisiran, for hereditary transthyretin amyloidosis, and inclisiran, for lipid lowering) already exist. Remarkably, their half-life is exceptionally long , allowing a dosing regimen of at most 2-3 injection per year[6].

Angiotensinogen siRNA and ASO are now being evaluated in phase 1/phase 2 clinical trials. To obtain a better understanding of their mechanism of action, we have recently investigated the effects of angiotensinogen siRNA in spontaneously hypertensive rats (SHR) and in rats with chronic kidney disease (CKD) following 5/6th nephrectomy[4-7]. In both models, siRNA lowered circulating angiotensinogen by >95%. As expected, in SHR renin rose considerably after this treatment. This allowed circulating angiotensin II levels to remain intact, while the renal levels of angiotensin II dropped by >50%. The latter indicates that it is particularly tissue angiotensin production that is sensitive to the siRNA approach. Remarkably, adding an ARB on top of siRNA in SHR led to an even further rise in renin, and now angiotensinogen became depleted, so that angiotensin II virtually disappeared, both in blood and kidney. The blood pressure-lowering effect of siRNA in SHR was comparable to that of an ARB or ACEi (Figure 1A), while in combination with an ARB blood pressure dropped

synergistically, reflecting the virtual annihilation of angiotensin II. Under these conditions kidney function (glomerular filtration rate) remained intact, while cardiac hypertrophy decreased in parallel with blood pressure.

The 5/6th nephrectomy CKD model is characterized by low renin levels, and the blood pressure-lowering effects of siRNA in this situation was therefore modest. It could not be enhanced by concomitant treatment with an ARB. No rises in renin occurred. Nevertheless, siRNA improved proteinuria and reduced glomerulosclerosis, and the reduction in renal angiotensin II content after siRNA turned out to be an independent determinant of this renoprotective effect (Figure 1B). Like in SHR, siRNA in the CKD rat model improved cardiac hypertrophy, while it did not affect glomerular filtration rate. Importantly, in both models, renal angiotensinogen virtually disappeared after liver-specific angiotensinogen siRNA treatment. This demonstrates that renal angiotensinogen, despite the occurrence of angiotensinogen mRNA in the kidney (which was unaffected by siRNA), is of hepatic origin after all.

These data indicate that angiotensinogen siRNA lowers blood pressure to the same degree as classical RAS blockers, yet at a much lower dosing frequency. Given its stable and sustained efficacy, lasting weeks, RNA interference may offer a unique approach to improving therapy adherence and treat hypertension. In addition, angiotensinogen siRNA exerts renoprotection in a blood pressure-independent manner, by specifically reducing renal angiotensin II levels, based on the fact that renal angiotensin generation relies on hepatic angiotensinogen. This may involve megalin-mediated reabsorption of filtered angiotensinogen in the proximal tubule[8].

Although the long-lasting effects of the siRNA approach might be considered as an advantage, it also poses a threat, for instance in women becoming pregnant during treatment, or in cases of emergency, when severe hypotension occurs, and the RAS is needed. Here novel tools ('REVERSIR') are now being developed, capable of acutely reversing the effect of siRNA[9]. This concerns short, synthetic, high-affinity oligonucleotides complementary to the siRNA guide strand, that can be targeted to the liver making use of the same GalNac approach. Finally, given the liver accumulation of the siRNA, one might speculate about liver toxicity, or inflammatory and immunological side effects. Yet, no such observations were made for liver-targeted proprotein convertase subtilisin/kexin type 9 siRNA (inclisiran) over a 6-month period[10]. Since this siRNA relies on the same GalNac principle, at present the safety profile of such drugs seems excellent.

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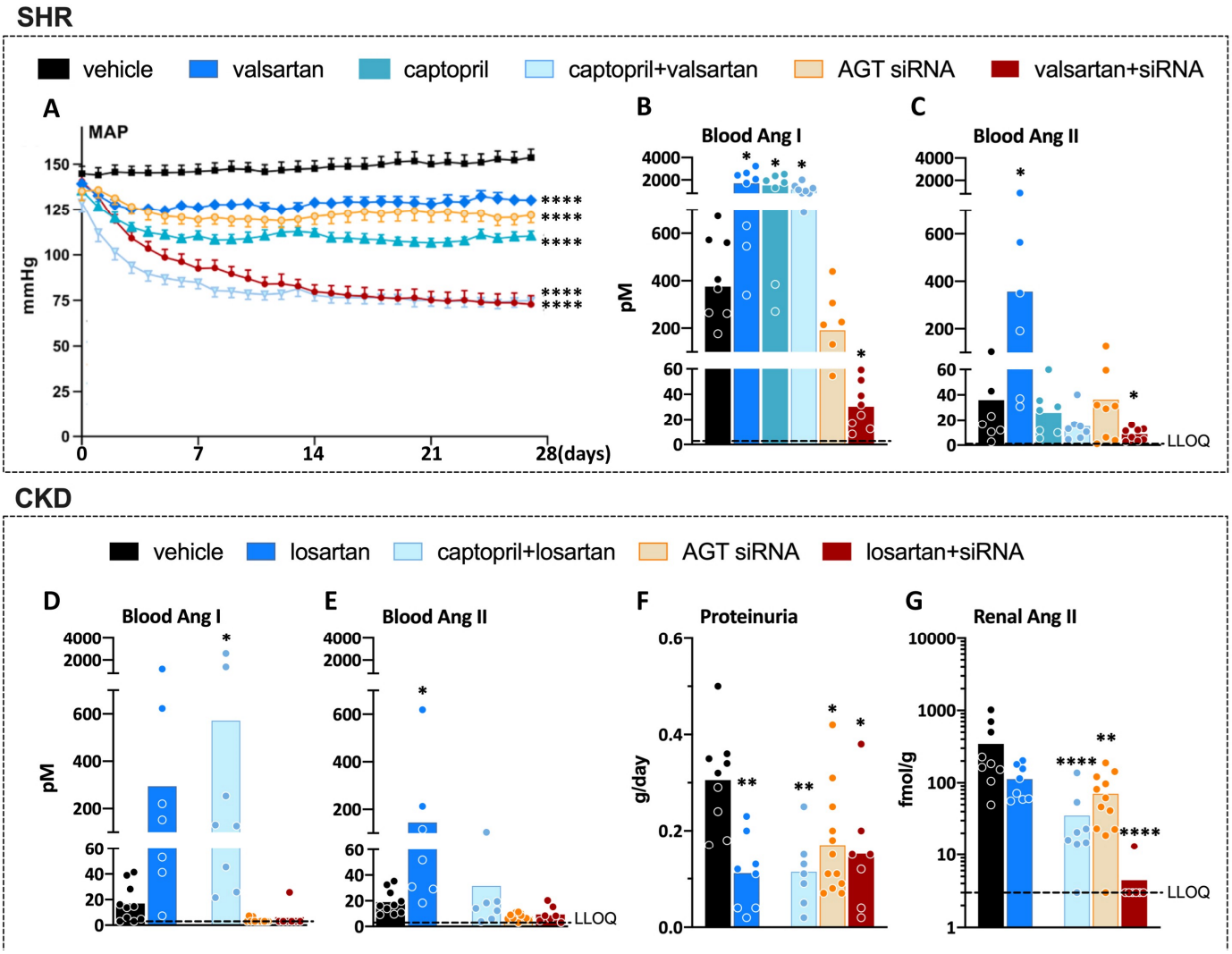

Figure 1. Panel A, effect of angiotensinogen siRNA, valsartan, captopril or their combination on mean arterial blood pressure (MAP) and circulating angiotensin I and II levels in spontaneously hypertensive rats (SHR). Panel B, effect of angiotensinogen siRNA, losartan, captopril or their combination on circulating angiotensin I and II, renal angiotensin II and proteinuria in rats with chronic kidney disease (CKD). Data are from references 4 and 7. *P< 0.05, **P<0.01, and ****P<0.0001 vs. vehicle.

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INSTITUTE FOCUS

Hypertension, Cardiorenal, and Metabolic Diseases Research at the University of Mississippi Medical Center

JOHN E. HALL

Arthur C. Guyton Professor and Chair, Department of Physiology and Biophysics; Director, Mississippi Center for Obesity Research;

Director, Cardiorenal and Metabolic Diseases Research Center

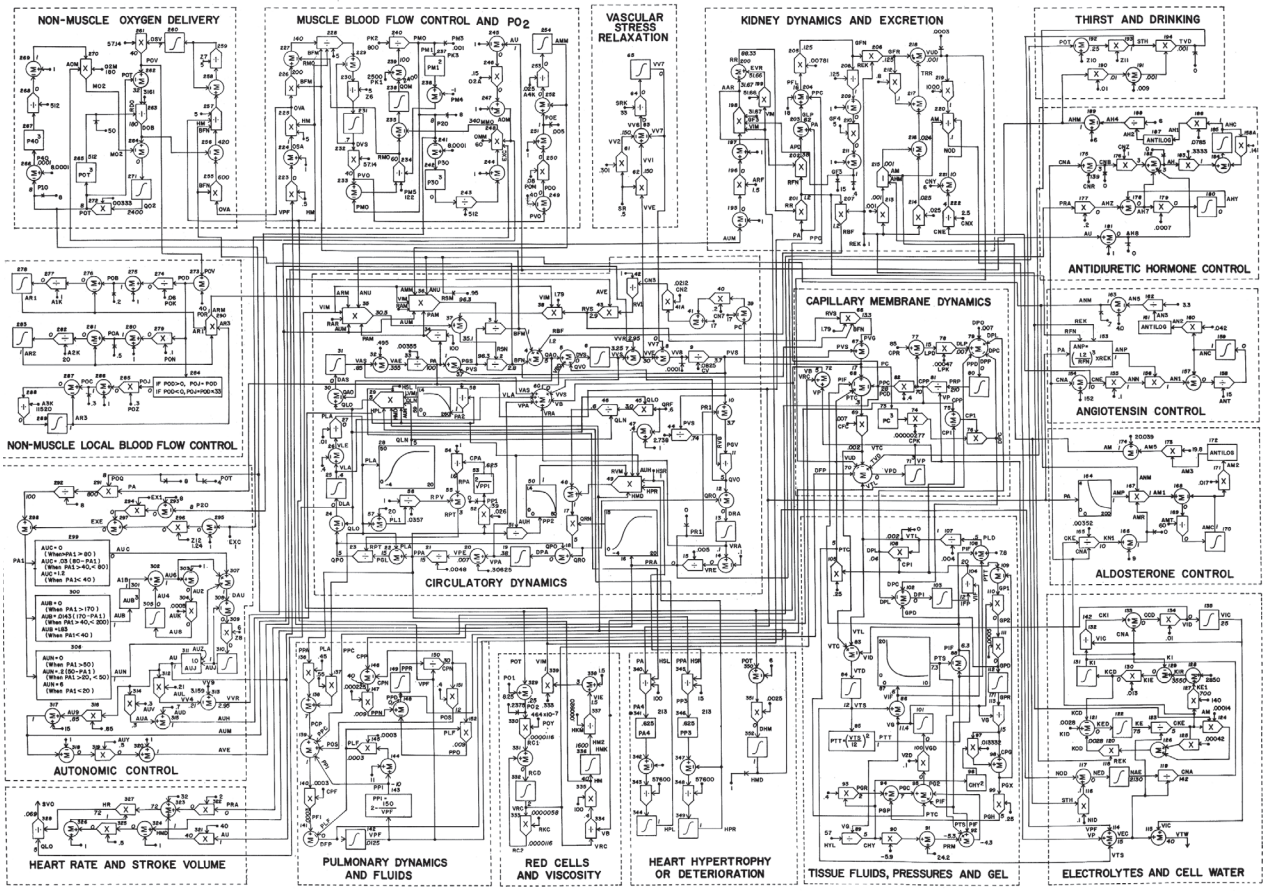
DOI: 10.30824/2112-9

The University of Mississippi Medical Center (UMMC) (click here) was established in 1955 as the only academic health science center and the only level 1 trauma center in Mississippi. Located in Jackson, UMMC includes seven health science schools: medicine, nursing, dentistry, health related professions, graduate studies, population health, and pharmacy. The Medical Center's three-part mission is to improve the lives of Mississippians by educating tomorrow's health care professionals, by conducting health sciences research, and by providing cutting-edge patient care.

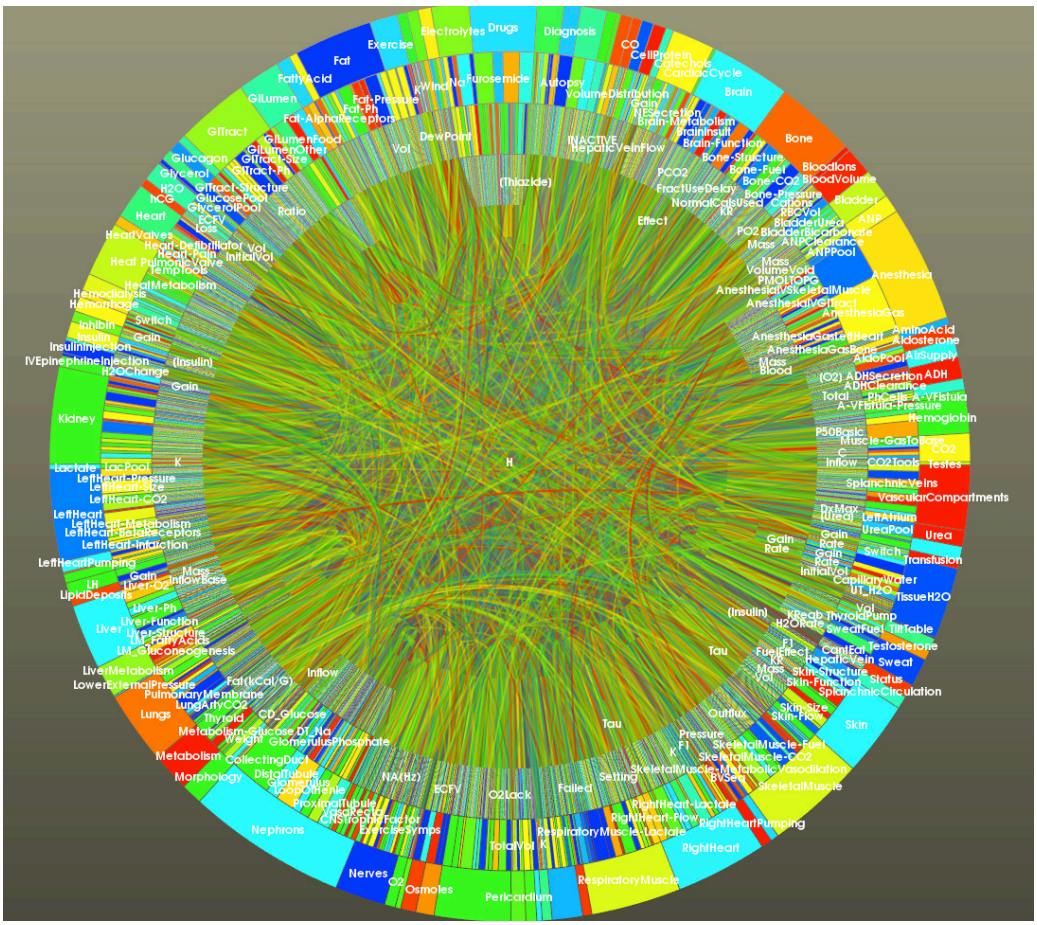
From its beginning, UMMC has been a leading center for cardiovascular research. The pioneering work of Arthur C. Guyton (click here) and his colleagues laid the foundation for UMMC as an internationally renowned center of research excellence in cardiovascular and renal physiology as well as in the pathophysiology of hypertension and cardiorenal diseases. Guyton, Thomas Coleman (Click here), and their collaborators published in 1972 the first large scale systems analysis of cardiovascular function, consisting of ~450 variables; over the ensuing years the model has been continuously expanded, mainly by Coleman, Robert Hester and their collaborators, and currently includes over 10,000 variables but continues to expand as new data are obtained. The interplay of mathematical systems analysis and experimental studies has been a major theme of the UMMC cardiovascular, renal and hypertension research programs for more than 50 years. This systems analysis approach has led to seminal discoveries related to short-term and long-term blood pressure regulation, as well as the multiple neurohormonal and intrarenal mechanisms that control cardiovascular and kidney function in hypertension and other pathophysiological conditions.

Another major figure in the history of cardiovascular research at UMMC was James D. Hardy (Click here). Professor Hardy was the first chair of the Department of Surgery at UMMC and a pioneer in cardiopulmonary surgery, leading teams that were responsible for groundbreaking operations such as the first human lung transplant in 1963, the first animal-to-human heart transplant in 1964, and a double-lung transplant that left the heart in place in 1987. Hardy also trained many prominent surgeons and continued productive research and training programs until his retirement in 1987.

University of Mississippi Medical Center



Guyton-Coleman Cardiovascular Model, 1972 (~450 variables)



Current model of human cardiovascular system (>10,000 variables)

The Department of Physiology and Biophysics

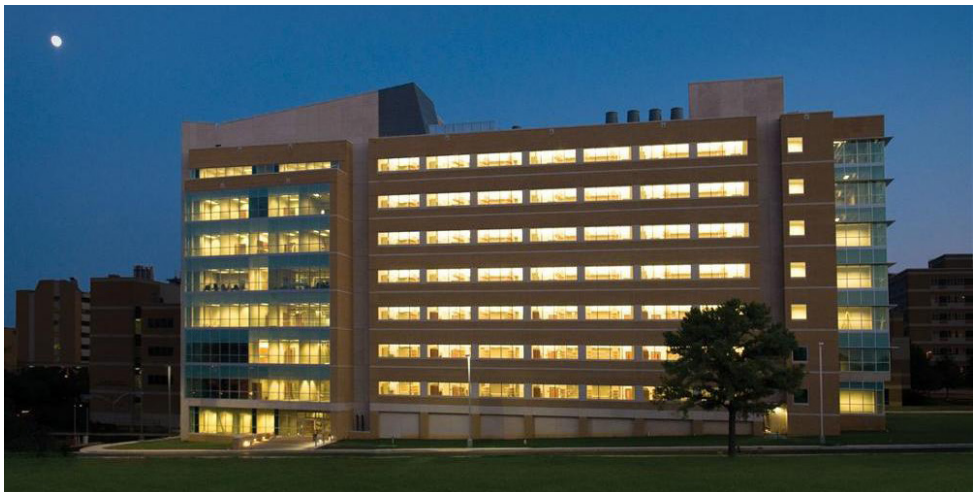
This Department of Physiology and Biophysics (click here) has a long history of teaching and research excellence. Professor Guyton was the first chair of the department and served in that position for 34 years until his retirement in 1989. John Hall was appointed as the Arthur C. Guyton Professor and Chair, a position he has held for the past 32 years, during which time the department has markedly expanded its research programs and its extramural grant funding. Thus, the department has had only two chairs in its entire history!

The department is widely recognized for excellence in basic research related to cardiovascular, renal, and endocrine physiology as well as translational research on hypertension, obesity, preeclampsia, fetal programming, kidney diseases, and heart failure. For the past several years, the department has been in the top 10 for total National Institutes of Health (NIH) research funding among all physiology departments in the United States.

The Department of Physiology and Biophysics is the home of five multidisciplinary research centers, including two major NIH-funded centers: the Cardiorenal and Metabolic Diseases Center of Biomedical Research Excellence (click here) founded in 2013; and the Mississippi Center for Clinical and Translational Research (click here), founded by James Wilson in 2017 and led by Joey Granger and Michael Hall since 2020. The department has also provided leadership for the Mississippi Center for Obesity Research (click here) founded by John Hall in 2006; the Cardiovascular-Renal Research Center (Click here), founded by John Hall in 1996 and currently directed by Joey Granger; and establishment of the Women's Health Research Center (click here), founded in 2010 by Jane Reckelhoff, who is currently Chair of the Department of Cell and Molecular Biology at UMMC.

The Department of Physiology and Biophysics training programs for undergraduate and graduate students as well as postdoctoral fellows are highly regarded and currently receive funding from NIH for the Hypertension and Cardiorenal Diseases Research Training Program (click here) for pre-and post-doctoral fellows. The department's Mississippi Diversity in Hypertension and Cardiorenal Research Program is also funded by NIH and is focused on increasing participation of underrepresented minorities in this field of research.

Faculty and former trainees from the Mississippi cardiovascular research program include 9 presidents of the American Physiological Society, more than 35 chairs of departments and deans, and leaders of other several professional organizations such as the American Heart Association (one national president and four chairs of the Council on Hypertension), the Inter-American Society of Hypertension (two presidents), and the Microcirculatory Society (four presidents). Former trainees and current faculty have served or are currently serving as editors or associate editors of scientific journals in the cardiovascular and renal fields, including Hypertension, American Journal of Physiology, Physiological Genomics, and the Microcirculation Journals, as well as authors and editors of several major textbooks including the Guyton and Hall Textbook of Medical Physiology, Comprehensive Hypertension, and others.



Arthur C. Guyton Research Center where Department of Physiology & Biophysics and its associated Centers are located

James G. Wilson

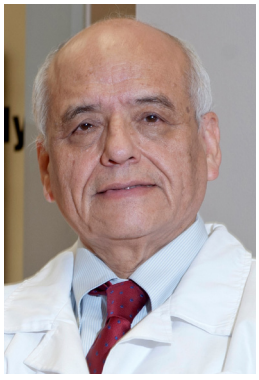
Joey P. Granger

Jane Reckelhoff

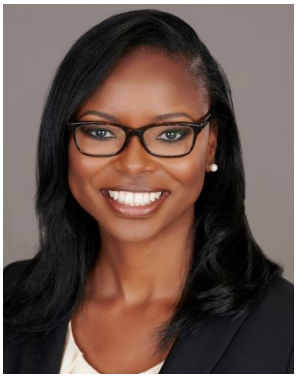
The Jackson Heart Study (JHS)

The JHS (click here) is the largest single-site, community-based epidemiologic longitudinal investigation of environmental and genetic factors associated with cardiovascular disease (CVD) among African Americans ever undertaken. Design of the JHS began in 1996 with Daniel Jones as its first principal investigator, John Hall as its first Scientific Directions Chair, and with funding from the National Heart, Lung and Blood Institute (NHLBI) and the National Institute on Minority Health and Health Disparities (NIMHD) in 1999. Herman Taylor (now at the Morehouse School of Medicine) served as the JHS director from 1999 to 2013. Adolfo Correa directed the JHS from 2013 to 2021 and April Carson began leading this important study in 2021. The JHS continues to elucidate CVD risk factors as well as for conducting community education and outreach activities to promote healthy lifestyles and reduce disease risk burden.

Daniel W. Jones



Adolfo Correa



April Carson

Thomas Mosley

The Memory Impairment and Neurodegenerative Dementia (MIND) Center

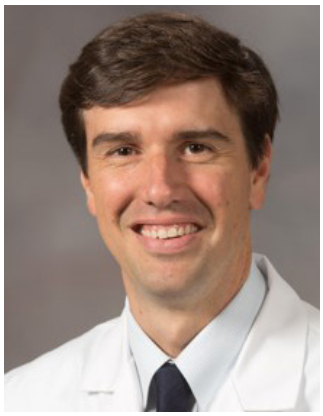
The MIND enter (click here), led by Thomas Mosely, is focused on Alzheimer's risk factors and is engaged in several NIH-funded studies including the large multi-site Atherosclerosis Risk in Communities (ARIC) Neurocognitive Study. Their team has shown that brain changes, such as atrophy, vascular disease and silent strokes, are surprisingly common, even in healthy, middle-aged people and are associated with cardiovascular disease (CVD) risk factors, including hypertension.

The Department of Medicine

Currently chaired by Javed Butler, the Department of Medicine (click here) is the largest department at UMMC and is the home for 13 divisions, including Cardiology, Nephrology, Endocrinology, and General Internal Medicine which treat patients for hypertension and related cardiorenal and metabolic diseases. The department has been a major contributor to many important clinical trials and studies related to hypertension and CVD risk management. Herbert Langford, William (Bill) Cushman (now at the University of Tennessee), and Daniel Jones were key investigators in several landmark clinical trials for hypertension treatment, including the Hypertension Detection and Follow Up Program (HDFP), Trial of Antihypertensive Interventions

Javed Butler

Michael Hall



Donald (Trey) Clark

and Management (TAIM), Trials of Hypertension Prevention (TOHP), Multiple Risk Factor Intervention Trial (MRFIT), Hypertension Optimal Treatment (HOT) study, Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and Systolic Blood Pressure Intervention Trial (SPRINT). Javed Butler serves on steering committees for several important heart failure clinical trials and as co-principal investigator of the recent EMPEROR-Preserved Trial. UMMC has also played an important role in enriching clinical trials for underrepresented minority populations; over 60% of currently enrolled cardiovascular clinical study participants at UMMC are Black. UMMC clinical investigators have also served in leadership roles and writing groups that developed guidelines and scientific statements for cardiovascular societies including the 2017 ACC/AHA Hypertension Guidelines; 2021 Management of Stage 1 Hypertension in Adults With a Low 10-Year Risk for Cardiovascular Disease: Filling a Guidance Gap, led by Daniel Jones; and 2021 Weight-Loss Strategies for Prevention and Treatment of Hypertension, led by Michael Hall.

UMMC has also been a leader in telehealth and in 2017 was recognized as one of only two Health Resources and Services Administration (HRSA) designated Centers of Excellence in Telehealth. With this designation UMMC was tasked to explore innovative ways to advance the modern practice of telemedicine. Donald "Trey" Clark serves as the Medical Director and runs a robust remote patient monitoring program for patients with hypertension.

Richard Roman

Babbette LaMarca

The Department of Pharmacology

The department (click here) has a record of outstanding research in hypertension and cardiorenal diseases. Richard Roman led the department from 2007 to 2021 and developed a strong research program focused on the molecular genetics of hypertension and kidney disease. Babette LaMarca assumed the chair position in 2021 and continues the research excellence of the department while building new programs focused on the immune system and inflammation in hypertension and preeclampsia.

Summary

UMMC has a rich history of seminal contributions to basic, clinical and population research in hypertension, cardiorenal and metabolic diseases. These topics continue to be a focus of research, education, and clinical programs at UMMC. A major driver of these chronic diseases in Mississippi and the rest of the world is the growing prevalence of obesity. Unfortunately, Mississippi leads the nation in the prevalence of obesity and associated disorders. Therefore, much work remains for all of us who are dedicated to improving lives through discovery, patient care, and education.

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INVITED PAPER

Is arterial stiffness a surrogate end-point for cardiovascular complications? A tentative answer given by the SPARTE Study

STÉPHANE LAURENT, MD, PHD,

on behalf of the SPARTE study investigators.

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Concept and objectives

Very few studies have tested whether reducing hypertension-mediated organ damage (HMOD) translated into a reduction of cardiovascular (CV) and renal complications beyond blood pressure (BP) reduction. This was the case for left ventricular hypertrophy and urinary albumin excretion[1-2] which, thus, qualified as surrogate endpoints[3]. Arterial stiffness, measured through pulse wave velocity (PWV, is the most characteristic clinical feature of vascular aging in response to both classical CV risk factors and poorly identified risk factors[4-5]; whether arterial stiffness is a surrogate end-point for CV disease has never been directly demonstrated by a controlled clinical trial. We set up the SPARTE trial as a Strategy for Preventing Cardiovascular and Renal Events Based on ARTErial Stiffness (ClinicalTrials.gov number, NCT02617238) [6-7]. We hypothesized that a therapeutic strategy targeting the normalisation of arterial stiffness in addition to the implementation of the 2007 ESC – ESH (European Society of Cardiology and European Society of Hypertension) guidelines for the management of hypertension[8] would reduce more CV and renal events compared to the unique implementation of the 2007 ESC-ESH guidelines (current guidelines at the time of the beginning of the study). Our secondary objectives were to demonstrate that monitoring vascular aging through repeated PWV measurements would result in better intensification of treatment, better prevention of vascular aging and better control of blood pressure.

Design and methods

All data have been previously published in detail[6-7]. SPARTE is a multicenter, prospective, open-label randomized controlled trial with blinded endpoint evaluation (PROBE design), undertaken at 25 French hypertension centers in university hospitals, and lasting 4 years. Patients were adults with primary hypertension, aged 55 to 75 years at inclusion, at medium-to-very high cardiovascular risk, according to the 2007 ESH-ESC guidelines for the management of hypertension[8]. Participants were randomly assigned (1:1) to two groups: an intervention group aiming at normalisation of PWV through a pre-specified therapeutic strategy (PWV group) and a control group where ESH-ESC Guidelines were applied, without reference to PWV (conventional group).

In both groups, attended seated office BP was measured during each visit, using validated semi-automatic oscillometric medical devices. Ambulatory BP monitoring (ABPM) was performed at baseline and at 6 and 48 months. Carotid-femoral PWV, central BP and augmentation index (AIx) were measured by applanation tonometry using the Sphygmocor device (Atcor Medical, Sydney, Australia)[4]. The follow-up study duration was 4 years, during which 2 scheduled clinical visits were performed per year for both groups. In the intervention PWV group, both patients and investigators were aware of PWV values, and treatments were adjusted to target a PWV of less than 10 m/s. For that purpose, non-pharmacological measures and antihypertensive treatment were adjusted and CV risk factors corrected until normalisation of PWV. Combination therapy using a RAS blocker (ACEI or ARB) and a CCB was recommended as first step. If BP was not controlled despite a triple combination (ACEI/ARB+CCB+Diuretic, second step), or side effects occurred, the third step was to go to the highest recommended doses of ACEI or ARB within the combination[9-10]. In the conventional group, the objective was to bring office BP below 140/90 mmHg. Both investigators and patients were strictly blinded for PWV. Thus, PWV was not used for adapting therapeutic strategy and only served for comparing groups afterwards.

Because SPARTE was an open-label study, blinding applied for the adjudicated endpoints in both groups (PWV and conventional groups).

The primary outcome was a combined endpoint including stroke and coronary events (myocardial infarction-MI, angioplasty, bypass), fatal or not, peripheral artery disease (angioplasty, bypass, amputation), hospitalization for heart failure, aortic dissection, chronic kidney disease (doubling of creatinine, dialysis), and sudden death. The endpoint adjudication committee[6] adjudicated all components of the primary outcomes of the study in a blinded fashion (allocation group and PWV value). Secondary outcomes, planned for a pre-specified statistical analysis[6-7], included all individual components participating to the combined endpoint; the time-course changes in brachial office and ambulatory BP, PWV and central BP; and the time-course changes in treatments, in terms of pharmacological class, dosage and number of medications.

Results

A total of 536 participants were enrolled in the study (264 in the PWV group and 272 in the conventional group) between July 2013 and January 2016, with a median follow-up of 48.3 months. Patients were young elderly (65 years old), 2/3 were males, most of them were at high to very high risk. All were hypertensive with good BP control at entry (134/77 mmHg at office, similar at ABPM) with 2.5 antihypertensive drugs. More than 80% had dyslipidemia, 1/3 were diabetics, ¼ had previously known CVD. Baseline characteristics were well balanced between groups, without significant difference.

Forty-one participants qualified for a primary outcome event: 17 (1.6% per year) in the PWV group and 24 (2.2% per year) in the conventional group. The hazard ratio was HR=0.74, however not significant (95% confidence interval [CI], 0.40 to 1.38; P=0.35) (Figure 1). Results were similar when adjusted on CV risk. Patients at medium+high CV risk had a significantly lower risk of presenting the primary outcome than very-high CV risk patients. In patients at very high CV risk, 6 events (2.0% per year) were observed in the PWV group and 12 events (4.0% per year) were observed in the conventional group (HR=0.49; 95% CI 0.19 to 1.32; P=0.16). Thus, despite continuing efforts, the SPARTE trial lacked sufficient statistical power to demonstrate a greater reduction in CV events in the PWV-based compared to the conventional treatment arm. Indeed, the SPARTE study included about three times less patients than initially planned (536 instead of 1500), due to competing protocols in study centers and insufficient financial support. The yearly incidence of the primary end-point was lower than initially estimated (10%). In addition, the number of CV deaths which occurred during the SPARTE study was twice lower than predicted from individual SCORE risks[11].

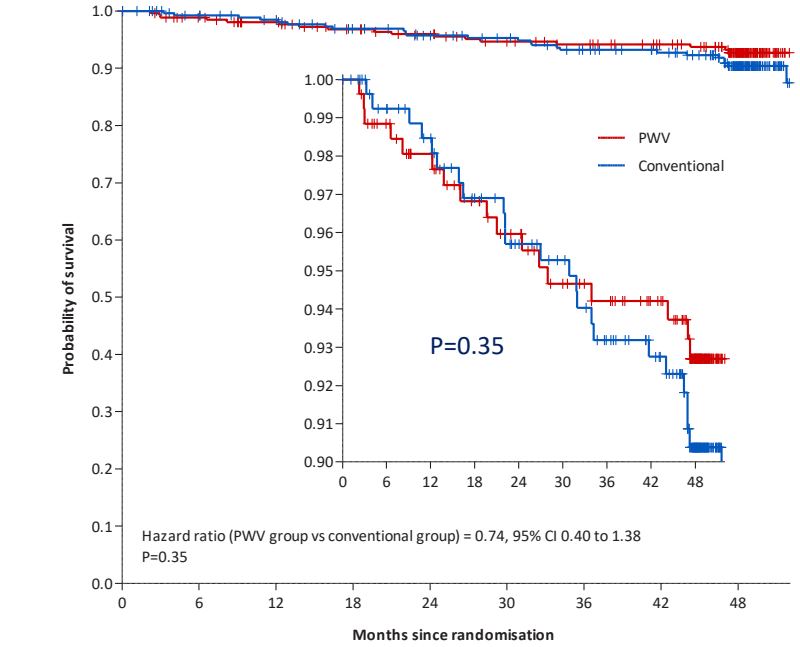
However, we observed a significant treatment intensification, reduction in office and ambulatory SBP and DBP, and prevention of vascular aging in the PWV group. Indeed, the number of BP-lowering drugs and the treatment intensity score significantly increased over time in the PWV-based group but not in the conventional group. The trajectories of office and 24h SBP and DBP over time were significantly different between groups, with a greater reduction rate in the PWV group than in the conventional group. And PWV trajectories over time were significantly different between groups, with no increase in PWV in the PWV group (Figure 2). These good results in the PWV group were obtained without increasing adverse events.

Consideration for clinical practice

An important finding of the SPARTE study is that it is possible to further lower BP in patients that were considered, for most of them, as having controlled BP. The lack of SBP reduction and the limited DBP reduction in the conventional group demonstrate that targeting the normalization of office BP within the 130-139/80-85 mmHg range is not effective enough in clinical practice, as lately suggested by the SPRINT trial[12]. At variance with, and beyond SPRINT, SPARTE study adds as an original contribution the importance of maximizing doses of "de-stiffening" drugs (such as RAS-blockers and CCBs), targeting the normalization of arterial stiffness through repeated PWV measurements and using these measurements as a tool for therapeutic education and sensitization of patients and physicians to treatment intensification.

Another important finding is that the intensification of antihypertensive treatment could reduce arterial stiffness and prevent arterial aging not only through BP lowering, but also independently of BP reduction, i.e., likely through long-term arterial remodeling [9-10]. Thus, the prevention of CV complications may require not only a good BP control, but also an effective prevention of arterial aging through adequate therapeutic measures including lifestyle changes and intensification of de-stiffening drugs, such as RAS-blockers and CCBs.

Finally, the SPARTE study, which has been underpowered for clinical events, should be replicated with a larger number of patients



Number at risk

PWV	264	252	241	230	223	214	209	198	150
Conventional	272	261	254	243	235	229	219	209	154

Figure 1: Primary outcome events. A primary outcome was confirmed in 41 participants: 17 (1.6% per year) in the PWV group and 24 (2.2% per year) in the conventional group (HR=0.75; 95% confidence interval [CI], 0.40 to 1.38; P=0.35) (With permission from Laurent et al. 2021, ref 7)

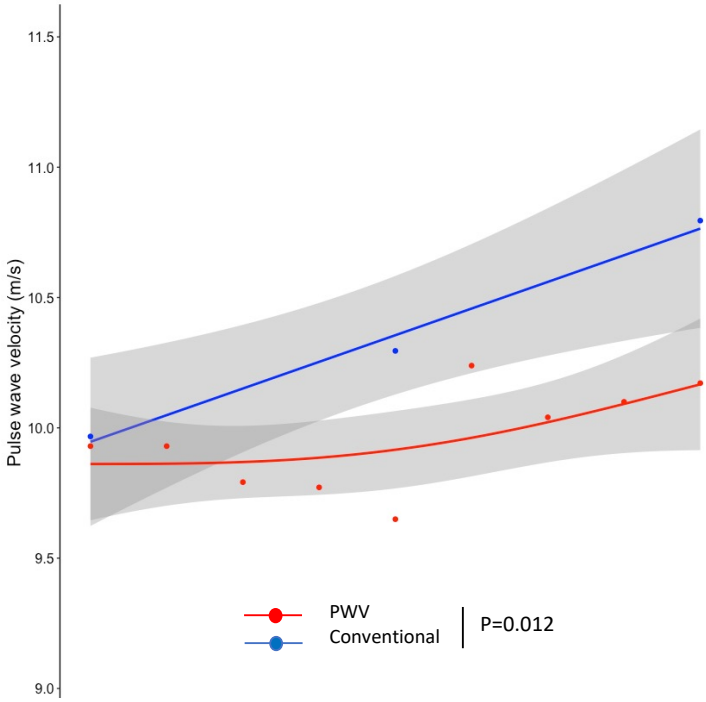


Figure 2: Trajectories of pulse wave velocity (PWV) in the conventional (in blue) and in the PWV-based (in red) treatment arm. In the conventional arm, PWV increased with a rate of 0.20 m/s/year (P=0.001). In the PWV arm, the PWV increase rate was not significant (0.06 m/s/year, P=0.140). Whereas PWV was similar at inclusion in the two treatment arms, PWV trajectories over time were significantly different (P=0.012). Dots indicate mean values. Lines indicate fitting smoothing spline curves with 95% confidence intervals in grey. Trajectories over time have been obtained with latent variable analysis. (With permission from Laurent et al. 2021, ref 7)

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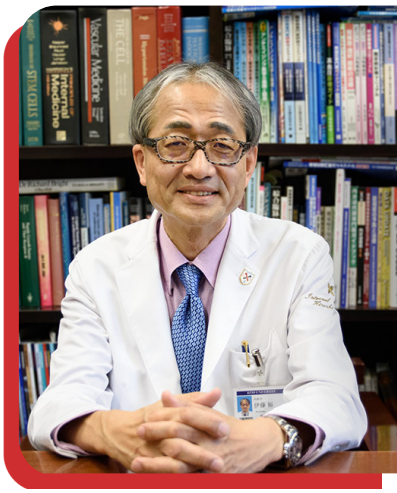
INVITED PAPER

ISH 2022 KYOTO: A good trend for the on -site meeting



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DOI: 10.30824/2112-11

The 29th Scientific Meeting of the International Society of Hypertension (ISH2022) will be held from October 12 to 16 in 2022 at Kyoto International Conference Center with the theme of "The Wisdom for Conquering Hypertension" (Figure 1). We will hold the meeting on-site in a hybrid format that will also provide online contents. The local organizing committee members are intensively preparing for the meeting hoping that hypertension researchers in the world will meet in person and share the scientific progress at Kyoto. Meanwhile, the utilization of online devices will be beneficial for participation of young researchers, students and colleagues in developing countries, for whom it has been difficult to visit Japan.

The number of patients with COVID-19 in Japan has decreased steadily since this September, and the number of newly infected persons is shifting between 100 and 200 people/day as of November 2021. The number per capita marks one of the lowest in the world. The isolation period for overseas travelers after entering Japan has been shortened, making it easier for overseas travelers to enter Japan. We believe that Japanese situation would be much more improved next year to welcome oversea participants to Japan. October is one of the best months to visit Kyoto because of the mild climate: little rain, neither too hot, nor too cold. Kyoto is the ancient capital of Japan with a current population of 1.47 million, where many cultural heritage sites and traditional scenery can be seen (Figure 2). The atmosphere from ancient times blends into the vibrancy of a big city.

By holding a face to face gathering at the ISH2022 Kyoto, our friends and colleagues from all over the world will communicate in person and share the scientific progress on conquering hypertension. The number of participants is estimated to be at least 4500 people. We are planning to prepare enough grants: travel grants for 300 young participants, poster awards for developing countries, and excellent presentation awards. Support from various organizations has been dedicated, including the Ministry of Health, Labor and Welfare in Japan, and the Japan Medical Association. The Science Council of Japan, which is one of the leading organizations for scientific research promotion in Japan under direct control of the Cabinet Office, has officially decided to support ISH2022, showing their high interests in the study of Hypertension, and acknowledging the importance of

Figure 1. The official poster of ISH2022 KYOTO. The background is "Senbon Torii", which is a path with thousand wooden gates of Fushimi Inari shrine in Kyoto.

it. To share the world's most advanced knowledge on hypertension research, outstanding intelligence from all over the world has been invited (Figure 3). As a speaker outside the field of hypertension research, Dr Hiroshi Ishiguro, who is an authority on robotics in the world, will give a lecture.

ISH2022 are focusing on the three main topics: Food (food and nutrition), Move (exercise and fitness) and AI (artificial intelligence and digital health), that are related to hypertension (Figure 4). The participants are expected to include not only academia and medicine but also members of various companies and local governments. The program committee members are intensively working to make ISH2022 innovative, impressive and informative for participants and has decided to cover the following categories. The symposiums will be organized by both the invited speakers of the state of art and those who are publicly recruited at the same session to seek the synergetic effects. In addition to general symposiums, programs such as TED style lectures, Debate and Case studies are included in the meeting.

Categories of the symposiums in ISH2022 KYOTO.

1. Hypertension for Sustainable Development Goals (SDGs) Toward 2030 World.

2. Global Health and Hypertension with Diversity (Racial, Economical Difference, Medical Resources).

3. Life-course and Hypertension (Preconception, Developmental Origins of Health and Disease (DOHaD), Cancer and hypertension).

4. Three Main Topics: Hypertension and Food, Move and AI.

5. Super-aged Society and Hypertension (Sarcopenia, Dementia, Social Capitals).

6. Hypertension Next Generation therapy (Renal Denervation, Single Compound Pills, Application).

7.Convergence of Communicable Diseases (Infectious diseases) and Non-Communicable Diseases (NCDs).

8. Japan Method for Conquering Hypertension (Hypertension Zero Town).

9. Pathophysiology of Hypertension: Chronicle to the Future.

10. Blood Pressure Measurement: Conventional and Future.

11. Imaging and Biomarker for Hypertension Management.

12. Hypertension Reigning Over Systemic Diseases.

13. Genetics, epigenetics, and microRNAs in blood pressure regulation.

We are also happy to announce the following important dates for the ISH2022 KYOTO.

Call for Abstracts: January 18 – April 19, 2022

Registration: Early Bird Registration will start in April 2022

We look forward to receiving abstracts from many of you.

The countdown for ISH2022 KYOTO has been stated on the official Twitter (@ish2022) as well as Instagram and Facebook. One year before the ISH2022 KYOTO, a countdown event was held at the Annual meeting of the Japanese Society of Hypertension in Okinawa, and the video of the event can be viewed on YouTube (Figure 5). 333 days before the ISH2022 KYOTO countdown was given by the ISH president, Prof. Maciej Tomaszewski, and other ISH core members will follow. Similarly, as we get closer to the ISH2022, we will be sending frequent countdown messages from the ISH members around the world. By sharing multidisciplinary wisdoms regarding hypertension and related diseases with each other, ISH2022 encourage the creation of novel paradigms for conquering hypertension. Through the participation to ISH2022 KYOTO on-site, we believe that participants will widen their knowledge, expertise and wisdom on hypertension by learning from the best lectures. We are looking forward to meeting you at KYOTO in 2022, and hope you enjoy the cultural and academic atmosphere of the city of Kyoto.

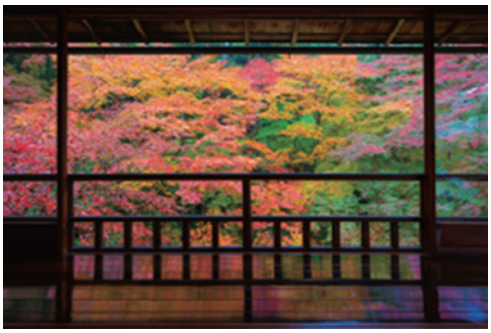
Please visit the official website for the updated information: https://www.ish2022.org/.

We are looking forward to meeting you in Kyoto in 2022.

Hiroshi Itoh (Keio University. President of ISH2022 KYOTO, Vice President of ISH, Former President of JSH) Kazutoshi Miyashita (Keio University. Secretary General of ISH2022 KYOTO)

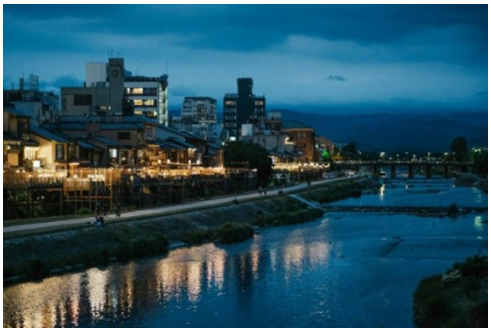
Figure 2. Cultural heritage sites and traditional sceneries in Kyoto. There are 17 different UNESCO World Heritage sites in the city, which make up one of the world's largest collections of temples and shrines.

The Togetsu-kyo Bridge which has been a landmark in Arashiyama district for over four hundred years.



The Jissoin Temple in Iwakura district is famous for the superb garden scenery especially in the autumn.

The Gion-Tatsumi Bridge which creates a photogenic scenery especially in the spring when the cherry blossoms are in full bloom.



The Kamo River which is in the urban area of Kyoto city. Many citizens walk and rest in the riverside parks.

Figure 3. Special guests who have been scheduled to give lectures at the ISH2022 KYOTO:

Dr. Hiroo Imura

President of the Japan Academy

Dr. Shinya Yamanaka

Professor of Kyoto University, 2012 Laureate of Nobel Prize in Physiology or Medicine, who discovered induced pluripotent stem (iPS) cells

Dr. Victor J Dzau

President of the United States National Academy of Medicine

Dr. Richard P. Lifton

President of the Rockefeller University

Figure 4. The three main topics of ISH2022 KYOTO scientific program: Food (food and nutrition), Move (exercise and fitness) and AI (artificial intelligence and digital health) that are related to hypertension.

Figure 5. Countdown for ISH2022 KYOTO. The background is the Japan National Stadium which is the main stadium for 2020 TOKYO Olympic and Paralympic games.

INFO ON THE PAPERS IN THE 2021 ISSUES

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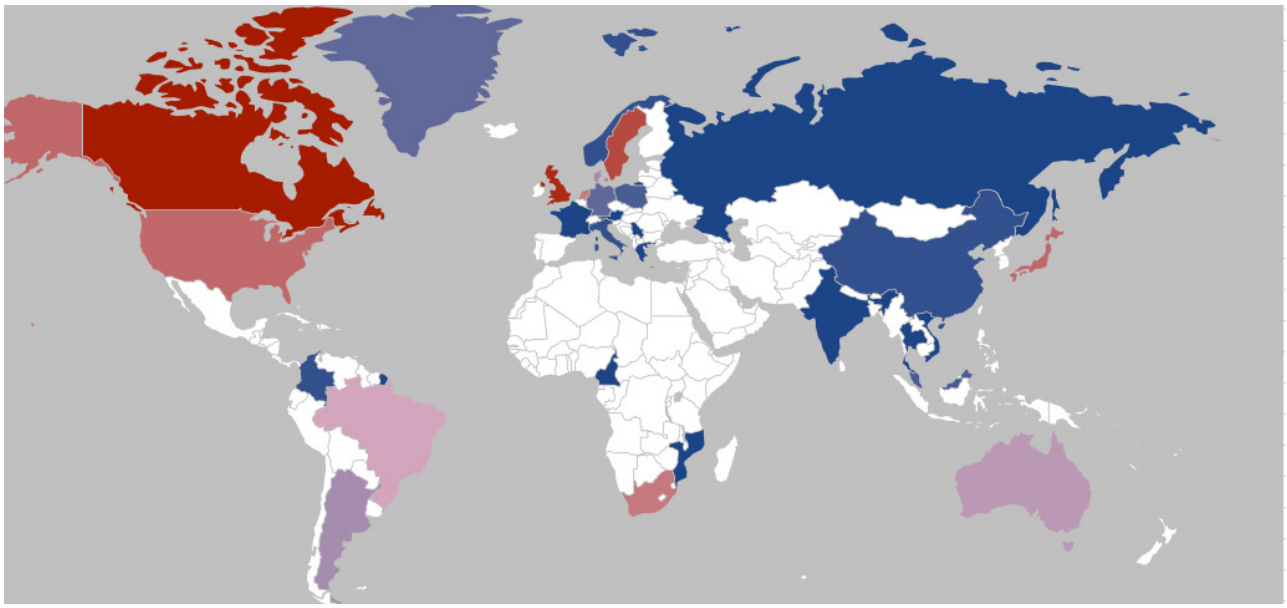
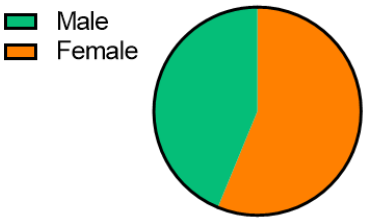
Typically this is where we would provide our readers with an update on distribution numbers for the prior edition of Hypertension News. However, as 2021 comes to a close the editorial board agreed that it would be appropriate to revisit our contributions from the past year. Hypertension News is committed to ensuring that our publications are as diverse and representative of ISH membership as possible. So how did we do among our 96 contributions in 2021? First, here is a red-blue heatmap showing contributions by country. Red colour indicates more contributions while blue indicates a lower number. Purple colour indicates an intermediate number of contributions while white indicates no contributions.



As you can see, we had a fairly global representation with all continents represented. I would note that the high numbers from Canada and Sweden stem in part from regular contributions from our board members. Japan also sees a large number of contributions as a result of the upcoming scientific meeting. There is also expected contributions from heavily active countries such as the United States, Australia, and the UK.

Here you can see the distribution between male/female authors, senior/early career researchers, and authors from high income countries (HIC) and low and middle income countries (LMIC).



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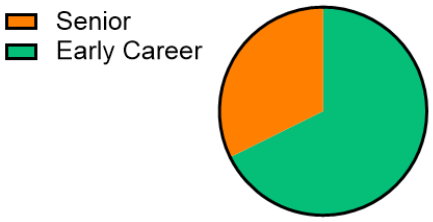

Total=96

Overall, there is a fair amount of diversity among our authors in 2021 but what is evident is that there is a need for greater representation from low and middle income countries, particularly from the continent of Africa where our contributions come almost exclusively from South Africa. Readers will see from Lars Lindholm's editorial that Hypertension News has recently welcomed Lebo Gafane-Matemane to the editorial board and she will be leading a new feature "African Voices" that is aimed at increasing opportunities and exposure for ISH members in Africa. However, ensuring that our contributions are diverse and truly international requires the support of ISH membership. If you are interested in contributing to a future issue of Hypertension News then please contact us at secretariat@ish-world.com

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MEANWHILE IN 'HYPERTENSION MEWS'...

it is well known, that dogs can be trained to find chanterelles in the Swedish forests, but it was news to us that this was true for our cats as well - or is that really so?

Photo by Li Winther from the Lindholm family

EARLY CAREER RESEARCHERS
Introduction

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Here, we have two more interesting papers by early career researchers both on different aspects of genetics; nutrigenetics and epigenetics.

First is Manja Zec, who is a postdoctoral research associate within the School of Nutritional Sciences and Wellness at the University of Arizona, US. Her paper provides a commentary on the theme of precision nutrition and nutrigenetics. She discusses the concept that an individuals' response to nutrients is dependent on their genetic variants with particular focus on the fatty acid desaturase (FADS) genes, fatty acid handling and the impact of that on vascular health, e.g. the increased conversion to omega fats.

From the US to Russia where researchers, Kristina Tolkunova (tbc), Lyudmila Korostovtseva (cardiologist and Senior researcher) and Oxana Rotar (postdoctoral researcher) at Almazov National Medical Research Centre present a project they are undertaking on the offspring of Leningrad Siege survivors. They provide a summary of research that has been carried out so far, which primarily focuses on the survivors themselves and in which higher rates of mortality from heart disease and stroke are observed. The group are hoping to investigate if these health complications persist in the children of the survivors due to transgenerational epigenetic inheritance.

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Nutrigenetics and blood pressure optimization – focus on fat intake and fatty acid desaturase function

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DOI:10.30824/2112-12

Precision nutrition based on targeted approaches such as nutrigenetics, has become an essential tool in lifestyle interventional strategies for managing cardiometabolic risk factors. Hypertension management remains instrumental in preventing cardiovascular disease, however, there is a huge gap between standard pharmacological approaches for optimizing blood pressure and lifestyle strategies for preventing its raise. Dietary actions based on salt intake reduction and prudent fat consumption are pivotal in sustaining optimal blood pressure levels, regardless of demographics or other health contexts. Customizing adequate fat intake gains increasing interest in light of genetic variability associated with fat and fatty acid metabolism and subsequent health implications.

Fatty acid desaturase gene cluster (including FADS-1 and -2 genes) resides on human chromosome 11 and encodes for the desaturase enzymes which catalyze endogenous conversion of essential fatty acids from foods towards highly unsaturated omega-6 and omega-3 plasma and tissue products. The omega-3 commonly refer to eicosapentaenoic acid (EPA, C20:5 n-3) and docosahexaenoic acid (DHA, C22:6 n-3), considered for their inflammation-resolving, endothelium-stabilizing and anti-thrombotic effects. Early research endeavors demonstrated the association between the FADS genes variability and levels of long-chain polyunsaturated fatty acids (PUFA) in plasma[1], then dyslipidemia factors such as high-density lipoprotein cholesterol and triglycerides [2]. A recent study indicated that the single nucleotide polymorphism in FADS-2 gene might be linked with diastolic blood pressure in men only and depending on the adherence to a Dietary Approach to Stop Hypertension pattern[3].

Several studies indicate a connection between long-chain PUFA profiles in plasma, and vascular function. Specifically in black Africans undergoing nutritional transition, plasma omega-6 PUFA were beneficially linked with blood pressure [4], while the inverse link was observed for DHA in Chinese, community dwelling subjects[5]. Importantly, certain populations, such as black Africans, have pronounced levels of long-chain PUFA in plasma [4], which could at least partly be explained by the ethnic-specific and race-specific distribution of FADS haplotype reflected in different metabolic conversion[6]. There is thus a sound rationalization to presume that a variability in FADS human genetic region might also be linked with endothelial stability and vascular function, and future studies are urged to assess the link between the variable FADS region, fat intake, FADS-dietary interactions, and vascular implications, specifically systolic and diastolic blood pressure. Accounting for the population-specific fat metabolism features in customizing public health and personalized guidelines and recommendations, might support combating disproportionate disease burden in vulnerable groups, ultimately alleviating cardiovascular disease across world-wide populations.

Previous reports proposed nutrigenetic protocols for implementing FADS genotyping in precision nutrition assessments for personalized dietary and nutritional plans, as a standard of care[7]. Should the FADS genetic information be interpreted as a predisposition towards various amounts of advantageous omega-3 PUFA but also omega-6 PUFA in plasma, this might complement the information about the level of individual cardiometabolic risk associated with excessive fat intake. This way the FADS individual genetic signature stands out as a valuable print in customizing personalized plans and appropriate fat intake, for overall wellness and fitness, possibly leveraging blood pressure levels. What's more, previous report encouraged the pharmaco-nutrigenetic approach in balancing blood pressure in subjects already taking anti-hypertensive medication and based on customizing their daily salt intake according to the genetically driven salt-sensitivity phenotype, with a few predictive genetic biomarkers already replicated in several studies[8]. The FADS nutrigenetic evaluation in routine precision nutrition practice remains envisioned strategy for successful blood pressure optimization in pharmaco-nutrigenetic setting, in addition to emerging

as a promising tool for preventing blood pressure raise across world-wide populations.

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Presentations from global experts, including Professor John Weinman of King's College London, were recorded and are now available for you to watch at acarepro.abbott.com

GLO2193968-2 November 2021

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Transgenerational effects of famine: initiation of the offsprings' study of Leningrad Siege survivors



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DOI:10.30824/2112-13

A wide range of intrauterine influences can change the pathway of fetal development. Starving during pregnancy and early life stage is one of the most important reasons of remote cardiometabolic disorders in adulthood[1]. Such disorders develop due to plasticity when in a certain environment the most suitable phenotype is expressed[2]. The disease progression in adulthood may result from poor functional capacity of malfunctioning vital organs[3].

The long-term nutritional effects during pregnancy can be assessed in human populations born during periods of natural disasters and wars. Given that the genetic composition of a population changes very slowly over many generations, DNA changes can hardly be evaluated to study the response to new environmental conditions4. On the contrary, epigenetics, defined as somatically inherited chemical modifications of DNA that do not entail changes in the sequence itself, is plastic and responsive to the environment. Since epigenetic layers respond to external and internal conditions by modulating their pattern of chemical modifications, they are sometimes called "mediators" between the environment and DNA[4].

The study involving the inhabitants of besieged Leningrad, who suffered a long-term lack of nutrition during Second World War, and their offspring can contribute significantly to this field. The average daily diet for the majority of Leningrad residents during the siege was about 300 calories and contained almost no protein. The longitudinal study of 3905 Leningrad siege survivors carried out by Sparen in 2004 demonstrated that they were more likely to have higher blood pressure, as well as higher rates of mortality from coronary heart disease and stroke5. In 1997, the study by Stanner et al showed that intrauterine malnutrition and starvation in infancy of siege survivors were not associated with metabolic disorder or cardiovascular disease (CVD) in adulthood6.

The influence of environmental factors, and starvation in particular, can contribute to epigenetic transgenerational inheritance of phenotype variability[7]. It can increase susceptibility or tolerance to diseases development in next generations. Only few studies involved offspring of Leningrad Siege survivors. Professor Khoroshinina et al. (2017) found that prolonged starvation contributes to higher rates of obesity and death at younger age in Leningrad siege survivors[8]. Professor Rachkov examined the survivors and their descendants who often manifest musculoskeletal, cardiovascular, gastrointestinal and respiratory diseases[9].

Our cohort study of 305 Leningrad siege survivors was carried out in 2009-2011. We found significantly lower anthropometric features and higher protective type of lipids (HDL) in survivors comparing with controls. The control group did not experience starvation and was comparable by sex and age. Telomere length has been suggested as a biomarker of aging and may be lifestyle related. Being the first study of T/S telomere length in survivors it showed significantly shorter ratio comparing with controls[10].

We are planning to examine the descendants of the Leningrad siege survivors comparing with sex- and age-matched controls. Our study aims at assessing the transgenerational effects of starvation at early stages of development on cardiometabolic disorders along with vascular ageing in 2 generations of survivors' offspring (children, grandchildren). The study is intended to estimate both early vascular ageing (EVA syndrome) and new phenotype SUPERNOVA[11]. SUPERNOVA patients

demonstrate extremely low vascular stiffness for their age and gender independently of cardiovascular risk factors. The data on cardiometabolic and vascular transgenerational effects of starvation can be used to improve personalized cardiovascular prevention.

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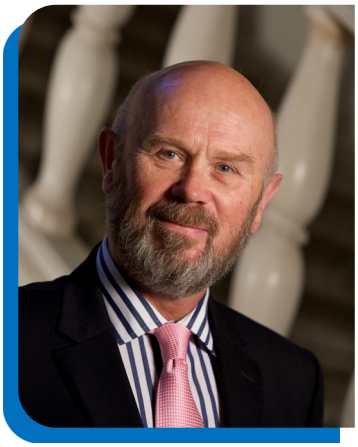
COMMITTEE REPORT

May Measurement Month prepares for 2022 launch



NEIL POULTER

Imperial Clinical trials unit, Imperial Colllege, London, London, UK

May Measurement Month (MMM) is a global blood pressure (BP) screening campaign which began in 2017 as an initiative of the International Society of Hypertension (ISH) and was designed to raise awareness of the importance of BP measurement. MMM also helps people to get their BP checked! MMM is wrapping up its extended programme for 2021 at the end of this month but is looking ahead to kicking off 2022 with lots of exciting new developments.

A total of 94 countries agreed to take part in MMM 2021, with 7 new countries joining for the very first time. Due to COVID-19, four countries have been unable to collect any data and we are expecting a significant reduction in the total number of adults screened. However, the data from each country are now being collated, and the global findings will be published as soon as possible before May 2022.

After a year heavily affected by COVID-19 restrictions, the global MMM team are now hopefully looking towards the return of the traditional 31 days of screenings in May 2022. Recruitment of participating countries has begun, with 33 countries already signed up to MMM in 2022 including Argentina, China, Denmark, France and Uganda.

The introduction due to COVID-19 of home screening as part of MMM 2021 will be carried forward as an option into MMM 2022, building awareness of the accessibility and value of home monitoring as well as increasing the participant base. MMM also began a sub-study into the link between air pollution and BP in 2021, which will be expanded in 2022. Plans are also in progress to expand on a small pilot study to screen for co-existent atrial fibrillation among MMM 2021 screenees. The expanded programme will also be in collaboration with AF-Screen, an international collaboration set up to promote awareness and screening of atrial fibrillation as a means of reducing strokes and saving lives.

Supported by its founding partner, the ISH, MMM has now established independent governance via a standalone charity to increase agility in managing the annual campaigns and have created a board of Trustees, which replaces the previous MMM Management Board.

MMM Chief Investigator, Prof. Neil Poulter, said "MMM will continue to be closely affiliated with the ISH – the founding partner of the campaign. However, taking over its own governance and financial control will help the MMM team to be more efficient and responsive to the challenges of running this large screening campaign and creating the associated research platform.

To access the third MMM supplement, including 47 national publications from 2019, visit the Oxford University Press website. For more information about how you can support MMM in 2022 and onwards, visit www.maymeasure.org

Meanwhile, a fourth supplement of National publications is in progress. It will compile data over two or three years from those countries which in any one year have generated insufficient data to validate an annual publication.

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ISH 2022 Kyoto will highlight

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Activity of the Japanese Society of Hypertension (JSH)

JSH Plan for the Future
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Reduce hypertensive patients by 7 million in 10 years, and Expand the healthy life expectancy
Through...

1 Medical System — Establish a lifetime-care system for individuals with hypertension
2 Academic Research — Promote research in hypertension and embody "Future Medicine"
3 Social Edification — Develop a social model for self-controlled blood pressure

STRIDE BP: International Initiative for Accurate Blood Pressure Monitors and Certified Blood Pressure Measurement Training

STRIDE BP MANAGEMENT BOARD:

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The accurate evaluation of blood pressure (BP) is essential for diagnosing hypertension and deciding long-term drug treatment. However, the performance of BP measurement is often taken for granted and, even in the scientific literature, the methodology of BP measurement used is often inadequately described, or not referenced at all. To add to this, most of the BP measuring devices available on the market are inaccurate, and a minority of then have been subjected to independent validation using an established protocol. Thus, many subjects with suspected hypertension are over- or under-diagnosed, and those being treated for high BP are over- or under-treated, due to a combination of poor measurement methodology and/or use of inaccurate devices.

STRIDE BP (www.stridebp.org) is an international scientific non-profit organization founded in the 2019 by 24 hypertension experts from around the world. Its mission is to provide international guidance on accurate BP evaluation and reliable hypertension diagnosis. STRIDE BP is supported by the International Society of Hypertension, the European Society of Hypertension, and the World Hypertension League[1]. Its website is available in the English, Spanish, and Chinese language and to date it has reached >180,000 views from >180 countries.

STRIDE BP provides guidance on BP measurement technology and methodology to (i) health care providers, (ii) public, (iii) regulatory bodies, and (iv) medical technology manufacturers. STRIDE BP presents (i) lists of accurate BP monitors and (ii) certified e-learning on BP measurement methods.

Lists of accurate BP monitors (https://www.stridebp.org/bp-monitors)

STRIDE BP provides independent evaluation of PubMed studies that assess the accuracy of BP monitors using an established validation protocol[1,2]. Devices that successfully pass the STRIDE BP review process are listed at the STRIDE BP website as "Validated" devices, whereas those fulfilling additional requirements are listed as "Preferred". "Equivalent" devices with BP measurement function identical to that of a STRIDE BP listed device, many also be approved after being subjected to standard STRIDE BP review process. To date STRIDE BP recommends 358 BP monitors, of whom 171 are "Preferred". This indicates that <10% of the BP devices available on the market have documented accuracy confirmed by a well-conducted validation study[2].

STRIDE BP recommends 47 devices for office BP measurement, 275 for home monitoring, and 35 for ambulatory monitoring. For adults 345 devices are recommended, for pregnant women 34, and for children only 21.

The STRIDE BP website provides updated downloadable lists of accurate devices for office, home, ambulatory BP monitoring in adults, children, and pregnant women (Figure 1), which to date have been downloaded >130,000 times.

Certified BP Monitoring E-Learning Program (https://www.stridebp.org/training)

STRIDE BP has recently launched an interactive accredited e-learning platform for health-care professionals, which provides interactive accredited training aiming to standardise the measurement of BP and the diagnosis of hypertension in clinical practice at global level.

The e-Learning platform includes 3 modules dealing with Office, Ambulatory, and Home BP measurement based on recent guidelines (Figure 2). Each module lasts 20'-30' and includes all the practical aspects of each method, regarding the indications, devices, implementation, and interpretation. After completing all the 3 modules, learners may take an evaluation test to be awarded with a pass certificate.

Useful resources, including single-page instructions and forms/posters are also available for free download and use in everyday clinical practice.

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Figure 1.

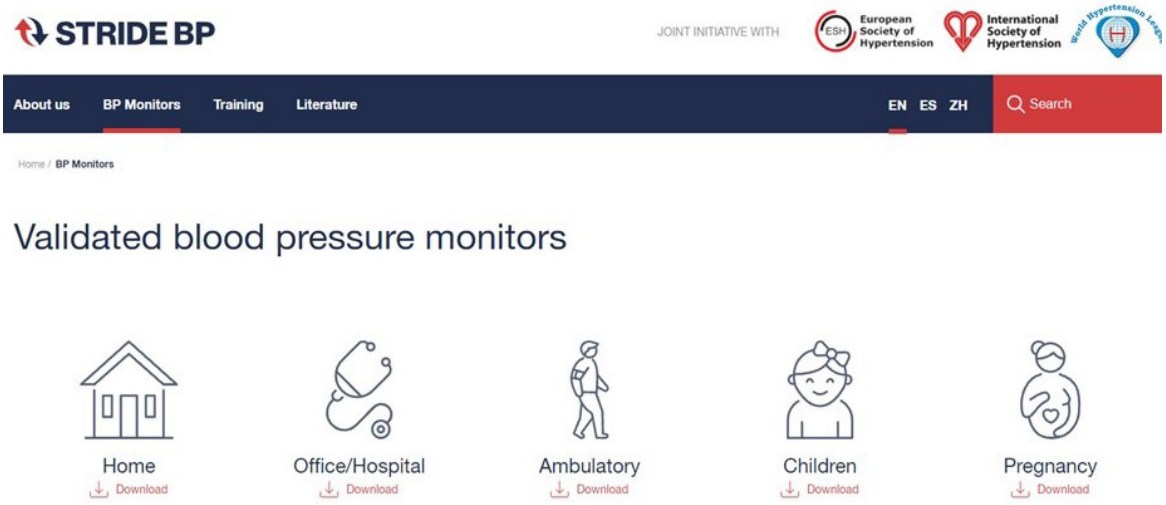
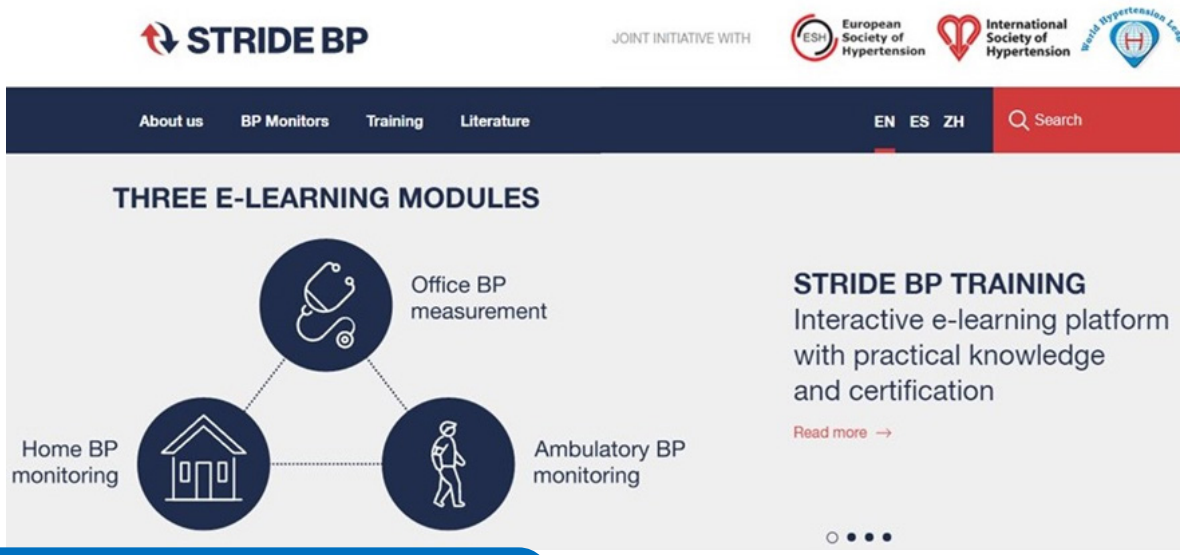


Figure 2.



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LINDON WING - A PERSONAL REFLECTION

LAWRIE BEILIN

Lawrie Beilin AO is a former President of ISH of HBPRCA

Lindon Wing, photo by Lawrie Beilin

It was so sad to hear of the death of Lindon Wing last week. Lindon was a very dear friend and colleague who contributed so much to hypertension research and teaching, both in Australia and Internationally. For around 50 years we shared common interests, with paths frequently overlapping in Oxford, at Hammersmith Hospital, on the High Blood Pressure Research Council of Australia, where he served as Secretary, and in the sentinel Second Australian National Blood Pressure Study, which Lindon so ably led to completion and publications. Throughout the decades the overwhelming impression of Lindon was his dedication, his passion for his research, his persistence, his resilience, and his generosity with colleagues. He had an incredible attention to detail, sometimes like a dog at a bone. It goes without saying Lindon had the highest ethical standards and would give short shrift to those who didn't.

Over the years my wife Brenda and I became close friends of Lindon and Barbara and shared many wonderful experiences around National and International meetings. At the social level Lindon's warmth, good humor and great love of life came to the fore. During a shared walking holiday in the Italian Dolomites, it was wonderful to see him set aside the serious issues he had to deal with as Dean of Flinders Medical School and stride up the mountains ahead of us all.

Lindon's relations with Barbara were a pleasure to see. Bridge was amongst their many shared interests, and it would have been interesting to have witnessed some games involving two such strong characters. Lindon was personally supportive to friends and colleagues in times of difficulty, which in my case included how to deal with major surgery for prostate cancer. He stoically dealt with complex treatments for his own condition, but sadly developed an unrelated cancer which took him from us.

I guess one can only emphasize how fortunate we have all been to have known him. He enriched many lives. Lindon leaves a wonderful legacy, not only as a distinguished contributor to Hypertension research, but as a very special human being who gave so much in terms of warmth, friendship and love for his friends and family.

Northern LIghts (aurora borealis). Photo by Christer Andersson, Umeå, Sweden

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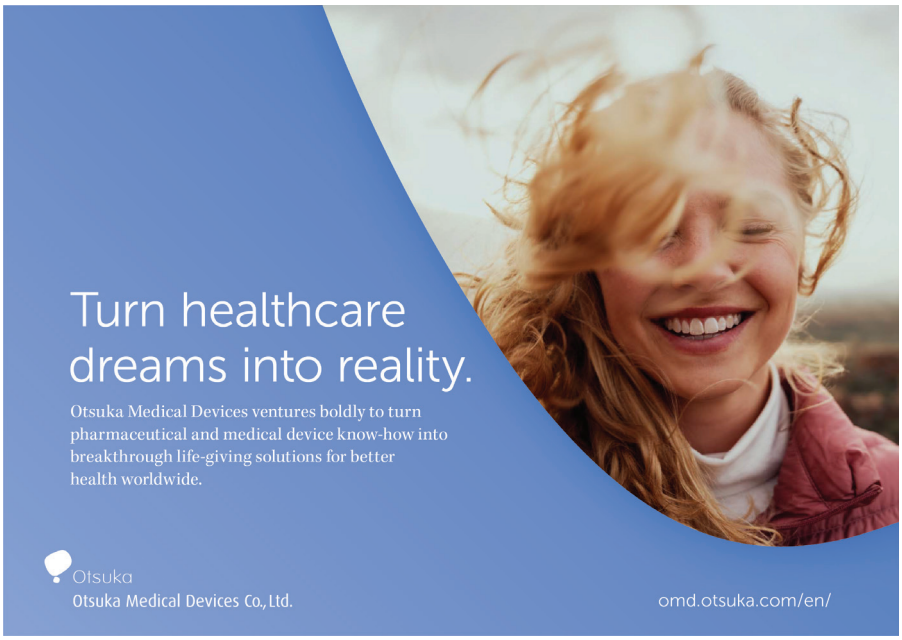

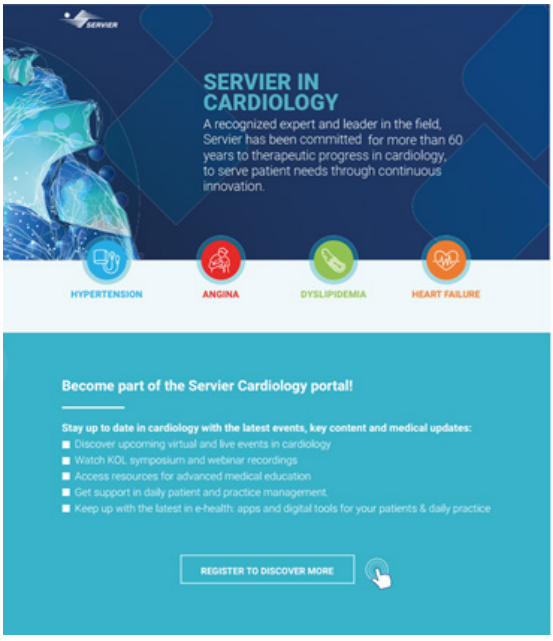

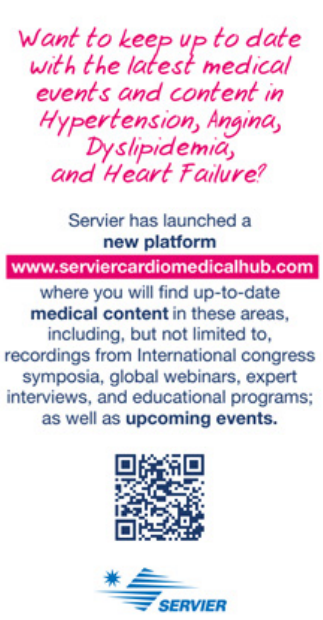

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