# HYPERTENSION NEWS

October 2020

International Society of Hypertension

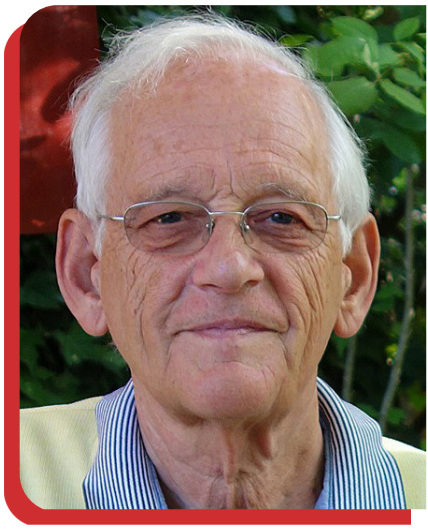
Opera 62 & 63

DOI: 10.30824/2010-1

# IN THIS ISSUE

# FROM THE EDITOR

## ISH adjusts to the new normal in 'Corona times'



LARS H LINDHOLM
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Editor

DOI: 10.30824/2010-2

Dear member,

Again, it is a pleasure for me to present a new issue of Hypertension News. We are delighted that the previous one, published in June 2020, was accessed by 8,156 readers in three months (page 29).

Today's Newsletter starts with three papers, which should be read together, on what has happened in the Society during the last two years and what the plans are for tomorrow. You will find that there is some consensus between the authors on what was most important in the past but some differences in how they see the future.

**First,** an elegant interview with Maciej Tomaszewski – the New ISH Man at the Helm -– by Stuart Spencer from The Lancet. ISH is fortunate to have Stuart as an honorary member and we owe him a lot of gratitude for the considerable time he has spent on this interview. Also, Maciej has been most cooperative and quick to respond to Stuart's provocative questions and I have the feeling that the two have enjoyed working together. Making sure that the Society adapts to the new reality during and after the Covid-19 pandemic is not an easy task to undertake for Maciej, and there are some financial concerns. It is unclear how far traditional conferences will return to normal in the future, but hopefully the biannual meetings can continue in the traditional format, starting in 2022 in Kyoto (see a welcome message on page 32). All organisations need to evolve and refresh, and Maciej's brilliant idea of having a combination of younger members with enthusiasm and vigour ("New Blood") and older members with experience involved in ISH matters gives hope for the future and longevity of the Society.

**Second,** a farewell from Alta Schutte who has had a challenging time as president of the ISH. Her watch started with the necessary move of the ISH Secretariat from Conference Collective in London to In-Conference in Glasgow and ended with the ESH/ISH meeting in June 2020 having first to be moved to April 2021 and then to be changed from a traditional format to a virtual meeting, because of the pandemic (see interview with Anna Dominiczak on page 30). In between, many things have happened. A five-year strategic plan for the ISH has been developed and the ISH Constitution has been revised. Moreover, new global hypertension guidelines have been developed and the Society has now added two new categories of members ("Health Professional Affiliates" and "Fellows of ISH") as well as several certification courses. Well done Alta!

**Third**, a final contribution from Thomas Unger as the ISH Secretary. Thomas is very experienced indeed and has previously had the responsibility for the scientific programmes of three very successful ISH meetings in Heidelberg (1986), Berlin (2008) and Beijing (2018). Thomas agrees with Maciej Tomaszewski that we need to recruit and foster a new generation of hypertension scientists from all countries, but not just from the established Western and Eastern world. He also underlines the great success of the *Young Investigator Initiative,* which was started by Stephen Harrap during my watch and was further improved by Maciej. Thomas writes that future members of the ISH Committees should be carefully selected, but it should be remembered that young scientists still need to invest most of their time in hospital care, university obligations, individual professional careers, and personal matters such as building a family. Words worth considering, since the add-on of pro bono work for a society takes a lot time if it is going to be successful! Hence, there should always be a mix of the spirited but non-experienced young and the experienced old in all society activities. Thomas also brings up the dominance of ISH presidents coming from the former British Commonwealth institutions during the last few decades and he has a point here! I joined the ISH Council in 2000, and during my time ISH has had 11 presidents and only two (18%) have come from countries outside the Commonwealth (from France and Sweden); if you look at the presidents' origin instead, this figure goes up to four (36%), when Argentina and Poland are added. Needless to say, this ought to be considered by the ISH Council in the future.

Maciej Tomaszewski, Alta Schutte, and Thomas Unger all point at the positive value of the May Measurement Month (MMM) project started by Neil Poulter, collecting blood pressure recordings from more than four million people living in about a hundred countries – a Flagship of the Society! ISH has previously substantially contributed to the funding of MMM, but external funders have now taken over most of the costs. This year, however, for security reasons, the Covid-19 pandemic has made the global blood pressure recordings impossible. Time will tell whether they can be made in May 2021.

The Newsletter continues with the usual sections and headlines. "Learning the Ropes" this time covers "Secondary Hypertension" and I strongly recommend you to read three interesting papers by Markus Schlaich, Maria-Christina Zennaro, and Peter de Leeuw, with an introduction by Ottawa Hypertension Research Group on page 15. We have also invited Mattias Brunström and Bo Carlberg to take a closer look at "Scientific misconduct in clinical hypertension research" and their findings are published on page 12.

In addition, three early-career-scientists: Ida T Fonkoue, Yan Wong, and Chudan Xu together with Augusto Montezano from the Society's Mentorship and Training Committee share their important experiences of working as a young investigator during a Covid-19 pandemic on page 50.

Finally, please don't miss Herman Haller's lovely paper on "What was the blood pressure of Mona Lisa?" on page 34 under "News, Old News, and Culture". To quote Thomas Unger in a comment to the Hypertension News team: "It's refreshing to have people in our society whose medical and human interest expands beyond blood pressure measuring!"

As always, sincere thanks to the authors and to the members of the Hypertension News team: Dylan Burger, Thomas Kahan, Thomas Unger, and Maria-Christina Zennaro for their superb pro bono work! Special thanks also to Araceli Segreto for her excellent secretarial work.

Have a good read!

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# NEW MAN AT THE HELM

## Interview with the ISH President Maciej Tomaszewski

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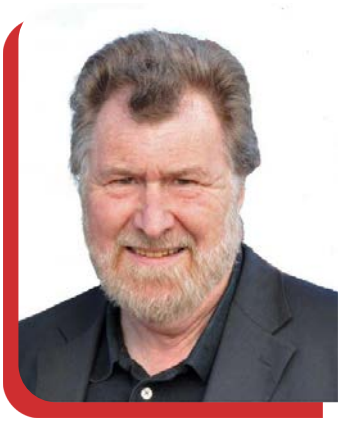
DOI: 10.30824/2010-3



After a calamitous start to 2020 around the world one could wonder if (to paraphrase Humphrey Bogart): the problems (of the ISH) don't amount to a hill of beans in this crazy world. For members of ISH, however, hypertension is a daily consideration and perhaps more tangible than a virus. An interview with the new president of ISH, Maciej Tomaszewski, probed what he saw as the opportunities and threats to ISH as a result of COVID-19, *the raison d'être* of ISH and if this should be amended, and how the Society might evolve under his stewardship.

Maciej acknowledges that the world has changed enormously. His vision at the time of his election has been turned on its head by the financial and logistical changes wrought by the pandemic: "ideas that have been crystallising in my mind since my election have now to align with the top priority – making sure that the Society adapts to the new reality post-COVID-19 pandemic." Safeguarding the financial security of ISH was always important but has become even more prominent. He accepts that funding from traditional sources will continue to decrease and new avenues will need to be explored, for example funding through the website and targeted campaigns in social media are alternatives he would like the Society to explore. It seems to Maciej that academic societies need to become more outgoing and visible, in the way that the American Heart Association now figures in the consciousness of many Americans.

In the past, as well as being a prime objective of ISH, seminars and conferences to disseminate and teach were an important source of funding. It is not yet clear how far traditional conferences will return in the medium-term future, but face-to-face meetings are currently not possible. The new president indicated that he would like to see the biennial international meeting of ISH continue in traditional format, but smaller regional meetings and seminars of 30 or so participants might not be able to survive in the pre-COVID format. He would "definitely consider transforming the bulk of our educational activities into a cheaper and safer internet-based mode."

When asked what he saw as the main function of ISH in the future he replied: "It is to exert the influence at the local, national and global scale to achieve our mission – reducing the burden of high blood pressure." In response to the observation that the Society did not appear to be doing well in reducing the prevalence, and increasing the treatment of hypertension, Maciej said the Society had limited assets and resources but can have influence through its publications and the standing of its members. He also pointed out the positive benefits of May Measurement Month (MMM) in raising awareness. Furthermore, he thinks his support for the alliance of the Society with PATH Coalition for Access to NCD Medications to improve access to affordable blood-pressure-lowering drugs, is an important way to reach the Society's objectives. At a local level, getting governments to change their policies on blood-pressure control was perhaps best achieved by ISH supporting local societies to influence individual national policies, he opined.

The new president agreed that members needed to see some tangible benefits to themselves or their countries. He said he is prepared to consider ideas from all ISH members, provided they align with the Society's vision – and are affordable. In the past, Maciej had been closely involved with the New Investigators and when asked if these people might be a source of change, he pointed out his support for the "New Blood" campaign (https://www.youtube.com/watch?v=Y6dvQnUmdjo) "to recruit new ambitious, talented, and dedicated people to re-invigorate the ISH leadership." He especially welcomed greater representation from low and middle-income countries, as this could make the Society more responsive to members' ambitions. When asked if he was concerned his "New Blood" campaign might upset the "Old Blood", he replied: "All organisations need to evolve and refresh and a combination of experience and the enthusiasm and vigour of younger members is the blend we should be aiming for. I would like to think I am naturally courageous and decisive. This should help to make difficult choices and decisions in the best interest of the Society."

Should ISH be involved in producing universal hypertension guidelines to replace the local guidelines? Writing guidelines is a key mission for many learned Societies, said Maciej. Unified guidelines would be more powerful, but the organisations that have regularly developed guidelines to underpin their portfolio of activities might be resistant. He saw that the best way forward might be to partner with these organisations in releasing widely endorsed position papers on controversial aspects of hypertension management. However, Maciej agreed that the idea of one global policy that regulates all aspects of hypertension management is a very attractive one but "logistically and politically extremely difficult". Hence, almost a *"Mission Impossible"*.

When asked how he envisaged he could integrate the onerous task of the position of president with his research, teaching, clinical and administrative obligations, Maciej replied that he is a good manager of time. His years on the ISH Council have provided good experience at coordinating the Society's needs with academic commitments, he continued. It is likely he will require reliable support from his Executive Committee and his plan was "to delegate wisely; there will be a very clear division of responsibilities within the new ISH leadership. Indeed, everyone needs to know exactly what is expected of them... I hope that the emphasis on fair distribution of responsibilities will be immediately visible in the new ISH leadership."

In view of the recent tumultuous events and the uncertainty that the future holds, it is perhaps not surprising that Maciej Tomaszewski is cautious in making firm statements on plans for ISH during his presidency. Some things do seem clear from this interview. The financial situation of ISH is of concern and new ways of keeping the Society solvent are required. Some of this might be through re-organisation of management, but it seems likely that the format of some scientific meetings will change, as will support for activities. Maciej's plan to recruit new, young, ambitious, talented, and dedicated scientists to re-invigorate the ISH leadership, however, gives hope for the future and the longevity of the Society. Time will tell!

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# FAREWELL FROM THE OUTGOING PRESIDENT

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DOI: 10.30824/2010-4

Dear Members,

If anyone mentions the word "unprecedented" again... I would rather have it said that this ISH President and the Council set the precedent to continue to achieve great things despite the obvious obstacle we all have gotten to know so well.

At the ISH Meeting in Beijing, September 2018, I took over the reins from Neil Poulter. Together with an exceptionally capable Council and Executive Committee I proclaimed to undertake several objectives as part of my Presidency. Several of these objectives were strongly influenced by my background in working in South Africa for the past two decades.

Looking back, I am proud on what we were able to achieve, and trust that we took the International Society of Hypertension forward a few steps aligned with our mission to reduce the global burden of raised blood pressure.

To develop the 2020 ISH Global Hypertension Practice Guidelines. Released online in May 2020 (and not at the planned main ISH event: Joint ESH-ISH Meeting in Glasgow May 2020), the guidelines were very well received – particularly due to our deliberate focus on providing guidelines suitable to low resource settings (essential standards of care) and high resource settings (optimal standards). These free publications in *Hypertension* and *The Journal of Hypertension* are amongst the highest for the journals according to their Altmetric scores. I remain grateful towards the whole dedicated Guidelines Committee, and Thomas Unger who chaired it so diplomatically.

To broaden the ISH footprint by including new categories of membership: Health Professional Affiliates and Fellows of the ISH. Although these developments were concluded, the Health Professional Affiliate membership of nurses, pharmacists and community health workers needs to be properly expanded to maximise its full potential. The Society, under the leadership of Richard Wainford and Dylan Burger, is also soon to launch the new ISHF, Fellows of the Society - a symbol of excellence.

To promote global certification courses for hypertension: The ISH joined forces with others, such as:

- Resolve to Save Lives and the Johns Hopkins Bloomberg School of Public Health;
- the Omron Academy, and
- the Public Health Foundation of India (Dorairaj Prabhakaran)
- the American Heart Association (developments ongoing)

With many of these already offering free online courses on hypertension management available to people across the globe.

Apart from these objectives Council Members worked tirelessly to develop a five-year strategic plan for the Society. With input from all Council members a powerful one-pager was developed, clearly specifying our vision to be leading the drive towards the global elimination of raised blood pressure and its complications (thanks to Richard Wainford in assisting to formulate the strategic plan), updating the ISH Constitution

(led by Thomas Unger and Maciej Tomaszewski), developing ISH policies on endorsing material (Claudio Borghi), or communicating events very effectively through our different media streams (Dylan Burger). We were able to continue with many regional activities, including May Measurement Month 2019 (Neil Poulter), New Investigator and Mentorship activities (Ruan Kruger, Francine Marques), and drastically expanding the Women in Hypertension Research Committee and Network (Muscha Steckelings).

Some Council members worked many extra hours behind the scenes, sorting out contracts, finances, and budgets, especially as the Society transitioned in 2019 to a new service provider. Special thanks to Markus Schlaich for being solid in his support. Fadi Charchar has also supported this transition and continues to lead the bids for the 2024 ISH Meeting.

It has been an honour to work with all ISH Members, including Council Members, the ISH Executive, and also Lars Lindholm and the supportive Editorial team of *Hypertension News*. Also the many partners around the world, the Glasgow Meeting organizing committee, World Hypertension League, European Society of Hypertension, American Heart Association, the many national societies, and last but not least, thank you to our Secretariat office hosted by In Conference. Your continued support during challenging times certainly made my life a lot easier.

Thank you for your unwavering support throughout the past two years (and yes, also through 'unprecedented times' with COVID-19). All activities continued one way or the other!

Until we meet again, whether in Glasgow, Kyoto, or elsewhere.

With my very best wishes,

Alta Schutte, ISH President 2018-2020

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# THE OUTGOING SECRETARY'S VOICE

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DOI: 10.30824/2010-5

This is my last contribution to *Hypertension News* as the Society's Secretary. I enjoyed my job very much but there is no reason for me to be sad since, as a famous German football (soccer) player once formulated "I never look back, I always look ahead"

I have served as a member of the Council and Chair of the ISH Beijing Committee from 2016-18 and in the following two years as the Society's Secretary. Before this, I was involved in the organization of the biennial ISH Congresses in Heidelberg in 1986, and in Berlin in 2008, meetings, that many of you remember.

After some years of involvement in other issues, I came back to ISH in 2016 and found the Society in good shape: Under the presidency of Neil Poulter, the Society's global mission was enforced especially with the establishment of the May Measurement Month (MMM) project. With an enormous energy and the help of many members of the Society, Neil created in a surprisingly short time, a network of collaboration comprising more than 100 countries across the globe. In the three years from 2017-19, MMM collected blood pressure samples from 4.2 Million individuals leading to first diagnosis of hypertension in almost 1 Million of them. MMM not only contributed markedly to the increased awareness of hypertension especially in the Low- and Middle-Income counties but also generated a substantial number of academic papers in renowned journals. The latest of them, published in a supplement of the European Heart Journal, deals with the individual MMM results in 40 countries again demonstrating the global reach of the initiative.

No doubt, MMM has been a flagship of ISH despite the fact that, for security reasons, the corona pandemic has rendered global blood pressure measurement actions currently impossible. We sincerely hope to resume MMM activities in the years to come. While during the first years the Society has substantially contributed financially to realize the project, external funding has now taken over so that the financial burden for ISH has been eased. This raises the question as to the future administration of MMM. On one hand, this initiative has certainly been an asset for the Society, on the other hand, one could also think of an administration by an independent MMM Managing Board associated with but not necessarily administrated by the Society. In any case, members of the ISH council involved in the acquisition of external funding should be part of the MMM Management Board.

One of my first tasks as fresh Council member was the overhauling of the ISH constitution. There were some incongruencies that had accumulated over the years and needed clarification. In particular, the role of the president and the different boards as well as the respective election procedures had to be actualized. The amended, approved constitution gives the president some special rights, for instance to appoint members of the Executive Committee (EC) which is running the daily business, but this implies that he or she uses the granted power prudently without trying to override decisions of the EC or Council. The two past presidents during my time as Council member and Secretary, Neil Poulter and Alta

Schutte, have run their office with great respect concerning these democratic usances.

A continuous pleasure has been my service on the Editorial Board of *Hypertension News*. From the beginning with some hundred readers, this online magazine has now gained a substantial readership with up to ten thousand downloads for each issue and can undoubtedly be called another flagship of the Society. Most of the credit goes to the tireless Editor, Lars H. Lindholm, with his enormous expertise and experience in hypertension affairs, but more recently also to the deputy editor, Dylan Burger, who is virtuoso playing on the keyboard of the social media. I am quite glad that I will be allowed to stay on the Editorial Board for the upcoming years.

A major task during my time in office was the creation of new ISH Hypertension Guidelines. This matter was dealt with extensively in the last issue of *Hypertension News* and I do not wish to reiterate what has already been written.

Needless to say, that this was a major challenge as Chair of the Guidelines Committee facing a lot of scepticism in the beginning, but finally a useful document appeared in May 2020, published concomitantly in Hypertension and Journal of Hypertension with the kind support of their respective editors, Anna Dominiczak and Guiseppe Mancia.

With the division between "optimal" (for the more affluent regions) and "essential" (for the Low- and Middle Income regions of the world) these "2020 ISH Global Hypertension Practice Guidelines" have a USP, a unique selling point, among the numerous national and regional Hypertension Guidelines currently available.

So far to the past, but what do I expect looking ahead

First, ISH is the only scientific society devoted to combat hypertension disease in a global fashion. This statement implies a lot: Different from national and regional hypertension Societies, the global aspect of the battle against hypertension is primordial. This is e.g. represented in the MMM initiative to increase the awareness of hypertension worldwide, in the division between optimal and essential recommendations in the recent ISH Hypertension Guidelines, also in the various activities of the Regional Advisory Groups (RAGs) and in collaborations with affiliated national hypertension Societies and the World Hypertension League. These activities must be maintained and wherever possible intensified.

It's global reach implies further that ISH assists in recruiting and fostering a new generation of hypertension scientists from all countries, not only from the established western and eastern world.

The *Young Investigator* initiative, originally created by one of the former ISH presidents, Stephen Harrap, has proven to be quite successful in this respect and needs to be expanded and exploited. The global mission of our Society also implies that its Council members need to be selected from all continents in a representative fashion. During the last decades, the presidents of ISH tended to come exclusively from countries belonging to the British Commonwealth, UK, Canada, Australia, South Africa. This led to the suspicion among some people that ISH is predominantly a British Commonwealth institution, a development which cannot be reconciled with the global claims of our Society.

Moreover, future members of the various ISH Boards and Committees should be carefully selected: being young, highly motivated and from diverse backgrounds are important factors but there should always be a balance between the non-experienced young and the established, experienced, old. Considered should also be the fact that young members, who still need to invest much of their time into hospital care obligations, individual professional carriers and personal affairs like building up a family, can only invest a limited amount of time and energy in Society matters. In addition, a scientific Society with global claims, whose officers predominantly belong to the group of assistant professors, will have difficulties to be respected by the outside world.

As a scientific Society, ISH has to support research into hypertension as well as its concomitant diseases and sequelae as much as possible. The biennial scientific ISH congress in different parts of the world constitutes a valid step into this direction but more can be done locally and regionally

to initiate and activate research activities, for instance with the help of the internet and its numerous possibilities. During the last "corona months" many of us have gained some expertise with virtual meetings. Admittedly, these can be effective, and they are undoubtedly cost saving. On the other hand, in my experience virtual meetings lack important features of conventional face-to-face meetings such as a certain team or group spirit which quite often develops during a physical meeting not seldom associated with inspiration and new energy, they further lack the free exchange of thoughts and scientific and personal matters during dinner or breakfast, all those exchanges which can be considered the lubrication of transmission in a Society. Thus, in my view, despite several advantages, virtual meetings can never replace the real ones, and my sincere hope is that we can reach an effective balance between physical and virtual conferences once the horrid pandemic is over.

Hypertension research has always been endangered from different sides because of its interdisciplinary diversity with no single organ pathology involved. However, this "shortcoming" can also be considered an enormous advantage if the chances are used in cooperation with other disciplines. ISH should actively promote such activities as far as resources allow.

Speaking about resources, While hypertension Societies two decades ago could heavily rely on the financial support of "big pharma", many of them being corporate members, this situation has changed dramatically for well-known reasons during the last fifteen years or so. One of the major future tasks of our Society will therefore consist in the recovery of external support from industry, pharmaceutical or other, and from other sources. We will have to increase the number of corporate members by offering win-win situations to them, a challenging but not impossible mission.

Let me close with an old Latin proverb as a congratulation message to the new president and his executives: *quidquid agis prudenter agas et respice finem*, will say: Whatever you do, be prudent in doing so, and consider the outcome.

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# HOT OFF THE PRESS: CLINICAL

## Antihypertensive treatment may reduce the risk for cognitive impairment and dementia

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DOI: 10.30824/2010-6

The association of hypertension and dementia and future cognitive impairment is well recognized. While some studies suggest that antihypertensive treatment can reduce this risk, other studies report no reduced risk for developing neurocognitive disorders by blood pressure lowering drug treatment. With an ageing population, and considering the high prevalence of hypertension in the general population, clarifying this issue of high clinical importance.

Recently, Hughes and collaborators reported on a systematic literature review and meta-analysis of the association of blood pressure lowering with dementia and cognitive impairment[1]. The authors accepted to include published randomized clinical trials up to 2019 (included), where antihypertensive medication and a control (placebo, other drug or less intensive drug treatment) were compared in more than 1000 participants, with a follow up of at least one year, and reporting appropriate outcomes. The primary outcome was dementia or cognitive impairment. The authors eventually included 12 studies with 92 135 participants in their results on the primary outcome (two additional studies were included for the reporting of secondary outcomes only). Mean age was 69 years, 42% women, mean blood pressure 154/83 mm Hg, and mean follow up was 4.1 years. A majority of the studies represented primary prevention, and a majority were placebo controlled.

Dementia or cognitive decline was diagnosed in a total of 5550 participants, corresponding to 7.0% of the actively treated group, as compared to 7.9% the control group (odds ratio and 95% confidence interval 0.93; 0.88–0.98). As for secondary outcomes, similar findings were observed for cognitive decline (0.93; 0.88–0.99), while change in cognitive score was insignificant.

Thus, the results of this study[1] extend earlier meta-analyses based on fewer studies[2-4] and suggest a modest but significant association between antihypertensive drug treatment and lower risk for dementia or cognitive decline. The risk reduction is smaller, and the time lag for the benefit appears to be longer, than what has been observed for stroke prevention. The association of hypertension and dementia and future cognitive impairment is stronger for hypertension in mid-life than for hypertension in later life. This may suggest that starting antihypertensive treatment early is of particular benefit in order to prevent neurocognitive decline. However, mean age in the current analysis was 69 years at study start, pointing to a benefit also when starting treatment in older patients. To demonstrate smaller changes in cognitive decline (i.e. changes in cognitive score but no major symptoms) will probably require large studies with much longer follow up. That said, the results of his study are encouraging and provide further support to offer more people with an elevated blood pressure antihypertensive treatment for prevention of future disease.

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# INVITED PAPER:

# Scientific misconduct in clinical hypertension research

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DOI: 10.30824/2010-7

The COOPERATE Study, published in The Lancet 2003, found that combination therapy with losartan and trandolapril "safely retards progression of non-diabetic kidney disease" compared with single therapy with each drug, respectively. Five years later, three authors, while performing a meta-analysis, found a strange observation in the previous publication. In 263 patients, randomization succeeded to create three nearly identical groups of patients, even for genetic polymorphisms[1]. The paper was retracted, and today it is common knowledge that the combination of ARB and ACE-inhibitors should not be used[2]

Retraction of original publications due to fabricated or falsified data is quite uncommon. In one study, scanning BioMed Central between years 2000-2015, 134 out of 190 514 articles were retracted (excluding supplements, corrections, retractions, and commissioned content)[3]. Fraud is often detected many years after the original publication. This was also the case with the Jikei Heart study, published in The Lancet in 2005[4]. Six years after the publication, someone read it and noticed that the statistician had an affiliation at a non-existing department at his university. Thereafter, it was found that the statistician was a Novartis employee, who had made changes in the data base, increasing the number of events in the control group, thereby making valsartan appear more beneficial. This was one of a series of five randomized controlled trials with valsartan (Kyoto Heart Study, Jikei Heart Study, SMART, VART and Nagoya Heart Study), published in high-impact journals between 2007 and 2012, that were found to include falsifications and got retracted, later referred to as "the valsartan scandal"[5-9].

Since January 2020, there have been an increasing number of retractions of original publications. Most of these retractions involve Covid-19 papers. According to Retraction Watch, at least 33 Covid-19 papers have been retracted so far[10]. High impact journals have not been protected, although a disproportionate amount of retractions have been from preprint services. The New England Journal of Medicine published the paper "Cardiovascular Disease, Drug Therapy and Mortality in Covid-19", claiming to have analyzed data from an international registry, called the Surgical Outcomes Collaborative (Surgisphere), including 169 hospitals in 11 countries[11]. Soon after publication, several authors requested the journal to retract the paper because they were not given access to raw data, and the primary data source could not be validated. The Lancet published the paper "Hydroxychloroquine or chloroquine with or without a macrolide for treatment of COVID-19: a multinational registry analysis" from the same registry in May 2020[12]. In June, it was retracted for similar reasons. Since then, Surgisphere´s social media accounts have been deleted and the website was taken offline. It is reasonable to assume that the intention to speed up our knowledge about Covid-19 have had some negative effects on the rigour among researchers, publishers, and reviewers alike.

Retraction of a published paper does not mean that there need to be a deliberate fraud. Sometimes, the authors find errors in their database, or the analytic method, after the paper has been

published, so called honest error. Plagiarism is a special case of research misconduct, that, although it should be quite easy to detect today, appear to be fairly common. One survey among 372 editors of scientific journals (half of them in medicine) estimated that they detected plagiarism in 2-5% of all submitted manuscripts[13]. In 2018, the European Journal of Pharmaceutical Sciences retracted an RCT comparing an olmesartan/amlodipine single pill combination with olmesartan or amlodipine single therapy because it was found that "The authors have published results from exactly the same clinical study and patient population in 6 separate articles, without referencing to the publications in any of the later articles"[14].

All involved in scientific publishing (authors, publishers, peer reviewers, and readers) are responsible for the quality of published papers. To reduce the risk of scientific misconduct, all aspects of the scientific process needs to be transparent. Table 1 lists, with no intention of being comprehensive, efforts that could be considered at each stage to improve transparency, quality, and hopefully uncover fraud. It is easy to imagine, that many of the examples listed above could have been discovered earlier, had the listed items been complied with. For example, the Surgisphere papers would probably not have been published if preregistration would have been required for observational studies. Many journals have, or plan to introduce, routines aiming to decrease the risk for publishing papers with dubious data. In a recent statement, The Lancet, announced they will, among other things, require at least two authors have access to the data, and, for publications from large real-world datasets, peer reviewers will include someone with knowledge about the specific dataset, as well as a data scientist[15].

In the March issue of HT News, we wrote a critical appraisal on the Hygia Chronotherapy Trial, published online in European Heart Journal in October 2019[16]. We raised several concerns regarding the randomization process, allocation concealment, outcome reporting, as well as the statistical analysis[17]. Our conclusion was that "It is difficult to draw conclusions from this interesting study as it is not transparently reported"; many of the concerns raised would have been clear had the paper been reported according to the CONSORT statement[18]. Many others have also published critical comments, including the present and several previous ESH presidents, advocating that the study should be disregarded[19]. It must be emphasized that this study has not been found to include fraud, nor has it been retracted. However, in April 2020, the editors of the European Heart Journal published an Expression of Concern on behalf of the European Society of Cardiology[20].

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"The content and conduct of this RCT is currently under investigation" according to the Editors.

*Full reference list is available here

**Table 1 – Efforts to improve transparency of published science**

| Stage in the scientific process | Item | Comment |
|---|---|---|
| Researcher | Preregistration | Registration of clinical trials has been required by most journals since more than a decade. However, for systematic reviews and observational studies, although encouraged, registration is seldom a requirement. |
| | Peer governance | Several recent investigations in Sweden have concluded that high-profile researchers are guilty of misconduct for being co-authors on papers where others have manipulated data. Data sharing and open dialogue within research groups should avoid such errands. |
| Publisher | Reporting guidelines | Most high-impact journals require checklists from reporting guidelines such as CONSORT, PRISMA, or STROBE, to supplement submitted manuscripts. Better reporting will not only improve readability, but also uncover irregularities in methods as well as results. |
| | Open data | Many journals, such as the BMJ, offer authors to share their data through open data repositories like Dryad. Open data will enable scrutiny and re-analysis by peers, post-publication; probably one of the most important steps towards transparency. One major obstacle that needs to be overcome is how to avoid invasion of privacy among study participants. |
| Reviewer | Use registers and checklists | Preregistration of scientific projects is only of value if someone goes back and compares the final manuscript with the registered protocol. Whether this is up to reviewers, or if it should be part of the editorial process, is debatable. Deviations from the original plan, like the massive increase in number of participants in the Hygia trial, should always be motivated thoroughly.<br><br>Whereas many journals require reporting checklists with the submission, these needs to be critically assessed to improve the quality of published articles. It is our experience that a ticked box does not always mean that the item assessed is reported adequately. |
| | Count the numbers | Many fraudulent papers have been discovered because numbers do not add up, or add up a little bit too well, as in the example with the COOPERATE trial. |
| Reader | Speak up! | Whereas an article might meet two or three reviewers and a couple of editors before publication, the number of people reading it post-publication are often hundreds or thousands. It is reasonable that irregularities will sometimes be detected after print. Whereas a letter to the editor should be the first step if misconduct is suspected, critical comments published on twitter, as well as post-publication discussion forums, have had real scientific impact in recent years. |

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# LEARNING THE ROPES

## A Primer on Secondary Hypertension

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In its "Global Hypertension Practice Guidelines", released earlier this year, the **International Society of Hypertension** noted that "Early diagnosis of secondary hypertension and the institution of appropriate targeted treatment have the potential to cure hypertension in some patients or improve BP control/reduce the number of prescribed antihypertensive medications in others." Despite such attention, it is generally agreed that secondary hypertension remains underdiagnosed. In this "Learning the Ropes" feature we discuss, at length, secondary hypertension. You will find in-depth features on the various causes of secondary hypertension from three world experts.

It has been about 80 years since Goldblatt established the concept of renal artery stenosis causing hypertension[1]. At the time of his seminal observations, and in the absence of blood pressure lowering drugs, surgical interventions such as aortorenal, splenorenal, and hepatorenal bypasses represented the only therapeutic options. By 2020 though, surgical interventions have been virtually replaced by renal angioplasties with stents. More importantly, several classes of blood pressure lowering drugs, developed over the past decades, provide an impressive armamentarium to treat the consequence of renal artery narrowing, that is lower the high blood pressure, and thereby avert the adverse consequences associated with high blood pressure. Furthermore, the ever-expanding knowledge of natural history of atherosclerotic plaque formation and stability together with the development of lipid lowering drugs such as statins and antiplatelet agents allows for comprehensive pharmacotherapy of atherosclerotic renal artery stenosis beyond blood pressure control *per se.* As Prof. Markus Schlaich elegantly points out in our first feature **"Atherosclerotic Renal Artery Stenosis"**, there appears to be an absence of evidence favouring angioplasty and stenting as compared to comprehensive pharmacotherapy of atherosclerotic renal artery stenosis associated hypertension. He points out though, that a significant gap in the evidence for management of patients with atherosclerotic renal artery stenosis caused hypertension remains, as patients with truly resistant hypertension, progressive renal function loss, and recurrent acute heart failure (in the absence of underlying ischemic or structural heart disease) associated with rapid and severe increase in blood pressure (flash pulmonary edema) were either excluded or underrepresented in the published

trial literature. Until such evidence becomes available, at least for these patients, renal angioplasty with stenting could and should be considered at experienced centres.

In our second feature, Prof. Maria-Christina Zennaro highlights the most common form of secondary hypertension, **"Primary Aldosteronism"**. Well highlighted is the fact that early detection and treatment is crucial as primary aldosteronism carries a disproportionately higher risk for subsequent cardiovascular complications compared with essential hypertension.[2] Importantly, much of the excess cardiovascular risk in primary aldosteronism occurs independent of blood pressure. While historically considered a rare condition, recent studies have highlighted the high prevalence of primary aldosteronism which remains vastly underappreciated with a large number of cases still undiagnosed.[3,4] Beyond the under-diagnosis of primary aldosteronism as defined by conventional clinical criteria, there is a growing appreciation for the existence of a continuum of renin-independent aldosteronism and excess mineralocorticoid receptor activation beyond these criteria that may contribute to a large portion of what we currently label as "essential hypertension". Over the coming years, we are likely to witness a transformation in our understanding of the true spectrum of primary aldosteronism that will allow for earlier identification and novel targeted therapeutic approaches for a much broader population aimed at cardiovascular disease prevention.

In the shadow of primary hyperaldosteronism and atherosclerotic renal artery stenosis remain other rare forms of hypertension. Adrenal gland pathologies range from tumor-related excessive production of hormones intimately involved in the regulation of circulatory homeostasis to the imbalance between hormones normally produced because of enzymatic defects. As Prof. Peter de Leeuw elegantly points out in our final feature **"Other Endocrine Causes of Hypertension"**, these forms of hypertension are rare, diagnosis is fairly complex and resource intensive, and more likely than not will require an involvement of a specialist. The same could be said about hypertension associated with hyperparathyroidism or acromegaly. As Prof Peter de Leeuw highlighted, systolic hypertension associated with hyperthyroidism is more a secondary rather than primary feature of the disease, though if missed and left untreated could lead to high output heart failure. Similarly, as for other forms of hypertension, diagnosis of these rare forms is crucial, as targeted/specific treatments are frequently available and curative. A missed diagnosis may, on the other hand, leave patients with these rare forms of hypertension labelled with "hypertension resistant to pharmacotherapy ".

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# LEARNING THE ROPES

## Atherosclerotic Renal Artery Stenosis

### A common cause of secondary hypertension

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DOI:10.30824/2010-9

Renal artery stenosis (RAS) is a common cause of secondary hypertension and mainly due to atherosclerotic renal artery disease (ARAS) and less frequently due to fibromuscular dysplasia (FMD). A hemodynamically relevant RAS predominantly activates the renin-angiotensin-aldosterone system and can present clinically in form of hypertension, ischemic nephropathy, and cardiac destabilization syndromes. Advances in imaging techniques and interventional approaches have led to improved detection of RAS and more widespread use of renal artery revascularization strategies. While revascularization appears as an obvious therapeutic choice, data from three larger randomized controlled clinical trials (RCTs) failed to demonstrate convincing clinical benefit, although their design and selection of patients have been discussed controversially in the literature. Current therapeutic management is predominantly based on conventional antihypertensive and anti-atherosclerotic treatment and identification of subgroups of patients with a hemodynamically significant RAS in the context of worsening hypertension, progressive renal insufficiency and/or cardiac destabilization syndromes.

RAS is defined as a vascular lesion that results in narrowing of the renal artery. As a consequence, a reduction in renal blood flow to the affected kidney can occur. Atherosclerotic renal artery disease (ARAS) is the most common primary disease affecting the renal arteries accounting for ~90% of lesions typically occurring at the ostium and the proximal third of the renal artery. The prevalence of ARAS increases with increasing age and presence of cardiovascular (CV) risk factors including diabetes, hypertension, ischemic heart disease and peripheral arterial disease[1]. The presence of RAS is associated with poorer clinical outcomes[2].

Advancements in non-invasive diagnostic imaging and interventional techniques have led to the improved detection of RAS and the widespread use of endovascular revascularization strategies in the management of ARAS. However, a number of prospective RCTs have failed to demonstrate clear clinical benefits from revascularization compared to medical therapy[3-5]. These trials have been discussed controversially regarding flaws in study design and inherent bias, making their interpretation challenging and causing uncertainties amongst clinicians on appropriate management of affected patients. Optimal medical therapy and selection of patients likely to benefit from revascularization strategies seems essential and can be guided by the clinical presentation.

**Clinical manifestations of ARAS**

ARAS is implicated in the pathophysiology of three clinically distinct syndromes including hypertension, ischemic nephropathy, and cardiac destabilization syndromes.

***Hypertension:*** In patients with acute, severe, or refractory hypertension, the prevalence of RAS is reported to be as high as 10-40%. RAS causes a reduction in renal perfusion pressure that results in the activation of the renin-angiotensin-aldosterone system. Renovascular hypertension is most profound in patients with bilateral RAS or RAS affecting a solitary kidney. In these patients rapid worsening of hypertension control

and recurrent sudden onset (flash) pulmonary oedema may occur[1]. Longer term consequences can include congestive heart failure, hypertensive encephalopathy, intra-cerebral bleed, end-stage kidney disease and aneurysms[1].

***Ischaemic Nephropathy:*** The exact pathophysiology of ischemic nephropathy remains uncertain. Although an association is seen between the severity of RAS and hypoperfusion leading to ischemic nephropathy and kidney atrophy, this is thought to be insufficient to explain deterioration of kidney function. Recurrent microembolisms may also be implicated in the loss of kidney filtration capacity[1]. Ischaemic nephropathy most commonly occurs in the context of severe bilateral RAS or unilateral RAS in a solitary functioning kidney.

***Cardiac Destabilization Syndromes:*** Uncontrolled HTN and volume retention mediated by RAAS activation associated with ARAS play an important role in the destabilization of patients with acute coronary syndromes (ACS) or congestive heart failure (CHF). Sudden onset "flash" pulmonary edema (*Pickering syndrome*) is a recognized destabilization syndrome resulting from ARAS[6]. Sustained excess of aldosterone promotes myocardial fibrosis and left ventricular remodelling thereby contributing to aggravation of CHF. The presence of these syndromes should prompt an investigation for RAS.

## Diagnosis

Diagnosis of RAS may include non-invasive and invasive imaging studies to evaluate the degree of stenosis and renal function, physiological studies to assess the renin–angiotensin system; and perfusion scanning to evaluate differential renal blood perfusion. The choice of imaging modality is largely determined by patient factors, as well as the local availability of tests and expertise. Doppler ultrasound, CT angiography (CTA) and magnetic resonance angiography (MRA) are useful first-line investigations. If clinical suspicion for severe RAS is high and non-invasive tests are inconclusive, catheter angiography including pressure measurements or IVUS should be considered. Although catheter angiography is the gold-standard test, it is invasive and therefore carries a risk of access site complications, contrast induced nephropathy and thrombotic and embolic events that need to be taken into account.

## Medical therapy

As with all forms of hypertension, the overall therapeutic goal is to reduce the morbidity and mortality associated with elevated BP. In the context of RAS, a second goal is to protect the circulation and function of the kidneys. Guideline recommended principles of hypertension treatment generally apply also to patients with RAS. Due to the pivotal role of RAAS activation in the development of renovascular hypertension, it seems intuitive that RAAS inhibitors should be preferred therapy. Indeed, several prospective, randomized trials utilizing ACE/ARB therapy for patients with atherosclerotic disease elsewhere indicate a mortality benefit during long-term therapy, particularly for those with reduced estimated GFR (eGFR). RAAS blockade is frequently used as part of the medical regimen, particularly with unilateral renovascular disease. Close monitoring of renal function is important and if unexplained loss of GFR develops, cessation of RAAS blockade, at least temporarily is appropriate.

## Interventional therapy

The development and refinement of endovascular interventional techniques has been a major advance in managing vascular disease. Restoring vessel patency is now possible in the majority of patients with high-grade ARAS. Stent placement is associated with greater long-term patency than angioplasty alone. Complication rates from atheroembolic disease have fallen with improvements in peri-interventional management. However, prospective randomized trials have failed to identify additional benefits from endovascular stent revascularization for ARAS when added to medical therapy3[-5]. These studies were systematically reviewed at the request of the Agency for Health Care Quality Research (AHCQR)[7]. The aforementioned trials were found to suffer from limited recruitment, partly due to reluctance from clinicians to randomize patients with severe disease that are known to benefit from treatment in some cases. The effects of revascularization on relevant outcome parameters including BP response and renal function are summarized below.

***Effect of Renal Revascularization on Hypertension:*** The CORAL study published in 2014, is the largest randomized control trial to date evaluating renal artery stenting versus medical management (Table 1)[3]. In this study, a consistent but only modest difference in systolic blood pressure favoring the stent group was reported. Notably, 40% of patients in this study had a RAS of <60% on duplex measurements and the frequency of bilateral renal artery stenosis was also low. Moreover, 29% of patients had a systolic BP of <140mmHg which could be one of the explanations why no significant changes in BP following revascularization were seen. Similarly, in the ASTRAL[4], STAR[5] and DRASTIC[8] studies, no significant differences in blood pressure between groups was observed over the follow-up period, however, the daily drug dose was reduced in both the ASTRAL and DRASTIC studies[4,8].

A subsequent meta-analysis of 8 studies including 2,223 patients did not demonstrate any change in systolic blood pressure from baseline with revascularization when compared to medical therapy alone[9].

***Effect of Renal Revascularization on Renal Function:*** In the ASTRAL trial, 59% of the patients had a RAS >70 %, and 60 % had a serum creatinine of ≥150µmol /L (4). At a mean follow-up of 33.6 months (range 1-4 years) differences in renal function, kidney and cardiovascular events were not significant, even in the highest risk groups, which included patients with global ischemia or impaired or rapidly decreasing kidney function. The primary study end-point, the decline in renal function over time, was marginally slower in the revascularization group, but this was not statistically significant. The STAR multicenter trial enrolled 140 patients to detect a 20% or greater decrease in creatinine clearance[5]. At 2 years, the primary end point was reached in 16% of patients in the stented group and 22 % of patients in the medical treatment group; although the difference s was not statistically significant, more than 50% of patients randomized to the stenting arm had a <70% RAS and 28% of patients did not receive a stent. In the DRASTIC study, GFR increased by 15 ml/min in the balloon angioplasty group whereas it slightly decreased by 1 ml/min in the control arm. However, the study was not powered adequately to show a significant difference[8]. In the CORAL Trial[3], progressive renal insufficiency was defined as a reduction from baseline of 30% or more in the estimated GFR. No significant improvement in renal function was seen in the follow-up period.

**Which Patients should be considered for revascularization therapy?**

The decision to perform RAS revascularization should involve a thorough review of the patients' co-morbidities, quality of blood pressure control and status of renal function. In light of the current available evidence, renal revascularization should be considered in patients with anatomically significant bilateral RAS who present with 'flash' pulmonary oedema, congestive heart failure with preserved left ventricular function or acute oligo-anuric renal failure with global kidney ischemia.

**Conclusions**

RAS is a common cause of secondary hypertension and associated with adverse outcomes. Modern imaging techniques combined with physiologic measures allows assessment of the degree of stenosis and hemodynamic relevance. Medical therapy with guideline recommended antihypertensive therapy including RAS blockers are usually effective in lowering BP while maintaining renal function. Benefit from revascularization therapy is likely to occur where there is a hemodynamically significant RAS, in the context of deteriorating arterial hypertension, progressive renal insufficiency, and cardiac destabilization syndromes.

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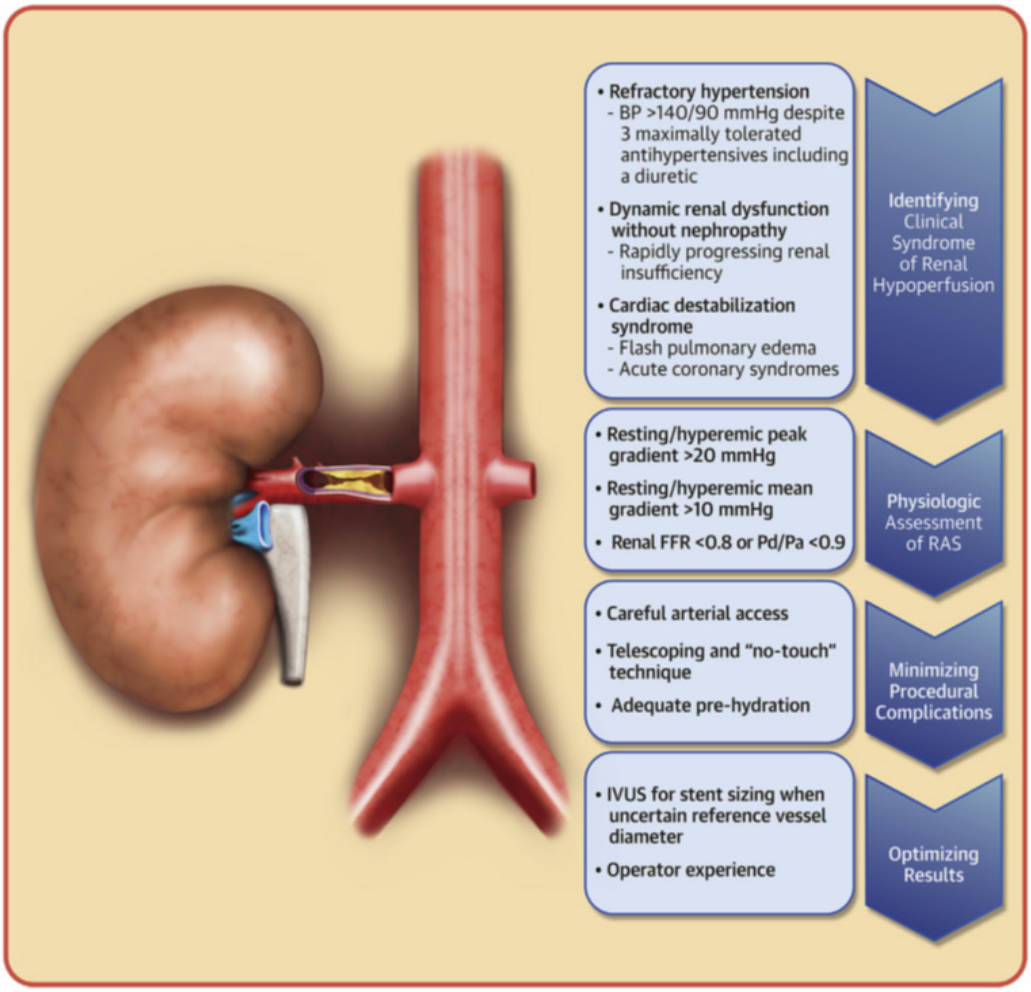
**Table 1: Summary of most relevant RCTs comparing renal artery revascularization with medical therapy (from (10) with permission)**

| Trial | STAR | ASTRAL | CORAL |
|---|---|---|---|
| Year | 2009 | 2009 | 2014 |
| Number of patients | 140 | 806 | 947 |
| Inclusion criteria | Impaired renal function (CrCl <80)<br>Ostial ARAS of ≥50% (CTA, MRA, DSA)<br>Controlled BP <140/90 mm Hg | Renal artery atherosclerotic disease in ≥1 renal artery amenable to revascularization<br>Clinician unsure if revascularization would provide clear benefit | Severe RAS angiographically defined as ≥60% but <100%, and hypertension with systolic BP ≥155 mm Hg on ≥2 agents or CKD defined as GFR <60 ml/min/1.73 $m^2$ |
| Exclusion criteria | Renal size <8 cm<br>Renal artery <4 mm<br>CrCl <15<br>Diabetes with proteinuria >3 g/day<br>Malignant hypertension | Disease needing surgical revascularization<br>High likelihood of needing revascularization in 6 months<br>Nonatheromatous disease<br>Prior RAS revascularization<br>Lack of informed consent | FMD<br>CKD from causes other than ischemic nephropathy<br>Cr >4<br>Kidney size <7 cm<br>Lesions that could not be treated with 1 stent |
| Primary endpoint | Worsening renal function >20% decrease of CrCl | Slope of the reciprocal of Cr over 5 yrs | Time to major renal or cardiovascular event (stroke, heart attack, CHF hospitalization, progressive renal insufficiency, need for dialysis) |
| Limitations | Patients had controlled BP<br>Considerable number of participants had <50% stenoses | Rate of complications much higher than reported<br>Smaller number of antihypertensive agents used in intervention group<br>Diagnosis of RAS made with noninvasive imaging without functional studies<br>Patients with kidney size <6 cm included in study<br>Patients with insignificant lesions included | Patients were not optimized on antihypertensive therapy<br>Inclusion of patients with mild stenosis<br>Only moderate correlation between angiography and hemodynamically significant stenoses |

**Figure 1: Illustration of a clinical pathway to optimize identification and management of patients with RAS and relevant associated clinical syndromes (from (10) with permission).**

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# LEARNING THE ROPES

## Primary aldosteronism

### The most frequent form of Secondary Hypertension

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DOI: 10.30824/2010-10

Primary aldosteronism (PA) is the most frequent form of secondary hypertension. Its early diagnosis and treatment are crucial to prevent deleterious cardiovascular outcomes related to aldosterone excess. Recent discoveries have improved our understanding on the pathogenic mechanisms responsible for the development of PA and opened new perspectives for improved management of patients (Figure 1).

**Prevalence, diagnosis and treatment of PA**

PA results from autonomous aldosterone production from the adrenal cortex, which is inappropriate for the salt status and relatively independent from the renin-angiotensin system and potassium levels[1]. It is due in the majority of cases either to a unilateral aldosterone producing adenoma (APA) or to bilateral adrenal hyperplasia. High aldosterone levels lead to volume expansion, sodium retention and increased urinary excretion of potassium, leading to hypertension, often associated with hypokalemia. Patients with PA are at increased risk of stroke, coronary artery disease, atrial fibrillation and renal damage compared to patients with primary hypertension[2]. The increased cardiovascular risk is due to deleterious effects of excess aldosterone on target organs, leading to cardiac and vascular fibrosis and tissue damage, independently of blood pressure levels[3].

PA is found in 5% of hypertensive subjects in primary care and up to 10% of patients with hypertension referred to specialist care; its prevalence increases with severity of hypertension and reaches up to 20% in patients with resistant hypertension[1]. However, the real prevalence may be even higher, as recent work shows that 24h-urinary aldosterone levels following an oral sodium suppression test are continuously increased throughout blood pressure categories. This suggests a continuum of renin-independent aldosterone production and undetected PA in patients with primary hypertension, which parallels the severity of hypertension and may play a role in the development of high blood pressure in the general population[4].

PA is a largely underdiagnosed condition. Currently, PA is most often diagnosed following the Endocrine Society guidelines for case detection, diagnosis, and treatment[5], which target patients with a high probability of the disease, given the complexity of the diagnostic workup. Therefore, it is estimated that a large part of cases is missed, and patients prevented from benefitting from appropriate treatment of their condition. The diagnostic algorithm for PA includes hormonal screening and confirmation testing, followed by identification of subtypes. Screening is based on the aldosterone to renin ratio, which should be assessed at normal dietary sodium intake and with hypokalemia corrected by oral potassium chloride, ideally without drugs interfering with the renin-angiotensin-aldosterone system. In the presence of an increased aldosterone to renin ratio, one of different confirmatory tests are performed to demonstrate the non-suppressibility of aldosterone production. These include the oral sodium loading test, fludrocortisone suppression test, saline infusion test and captopril challenge test[5]. Once the diagnosis is confirmed, PA subtyping

of unilateral versus bilateral forms is performed by adrenal imaging and adrenal vein sampling[1, 5]. Surgical adrenalectomy is the treatment of choice in lateralized primary aldosteronism, while mineralocorticoid receptor antagonists are recommended for patients unable or unwilling to undergo surgery and in patients with bilateral forms of the disease[5]. Adrenalectomy reduces cardiovascular risk in patients with lateralized PA, allowing regression of left ventricular hypertrophy and decreasing risk of atrial fibrillation.

**Genetic forms of primary aldosteronism and new perspectives for patient management**

While the majority of cases of PA are sporadic, 6% of cases are found in a familial context[1]. Four different familial forms of the disease have been identified, familial hyperaldosteronism I-IV, which are transmitted as autosomal dominant traits and result from different genetic defects[6]. Given the low cost of genetic screening and the benefits of early diagnosis in affected families, genetic screening of patients with early-onset PA and/or a family history of the disease should be offered for improved management of patients[1], as deleterious aldosterone-dependent end organ damage may occur well before patients become hypertensive[7]. FH-I, also called glucocorticoid remediable aldosteronism, occurs in approximately 1% of patients with PA and is associated with a high prevalence of cerebrovascular events at young age. It results from the formation of a chimeric gene between the highly homologous *CYP11B1* and *CYP11B2* genes encoding 11β-hydroxylase and aldosterone synthase. The resulting protein codes for an enzyme that synthesizes aldosterone under the control of ACTH. High concentrations of the hybrid steroids 18-oxocortisol and 18-hydroxycortisol in urine are found in these patients in addition to typical features of PA. Remarkably, patients respond well to treatment with low dose of dexamethasone alone or in combination with mineralocorticoid receptor antagonists[1, 5]. FH-II is the most frequent form of familial PA. Patients are indistinguishable from those with sporadic PA and the diagnosis is based on the presence of two or more affected family members. Genetic discoveries have shown that the clinical entity very likely comprises several forms with different genetic defects. Recently, FH-II has been associated to the presence of different heterozygous gain-of-function mutations in the *CLCN2* gene, coding for the chloride channel ClC-2 [8,9]. FH-III is an early-onset severe form of PA, showing severe hypertension and profound hypokalemia, high levels of 18-oxocortisol and 18-hydroxycortisol in urine, associated with massive bilateral adrenal hyperplasia and requiring bilateral adrenalectomy to correct blood pressure. It is due to recurrent germline mutations in *KCNJ5*, coding for the potassium channel GIRK4[10]. A milder form of the disease has also been described, which responds well to treatment with mineralocorticoid receptor antagonists. Finally, FH-IV is caused by germline mutations in the *CACNA1H* gene coding for the α subunit of the T-type calcium channel Cav3.2. The clinical presentation of FH-IV shows incomplete penetrance and varies from early-onset PA to cases indistinguishable from sporadic PA. Given the variability of the clinical presentation, some patients with *CACNA1H* mutations are initially diagnosed as FH-II. This is also the case for patients with mild FH-III; in both conditions, genetic testing allows reclassifying the disease and personalising patients care.

In addition to germline mutations in familial forms of PA, recurrent somatic mutations, identified in DNA extracted from tumour tissue, are found in up to 90% of APA. Those mutations affect in part the same genes involved in familial hyperaldosteronism (*KCNJ5, CACNA1H, CLCN2*) as well as other genes involved in maintaining ionic balance in zona glomerulosa cells of the adrenal cortex (*CACNA1D, ATP1A1, ATP2B3*) or involved in adrenal cortex development (*CTNNB1*). Although different somatic mutations are correlated with clinical and biochemical features (for instance, *KCNJ5* mutations are more frequent in women and in young patients), the usefulness of genetic screening is currently under investigation. Possible applications include development of surrogate biomarkers for the mutation' status, in particular specific steroid profiles, which would allow identifying patients who are suitable candidates for AVS, thus simplifying current diagnostic procedures. A seven steroid fingerprint has been described that correctly classifies 92% of APA according to genotype in peripheral venous plasma[11]. In the same context, mutated *KCNJ5* channels are highly sensitive to macrolide inhibition and current clinical protocols evaluate the possibility of using those compounds

to diagnose patients with *KCNJ5* mutations by measuring changes of plasma concentrations of aldosterone and renin in peripheral venous blood of patients with PA after roxithromycin administration[12].

In conclusion, PA is the most common form of secondary and curable hypertension. Its prevalence may be higher as currently thought, due to a continuum of inappropriate aldosterone production within the spectrum of blood pressure levels. Work is currently undergoing to identify new biomarkers for the disease, allowing fast and simple diagnostic procedures, in order to improve early diagnosis and treatment and prevention of cardiovascular complications.

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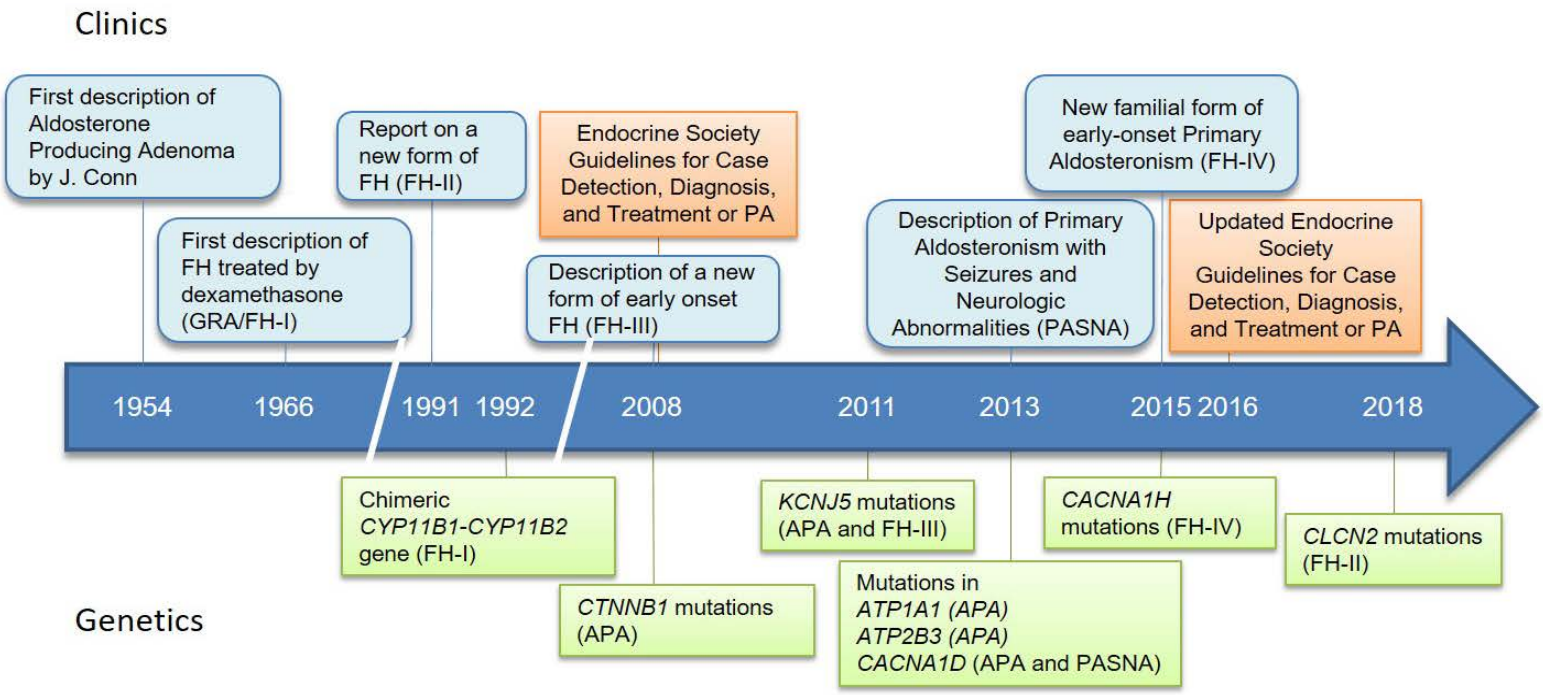
**Figure 1. Major discoveries in PA. The upper part of the panel represents clinical advances, in particular discoveries of new clinical forms of the disease and publications of guidelines for its management. The lower part represents major genetic discoveries in the field. APA, aldosterone-producing adenoma; FH, familial hyperaldosteronism.**

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# LEARNING THE ROPES

## Other Endocrine Causes of Secondary Hypertension

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DOI: 10.30824/2010-11

Although primary hyperaldosteronism undoubtedly is the most frequent endocrine-related cause of hypertension, there are several other endocrine disturbances that may lead to an elevated blood pressure. Adrenal abnormalities such as Cushing's syndrome and pheochromocytoma are probably the most well-known, but diseases of the pituitary gland (acromegaly), the thyroid and the parathyroids may cause hypertension as well.

### Adrenal corticoid hypertension (Cushing's syndrome)

Cushing's syndrome is characterized by glucocorticoid excess. The overproduction of cortisol produces a number of clinical features of which hypertension is one. Recent data suggest that hypertension is present in more than 75% of patients with Cushing's syndrome and quite often even is the presenting symptom[1,2]. Typically, the nocturnal blood pressure dip is blunted or absent in patients with Cushing's syndrome. The

pathogenesis of hypertension in this condition is still incompletely understood but involves a variety of mechanisms, including retention of sodium and water due to mineralocorticoid receptor activation in the kidney, enhanced sensitivity to the action of angiotensin II (levels of which are usually low) as well as other vasoconstrictors and vascular remodeling. In addition, cytokines and several other mediators may contribute to the development of cardiovascular complications[3].

Hypercortisolism may stem from autonomous adrenal production or from excessive stimulation by ACTH. Whenever Cushing's syndrome is suspected on clinical grounds, at least two of three available tests should be applied for screening. These are: measurement of 24-hour urinary excretion of free cortisol, determination of nighttime cortisol in saliva and the overnight dexamethasone suppression test[4]. Once overproduction of steroid hormones has been established, imaging studies should follow to localize the abnormality. There is little doubt that CT and magnetic resonance imaging (MRI) are the most suitable methods for detecting adrenal masses. Even small lesions can be picked up this way. One should realize, though, that these modern imaging techniques may also discover other (variant) types of abnormalities. It remains necessary, therefore, to match the images with the results of (dynamic) hormonal testing. Determination of plasma ACTH, if necessary, to be completed with functional tests and selective venous sampling, is necessary to differentiate between pituitary, adrenal and ectopic sources of hypercortisolism. Again, CT and/or MRI are useful for localization of extra-adrenal abnormalities.

Minimally invasive surgery is the treatment of choice, but hypertension may persist after removal of the lesion. All types of antihypertensive agents can be used for treating hypertension before and after surgery. There is some indication that cortisol-lowering medical treatment can also lower blood pressure[5] but this needs to be substantiated further.

**Apparent mineralocorticoid excess**

Apparent mineralocorticoid excess is an extremely rare autosomal recessive abnormality that causes a form of hypertension in which primarily mineralocorticoid mechanisms are involved. Due to an absolute or a relative lack of the enzyme 11-β hydroxysteroid dehydrogenase (11-β OHSD) type 2, the conversion of cortisol into the inactive cortisone at the level of the mineralocorticoid receptor in the distal renal tubules does not work properly. As a result, cortisol which is present in far greater concentrations than aldosterone competitively displaces aldosterone from its receptor. Low-renin hypertension due to sodium retention and hypokalemia ensue. In the urine, one will find an increased ratio of cortisol metabolites over cortisone metabolites. Probably, mineralocorticoid receptor antagonists are the best choice for treating the hypertension although convincing studies in this regard are lacking.

**Other forms of steroid excess**

Increased production of deoxycorticosterone (DOC) occurs primarily in congenital adrenal hyperplasia, where deficiency of either 11β-hydroxylase or 17α-hydroxylase impairs cortisol production. DOC-producing tumours and primary cortisol resistance are also associated with elevated DOC concentrations, but these conditions are rare. Due to its agonistic activity on the mineralocorticoid receptor, DOC causes a form of low-renin, low-aldosterone hypertension with hypokalemia. Except for the abnormalities at physical examination, one finds increased levels of DOC and adrenal androgens in 11β-hydroxylase deficiency but low levels of androgens in 17α-hydroxylase deficiency. In addition, 11-DOC is high in the former, while corticosterone and 18-hydroxycorticosterone are high in the latter. Table 1 summarizes the most important laboratory features, which may help in the initial work-up of patients with a suspected adrenal form of hypertension.

In cases of DOC excess, glucocorticoid replacement therapy will ameliorate clinical symptomatology.

**Pheochromocytoma**

Although pheochromocytoma may be found accidentally, in most cases there will be symptoms related to catecholamine excess. The prevalence of pheochromocytoma is low: less than 1% of the hypertensive population. When the diagnosis is suspected, the initial biochemical testing should include measurements of

plasma free metanephrines, preferably after 30 minutes of recumbency, or urinary fractionated metanephrines when a plasma assay is not available[6]. Repeat testing is recommended when initial test results are negative but clinical suspicion is high. Importantly, elevations of plasma metanephrines may also be false-positive, particularly in patients using tricyclic antidepressants or phenoxybenzamine[7]. Occasionally, and particularly with borderline elevations of metanephrines, one has to turn to the clonidine suppression test. Normally, plasma levels of normetanephrine or norepinephrine fall by about half but failure to do so strongly suggests the presence of a pheochromocytoma.

When there is biochemical evidence of a pheochromocytoma, CT scanning is the preferred method to localize the tumor. Given its suboptimal performance and the fact that the uptake of [$^{123}$I]-meta-iodobenzyl-guanidine (MIBG) may be decreased by several drugs, imaging with this agent should not be applied routinely.

Before the surgeon can remove a pheochromocytoma, preferably by laparoscopy, one must be sure that the patient has had adequate treatment with an alpha-blocking drug. Pheochromocytomas are usually benign and patients are cured after removal of the tumor. In case of malignant disease, however, long-term follow-up is necessary.

**Acromegaly, thyroid and parathyroid disorders**

Hypertension and its associated cardiovascular complications may occur in up to 60% of patients with acromegaly. In particular, diastolic pressure is elevated, and the nocturnal dip is often absent. In the pathogenesis of acromegaly-associated hypertension volume expansion plays a major role but several other factors, similar to those in Cushing's syndrome are also involved. All antihypertensive agents can be used to control the pressure but treatment of the primary abnormality improves blood pressure as well[8].

Hypertension, mainly isolated systolic hypertension, is present in about 10% of patients with hyperthyroidism and is related to an excess of T3 causing increased cardiac output, increased arterial stiffness and activation of several neurohumoral systems[9]. Treatment should preferably include beta-blockers. Per contra, hypothyroidism is predominantly associated with a rise in diastolic pressure, a narrow pulse pressure and increased vascular resistance. It often disappears when the patient becomes euthyroid.

Finally, primary hyperparathyroidism has been identified as a cause of hypertension and cardiovascular complications with a prevalence of about 50%[10]. The mechanisms involved are not well understood but are likely related to increased cellular calcium influx and sensitization of the vascular wall to vasoconstrictor agents. Although parathyroidectomy may resolve the hypertension, there is insufficient information as to how often this occurs.

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**Table 1 : Laborarory Features Of Various Forms of Corticoid-Related Hypertensive Disorders**

| | Serum potassium | Renin | Aldosterone | Other biochemical features |
|---|---|---|---|---|
| **Cushing's syndrome** | Normal or low | Normal or low | Normal or low | Elevated cortisol |
| **Apparent mineralocorticoid excess** | Low | Low | Low | Increased urinary excretion of tetrahydrocortisol plus 5α-tetrahydrocortisol, relative to that of tetrahydrocortisone |
| **Deoxycorticosterone excess** | Low | Low | Low | Increased plasma concentration of deoxycorticosterone; additional abnormalities depending on the nature of the defect |

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# "DDD" DYLAN'S DISTRIBUTION DATA

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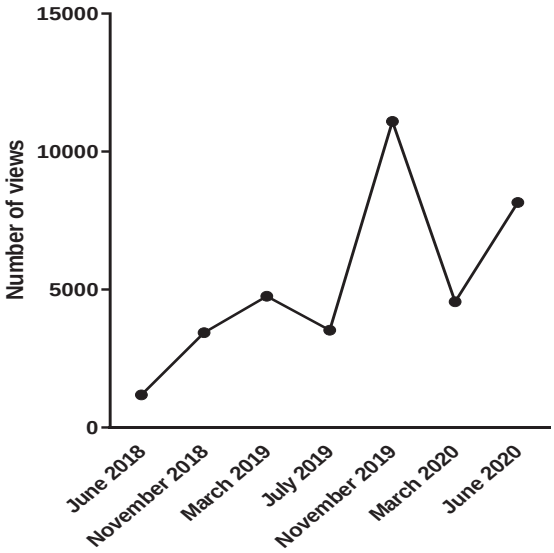
Featuring a comprehensive summary of the ISH Global Hypertension Practice Guidelines, and a rapid feature on COVID-19 and hypertension, the June issue of Hypertension News was well received by membership. In fact, it was the second most downloaded issue to date and represents a return to the steady growth that we had seen prior to the March issue. In my previous report I had speculated that the low numbers for the March issue were impacted by COVID-19 challenges facing readership. That may indeed have been the case but, it seems that readers are once again turning to Hypertension News in large numbers. On a side note I would like to thank the many members who took the time to acknowledge the efforts of the Hypertension News team in the 2020 membership survey. This was greatly appreciated by the editorial team and lend further credence to the numbers below.

| Dylan's Distribution Data (June 2020-September 2020) | |
|---|---|
| **Total Estimated Readership** | **8156** |
| Accessed via Twitter | 627 |
| Accessed via Facebook | 553 |
| Accessed via DOI | 6561 |
| Accessed via Web Site | 415 |

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## MEANWHILE IN 'HYPERTENSION MEWS'...

*Social distances in Corona times in Sweden: Don Pudro (left) and Carmencita (right) didn't quite get it, but they come from the same family so it should be all right...*

*Photo by Li Winther (from the Lindholm family)*

# JOINT MEETING ESH-ISH 2021: UNCHANGED VISION, ADDED NEW TOPICS, AND VIRTUAL

## Interview with Anna Dominiczak, the Chair of the Joint Meeting ESH-ISH 2021

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DOI: DOI: 10.30824/2010-12

The year 2020 is not like any other year. Covid-19 made the start of the year very different, and we have yet to see if and when things will return to what we previously considered normal. In view of the global unprecedented situation related to the pandemic, the Joint Meeting ESH-ISH 2020 in Glasgow had to be rescheduled to 2021. The event will now take place on April 11–14, 2021. This brief interview with Anna Dominiczak, the Chair of the Joint Meeting ESH-ISH 2021 give some insights in how this all came about.

With the start of the pandemic, Anna explains, the three organizing societies (ESH, ISH, and BIHS) worked as team to find the best possible solution. As nobody would travel with all pending travel restrictions, and the congress venue had been turned into the Nightingale Hospital there was no possibility to hold the congress as originally scheduled in 2020.

*There was only one decision. Clearly, there was only more and more disease. We decided together as a team to postpone the congress. I am very grateful for the great help and support from Reinhold Kreutz, Alta Schulte, and Una Martin, representing ESH, ISH, and BIHS in this, and for the planning of the rescheduled meeting in April 2021, says Anna. We are also grateful to Guiseppe Mancia and colleagues for sacrificing their originally planned ESH 2021 Meeting in Milan,* she adds.

*We were told that there was limited availability to the conference center in 2021 and the only time we could get was in April. But it became obvious several weeks ago that things are not getting better, and the plans to have a face-to-face meeting in April 2021 was a dream that would never come true. Time made the decision for us and the meeting will be entirely virtual, Anna continues. With the current situation given, we have in recent time gained experience in virtual scientific and educational meetings. There are several examples of highly successful large European and American scientific cardiovascular meetings. Virtual meetings equalize access for everyone*, she says.

In the upcoming meeting in April next year the core of the program remains the same, plus new added sessions including sessions on covid-19 and hypertension. As the societies come together there will be several plenary sessions. The BIHS will also provide a one-day program dedicated for general practitioners. All existing abstracts remain in, and there has been a call for new abstracts, with a good response. This will ascertain a scientific program of high standards.

*I will be pushing for interactive sessions. My experience is that this is feasible also with virtual meetings, Anna points out. Also, the opportunity for virtual interactions and virtual coffee breaks are important during the conference, and will be provided. However, face-to-face interactions and virtual interactions are different,* she continues. *Also, the timing for interaction is more difficult in virtual meetings, depending on the different time zones of the participants*, she adds.

With several successful annual very large cardiovascular congresses, is there a place for large international hypertension meetings?

*I think there is a role. Because hypertension is the cheapest and easiest risk factor to fight. The beauty of hypertension meetings is the collegiality and ability to see people who have a similar point of view, a similar view to see the scientific world, Anna continues. There is enough multidisciplinarity, yet thinking that hypertension is really important. When asked, she believes the ideal format for future hypertension meetings would likely be a mixture of face-to-face meeting with some integrated virtual sessions to equalize access for everyone. Human contact is something we need,* she says.

Time will tell how future clinical and scientific interaction within the hypertension community will take place. Until then, the Joint Meeting ESH-ISH 2021 welcomes your active participation in sharing your research, your insights, and your expertise.

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# INVITED PAPER

## ISH2022 Welcome message for Hypertension News

HIROSHI ITOH
Local Chair, ISH 2022 Kyoto.
President, The Japanese Society of Hypertension

Dear Colleagues,

On behalf of the organizing committee, we are delighted to cordially invite you to the 29th Scientific Meeting of the International Society of Hypertension (ISH2022), which will be held on October 12(Wed)~16(Sun) in 2022 at the beautiful city of Kyoto, Japan. The meeting will be taken place in collaboration with the 17th Congress of the Asian Pacific Society of Hypertension (APSH) and the 44th Annual Meeting of the Japanese Society of Hypertension (JSH) (Fig.1).

ISH2022 will bring "The Wisdom for Conquering Hypertension" through diverse and extensive scientific programs that are focusing on innovation, advanced technology, and health promotion including food, sports, and AI dimensions (Fig.2). The organizing committee promises to offer an outstanding experience of special lectures, plenary lectures, award presentations, symposia of current topics, workshops, and industry sessions. The Nobel Prize in Physiology or Medicine 2012 laureate, Professor Shinya Yamanaka (Kyoto University), who discovered induced pluripotent stem cells (iPS cells) and has recently been devoted to providing information regarding COVID-19 for Japanese citizens, is appointed as one of the special lecturers. By bringing together multidisciplinary wisdom regarding hypertension-related diseases, we aspire to explore new directions in diagnostics, prevention, and treatment; as well as generate a new paradigm in our shared mission to conquer hypertension.

At present, the unprecedented COVID-19 is intensifying and restrictions on overseas travel are continuing, however, the organizing committee hopes to hold ISH2022 locally at Kyoto as much as possible. We will make all possible preparations by assuming both cases that COVID-19 will end and it will be possible to hold a local meeting almost the same as usual, and the situation will worsen and it will be closer to the complete web meeting. Even when we can hold the meeting locally, we will include the web program, taking in mind to utilize the merits of digital transformation of the meeting, such as enabling a wide-range participation of developing countries from where it is usually difficult to visit Japan.

We consider that ISH2022 is a challenging opportunity to seek for New Normal of the meeting style in the era of post/with-COVID-19. We would like to introduce innovative attempts to allow lively discussions on the web even if the participants cannot visit Japan. By offering diverse and extensive scientific program in the web contents, we will strive to involve the largest number of young participants ever, who are busy with daily duty. We would like to encourage the participants from developing countries by providing a special discount fee for them to enable the web participation. In addition, the organizing committee plans to spend more than 200,000 USD to provide travel grants for 300 persons of young investigators whose abstracts have been selected for either oral or poster presentation. Initially, we expected 3,500 participants who visit Kyoto from all over the world and are now planning to have 4,500 participants by including web participants.

Kyoto, the ancient capital of Japan, is famous for its long history and unique culture. It is also home to high-tech companies, such as Nintendo, Kyocera, and Omron. CiRA, the Center for iPS Cell Research and Application headed by Professor Shinya Yamanaka is established in Kyoto University, which is also the

birthplace of SHR, spontaneously hypertensive rat models, established in 1963 by Professor Kozo Okamoto. We welcome all doctors and researchers who devoted to studying and treating hypertension to ISH2022 Kyoto to foster intensive discussions and facilitate further development in the field.

It is with pride that we invite all of you to participate in ISH2022. We strongly believe that, if you can visit Kyoto, you will find the Japanese hospitality extremely satisfying and will be able to deepen and widen your knowledge and expertise to learn from the best and create professional connections. The official web site of ISH2022 Kyoto is now available at https://www.ish2022.org/. The promotion video is at https://www.youtube.com/watch?v=EWRJwvfBED0.

**We are looking forward to welcoming you to ISH2022.**


**Figure 1.** The official poster of ISH2022 Kyoto. The photograph was taken at "Senbon Torii", which is a path with thousand wooden gates, of Fushimi Inari-taisha in Kyoto. It is the head of the Inari shrines which are located as many as 32,000 places throughout Japan. They pray for a good harvest of agricultural products. The Chinese character pronounced as "Chi" on the left side of the photo means "wisdom". The poster means a wish for ISH2022 Kyoto to be filled with the rich wisdom for conquering hypertension.


**Figure 2.** The three primal subjects of the ISH2022 meeting: FOOD, MOVE and AI which are expressed in "Mitsu-Domoe", a traditional Japanese family crest that represents three spirits influencing each other.

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# NEWS, OLD NEWS, AND CULTURE

## What was the blood pressure of Mona Lisa?

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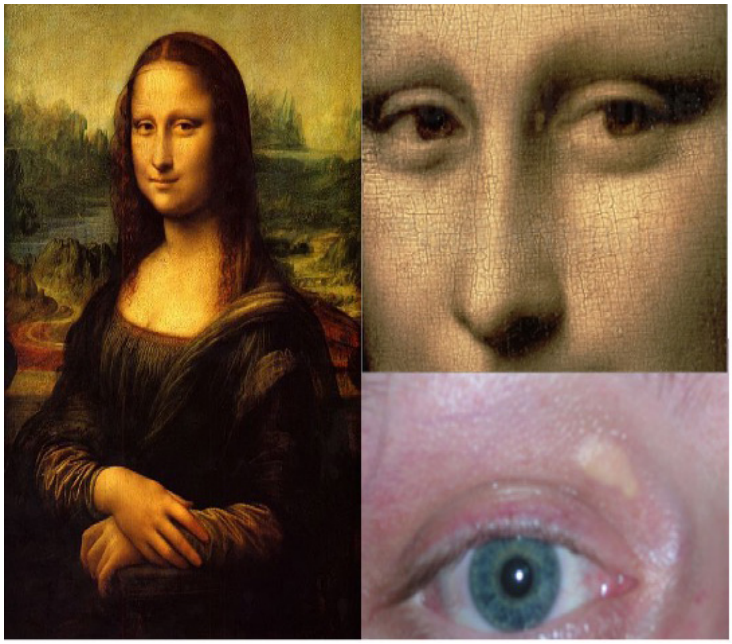
DOI: 10.30824/2010-13

Millions of tourists look every year at the most famous painting by Leonardo da Vinci in the Louvre. Difficult to see under a heavy pane of glass and only barely visible from far away over the heads of dozens of tourists in front of you it is difficult to distinguish individual features on this famous portrait. However, when one uses illustrations and has a closer look at Mona Lisa it is obvious that besides the famous smile on her face other features also want further examination: For instance, there are the eyebrows. There are no visible eyebrows and one wonders whether this has to do with the way the painting has been treated first by Leonardo who carried it along on his journeys from Rome to Milan, to France or during the time the painting was at the French court or whether indeed it was damaged when it was stolen from the Louvre in 1910. Or was it the fashion at the time not having eyebrows for Florentine ladies? Or is it a sign of an underlying medical disorder? A closer look shows that Mona Lisa has other abnormalities. For instance, there is this swelling on the right hand that may be an abnormality of the joint of thumb or a swelling that would indicate a lipoma.

Is it justified to look at these paintings with a medical view and make diagnosis? Medical doctors have done this for a long time. In fact, at Yale University in 2001 a course was created where medical students went with their professor to the local art gallery and stood in front of pictures to make medical diagnosis. A comparable course was done at Harvard more than 20 years ago. I have started to give seminars on medical diagnosis on paintings at Hannover Medical School more than ten years ago. Every year I gather interested students and we enjoy lectures on paintings ranging from Leonardo da Vinci's Mona Lisa to the Death of



Mara by Jacques Louis David. Rubens, Rembrandt, Raffael, Dürer, Hohlbein and others have painted portraits and people with abnormalities which can be identified and diagnosed. This not only sharpens the medical eye of the students, but it also provides them with a better understanding of the historical situation of the patient and the implications of disease over a time. Was a certain medical diagnosis in the 16th century the same as it is today? What did a specific diagnosis mean for the medical profession at that time? And how was "medicine" organized in the 16th century?

Let us go back to Mona Lisa. On a closer observation, we can see in the angle of her left eye a yellowish dimple.

Since Leonardo is one of the most diligent painters known in history it is rather unlikely that this small abnormality is there without purpose. On closer observation, there are not many general conditions, which look like that. In fact, it is obvious that such a yellowish artefact in this position is most likely a xanthelasma. If we agree on this, we have an interesting medical case. Mona Lisa, a young woman from Florence, with a xanthelasma.

Which medical conditions are associated with xanthelasma? Xanthelasma indicates a high circulating of cholesterol. In fact, xanthelasma appear when we have a rapid elevation of high circulating cholesterol.

This would indicate that Mona Lisa has high cholesterol levels and therefore xanthelasma. What are our next questions?

Circulating cholesterol levels may occur under two conditions: It can reflect a genetic abnormality of LDL metabolism resulting in hypercholesterolemia and early atherosclerosis. Is this the case with Mona Lisa? Most likely not. From what we know the portrait of Mona Lisa is Lisa del Giocondo, the wife of a Florentine banker in the beginning of the 16th century. In fact, the most likely interpretation of the portrait is that the husband gave Leonardo the task to portrait his wife after the marriage. We know that Mona Lisa lived a long life and died at the age of 76 in Florence. Therefore, hypercholesterolemia and xanthelasma may not be caused by a genetic abnormality of cholesterol metabolism since it would be very unlikely for her to reach such a high age with a genetic abnormality, which normally results in atherosclerosis and chronic inflammatory vascular disease. The other medical conditions that can explain xanthelasma are either the massive loss of protein in the urine, i.e. with a glomerular disease such as focal segmental glomerular sclerosis. Another explanation could be a diminished production of thyroxine. In hypothyroidism, the serum cholesterol is also elevated and xanthelasma have been observed in these patients. How can we solve the question whether Mona Lisa has hypothyroidism or a renal disease? This is where the blood pressure comes in. Kidney disease would be associated with an increased blood pressure. On close observation one of my students observed that the fingers of Mona Lisa are rather swollen. In fact, when one compares the hands of Mona Lisa with other hands of women Leonardo has painted it becomes obvious that the swelling of the fingers is actually the case. The joints of the fingers are not clearly visible indicating fluid retention. And yes, the puffy face of Mona Lisa has been observed over the centuries. This would indicate focal segmental glomerular sclerosis i.e. renal disease with high blood pressure and proteinuria. On the other hand, in hypothyroidism the blood pressure would be low. It would therefore be of considerable importance to know the blood pressure of Mona Lisa to make a differential diagnosis. Unfortunately, it would take another 110 years before the circulation of the blood was discovered and understood. Did Leonardo know about blood vessels? Yes, of course he made famous contributions to our understanding of blood vessels, their structure in various famous drawings. However, their function eluded him. During his time the concept of blood circulation was still not established. There was a firm belief that the blood exploded in the chambers of the heart, was then expulsed into the large blood vessels, and disappeared into a gaseous form in the periphery. Blood was then formed again in the liver from where it was transported to the heart and the next explosion followed.

While the presentation of disease may remain the same over centuries our explanation and the underlying pathophysiology change.

A little more than 15 years later a colleague of Leonardo da Vinci, another famous painter of the Italian High Renaissance Raffaello Sanzio painted the Transfiguration of Christ. The painting was finished in 1520 and turned out to be the last, most famous painting by Raffael. While today perhaps the Sistine Madonna is best known by Raffael, in his days the Transfiguration of Christ was his most successful painting. It was on exhibition a couple of days after his untimely death in April of 1520 and more than 20.000 people came to have a look at it. The painting was actually part of a competition: Two paintings were commissioned by Cardinal Gulio di Medici. He wanted one painting for Narbonne Cathedral in France.

Knowing that competition is always good for excellent art (and science), he commissioned two paintings: One from Sebastiano di Piombo, one of the pupils of Michelangelo, and the other from Raffael. Raffael presented a masterwork and won clearly. The painting by Sebastiano di Piombo is today in the National Gallery in London and much less known than the painting by Raffael.

When we look at the Raffael painting it is obvious that in the lower half of painting something is happening. On the right-hand side, we see a young boy and this boy shows all the signs of an epileptic fit.

The eyeballs are rolled, the arms are outstretched and if the father did not hold the boy, he would fall to the ground.

Everybody is either pointing at the boy or pointing towards Christ making an obvious relationship between Christ, the Healer, and the boy with epilepsy. We can use this painting to describe clearly all the clinical sign of epilepsy to students. In fact, the painting has been used for a long time for the description of clinical signs of a grand mal fit. Interesting is also the historical background of the painting. The painting was commissioned by Cardinal Gulio di Medici. Guilio di Medici became pope Clement VII in 1523. Raffael chose a subject where the name of the Medici (doctor) is clearly associated with the healing powers of Jesus Christ and the Christian Church. He also used all his abilities to construct a lively scene with different colors and variety of expressions. The painting has a long and famous history. It was admired for centuries in Rome and in 1798 brought by Napoleon I to Paris where it was present during his wedding to Marie-Louise of Austria. It is now in the Vatican Museum in Rome and you need a good physical condition to reach it on your long walks through the Vatican Museum.

The last example on how to make a medical diagnose on paintings is also by Raffael but it includes Michelangelo, the third of the famous renaissance Italian painters. In 1508 Raffael was painting in the Vatican the walls of the personal living quarters of Julius II. On the wall in the first room, most likely the library, he painted the "School of Athens". This fresco is a daring composition where for the first time all the philosophers and scientists of ancient times and of the High Renaissance are brought together in one painting. We will not discuss all the different philosophers on the painting but concentrate on a lonely man sitting on the stairs on the left-hand side.

This lonely person was the last figure Raffael painted into the already finished painting. We know that because the last cartoon, the drawing which was made before the fresco was finished, by Raffael did not show any signs of this last figure. The man is sitting with leather boots on the stairs, rather isolated from the others and looks at a marble stone. It has been suggested for a long time that this person is Michelangelo himself.

It is rather ironic that Raffael would paint Michelangelo into this fresco. Michelangelo was during the same time painting, just a couple of rooms away, the ceiling of the Sistine Chapel. This was also a competition of the two artists, and we know from Vasari that Michelangelo kept the doors to the Sistine Chapel locked so that Raffael could not copy his paintings.

We do not know what Raffael thought but the interpretation of the lonely man sitting on the stairs looking at the marble stone has an ironic touch to it. It could say: Michelangelo, why don't you stay with your marbles and leave the paintings to me?

On closer observation the knees of Michelangelo need our medical attention. The knees are swollen. They have an irregular surface, and we ask the question: What is the condition of his knees? What is the pathology behind it? The differential diagnosis is wide, but it narrowed to either hyperuricemia, gout, venous thrombosis or arthrosis. Hyperuricemia as a diagnosis is highly unlikely because we know that Michelangelo died at the high age of 80 and we have no reports about other symptoms of hyperuricemia throughout his life.

Therefore, it could be either the venous thrombosis or arthrosis. Since we know that Michelangelo was working hard on his knees and on his back while working on the frescoes of the Sistine Chapel it could rather be that this is demonstration of a damaged knee from too much work on painting the ceiling. We know from his own descriptions that Michelangelo suffered seriously during this hard work over years and months. Especially during the wintertime, it was cold in the Chapel and he was suffering from joint pain.

These are three examples of how to find medical conditions on paintings. I have chosen these examples because of the three most famous Renaissance painters in Italy. And because all three examples have been described and discussed in the medical literature. What I like about making diagnosis on painting is that on the one hand it sharpens the wits of my students and myself, forces me to look more closely at these paintings and to use my medical eye and the medical brain to understand what is going on. In addition to find and describe “pathologies” on these paintings, it is interesting to know the background of the painting or the people who are painted in order to make not only visible diagnosis but to include the

history of the patient into the diagnosis. Lastly the history of the painting and the history of the painters widens our horizon. Last not least it provides reasons to discuss medical diagnosis. I am not sure that you are "buying" all the diagnoses I have described. Here we go, your analysis of the painting and your thoughts about the diagnosis, this is what scientific discussion is all about.

We started with the question of the blood pressure of Mona Lisa. It would be interesting to know how many of us would opt for 160/110 mm Hg. Which would indicate renal disease and, possibly, FSGS. However, the blood pressure measurement would not rule out hypothyroidism. So, in addition to her blood pressure we would like to see her shins and measure protein in the urine. This leads us into the question of the natural course of these diseases, both focal segmental sclerosis and hypothyroidism. After all, Lisa Gherardini, married to Francesco del Giocondo, the most likely model for this paining, lived for another 40 years. Her medical condition which caused swelling of the fingers and a xanthelasma must have healed by itself. It is obvious that we have more questions the further we dig into the problem. We started with a painting, a sharp eye, an open mind, and we could discuss in the best of academic tradition with students and fellows for a long time.

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# ORBITUARY

## Peter Sleight

(1929–2020)

Lars H Lindholm
Editor

It is with great sadness that I must inform you that Professor Peter Sleight, Oxford, has died on Wednesday 7 October at the age of 91. I have had the privilege of knowing him and his wife Gillian since the early 1980s and we have shared many unforgettable moments in Italy, Greece, Australia, England, and elsewhere when I was secretary of the European Society of Hypertension (ESH) for eight years and he was a member of the ESH Council from 1991 to 2000. Peter Sleight was a great source of inspiration to us younger scientists in hypertension in the 1980s, not only in the academic field, but also in his way of living, his happiness, his family, and his friendship – all good examples of how to live! Moreover, he generously shared his impressive knowledge of high-quality wines with us and others!

Professor Peter Sleight, was a distinguished internationally well-known researcher in the cardiology field and an Honorary Consultant Physician at the John Radcliffe Hospital in Oxford. He co-authored about 500 scientific papers on topics such as: blood pressure monitoring and control, autonomic control of the circulation, the prognostic value of measures of heart rate variability, the pathophysiology of ischemic heart disease, heart failure, and hypertension. Peter Sleight was also involved in studies of the effect of aspirin on ischemic heart disease and stroke prevention, as well as on statins in cardiovascular prevention. Acting in various roles, he participated in several large randomized controlled trials, e.g. the ISIS-studies, HOPE, HPS, ASCOT, ADVANCE, VALUE, and ONTARGET. His impressive scientific work has been published in several prestigious journals such as The Lancet, New England Journal of Medicine, and Circulation and has been cited more than 50,000 times, without self-citations.

In 1990, Peter Sleight received the International Society of Hypertension's Robert Tigerstedt Lifetime Achievment Award. He is survived by his wife Gillian and two sons Christopher (living in Wales) and James (living in Australia). The Society expresses its deep condolences to the Sleight family.

**Lars H Lindholm - lars.h.lindholm@umu.se**

Photograph by Christer Andersson, Umeå, Sweden

# INSTITUTE FOCUS

## The Cardiovascular Endocrinology Unit at Brigham and Women's Hospital, Harvard Medical School

ANAND VAIDYA

Cardiovascular Endocrinology Unit (CEU) Division of Endocrinology, Diabetes, and Hypertension at Brigham and Women's Hospital (BWH) and Harvard Medical School,

Boston, U.S.A.

The Cardiovascular Endocrinology Unit (CEU) is a clinical-translational collaborative located in the Division of Endocrinology, Diabetes, and Hypertension at Brigham and Women's Hospital (BWH) and Harvard Medical School, in Boston, U.S.A. The CEU is a multi-investigator, translational group that focuses on human hypertension, as well as adrenal and cardiovascular disease.

BWH has a long history of expertise at the intersection of hypertension, endocrinology, and cardiovascular medicine. Under the leadership of Dr. George Thorn, and subsequently Dr. Gordon Williams, BWH created a division dedicated to Endocrinology, Diabetes, and Hypertension, and an infrastructure to support patient-oriented research. Now known as the Center for Clinical Investigations at BWH, it currently houses a large inpatient and several outpatient research facilities with core units in dietary services, biostatistical consultation, clinical trial support, specialized research assays, genetics consultation, imaging and education. Dr. Gordon Williams was the former chief of the division for nearly 35 years, the director of the Clinical Research Center and founder of the CEU. Dr. Gail Adler is currently the section chief of the CEU and associate director of the Clinical Research Center.

There are two integrated sub-units in the CEU that are outlined below:

1)The Human Cardiovascular Endocrinology Research Group (CERG); and

2)The Basic Science Laboratories of Hormonal Mechanisms of Cardiovascular Injury (HMCI).

### The Human Cardiovascular Endocrinology Research Group (CERG)

The CERG is a multi-investigator group that focuses on human hypertension, adrenal disorders, and cardiovascular disease research by using deep-phenotyping studies, genetics, imaging, and metabolomics. The CERG currently includes 8 principal investigators, 4 to 5 post-doctoral fellows or students and nearly 20 dedicated research coordinators. CERG members pursue translational research projects focusing on a variety of topics that are often merged with clinical care centers.

- *Genetic Underpinnings of Hypertension:* For nearly three decades, CERG faculty have been investigating the complex genetics of hypertension, using the Hypertension Pathophysiology (HyperPATH) cohort. Initially created by Dr. Gordon Williams, and currently directed by Dr. Jonathan Williams, thousands of human participants have undergone deep-phenotyping protocols to characterize their underlying hormonal physiology, including the renin-angiotensin-aldosterone system, the hypothalamic-pituitary-adrenal axis.

  In parallel, genotyping using next-generation sequencing methods has created a large infrastructure to evaluate genotypic predictors of hypertension phenotypes.

- *Stress, Cardiovascular Autonomic Neuropathy, and Cardiorenal disease:* Dr. Adler and Dr. Haas lead a multi-disciplinary, translational research program focusing on hormonal mechanisms of cardiovascular disease with an emphasis on the roles of adrenal steroids, key mediators of

the body's response to stress. The research focuses on: 1. The role of the mineralocorticoid receptor in the pathophysiology of coronary microvasculature function, cardiac fibrosis/inflammation, coronary artery inflammation and renal disease in individuals with HIV, obesity, diabetes and hypertension. 2. The effects of hypoglycemic stress and activation of the ACTH-adrenal axis on autonomic control of cardiovascular function. 3. Regulation of aldosterone production, including investigations into how lipophilic statins have a novel cardioprotective effect of reducing aldosterone production by inhibiting aldosterone synthase activity.

•*Hypertension Center and Innovation:* Naomi Fisher MD is director of the clinical Hypertension Service and Hypertension Innovation at the BWH. She leads the Hypertension pathway of our remote, algorithm-driven disease management program, which utilizes patient navigators and pharmacists to initiate and titrate medications according to clinical algorithms, order laboratory tests and provide education at preset intervals until treatment goals are achieved. Clinical staff are supported by a custom-build software program that provides decision support and patient-relationship management and communication tools. This system is a model for expanding remote healthcare delivery to increase access to care, reduce health inequities, and improve healthcare quality. Dr. Fisher is also PI at the BWH for the Radiance-HTN studies investigating renal denervation with ultrasound for the treatment of patients with hypertension.

•*Center for Adrenal Disorders:* The Center for Adrenal Disorders is a multi-disciplinary center dedicated to advancing clinical care and research investigation focused on adrenal diseases. The center is directed by Dr. Anand Vaidya who works in conjunction with geneticists, oncologists, surgeons, pathologists, and radiologists to provide comprehensive care for patients with adrenocortical carcinoma, pheochromocytoma and paraganglioma syndromes, primary aldosteronism, Cushing syndrome, Addison's disease, and congenital adrenal hyperplasia. Dr. Vaidya's research program is closely linked with the clinical center and utilizes a combination of deep-phenotyping studies to investigate adrenal hormone pathophysiology, prospective intervention trials, epidemiology approaches, and a prospective registry of patients from the clinical center. Major research efforts focus on characterizing the syndrome of primary aldosteronism, the distribution of clinically relevant adrenal hormone excess that imparts adverse health effects, the pathogenesis and treatment of adrenal tumors, and improving quality of life for patients with adrenal insufficiency.

•*Pregnancy and Cardiovascular Risk:* Dr. Ellen Seely's research group studies pregnancy complications that are associated with increased cardiometabolic risk with a focus on gestational diabetes and preeclampsia. Dr. Seely's work has highlighted the higher risk for cardiovascular and metabolic disease in women who have had prior pregnancies and focuses on interventions to increase monitoring and education. She works with Dr. Rachel Blair on interventions, especially mobile-delivered ones, such as Balance after Baby and Heart Health 4 Moms to improve the risk trajectory of women with these conditions.

<u>Basic Science Laboratories of Hormonal Mechanisms of Cardiovascular Injury (HMCI)</u>

The HMCI is a multi-investigator group that focuses on pre-clinical translational, hypertension and cardiovascular disease research by using genetically modified rodents, molecular biology, imaging, diet, epigenetics, and acutely isolated or cultured cells. The HMCI currently includes 4 principal investigators, 6 post-doctoral fellows or students and a dedicated research support staff.

•*Diabetes, Nutrition, and Renin-Angiotensin-Aldosterone Lab:* Dr. Gail Adler leads a basic research group focused on understanding the regulation of the renin-angiotensin-aldosterone system (RAAS) in obesity and diabetes, and regulation by environmental factors such as dietary sodium intake and caloric restriction. Using animal models and sophisticated molecular biological techniques, her group has shown that diabetes is

associated with an activated RAAS leading to renal injury and adipose dysfunction/ inflammation; blocking aldosterone and reducing dietary sodium reduce injury. Recent studies demonstrating that statins can decrease aldosterone production by inhibiting aldosterone synthase activity suggest a novel mechanism by which some statins may provide cardiovascular benefits.

•Cardiometabolic Dysfunction Lab: Dr. Pojoga's group uses state-of–the-art approaches to perform in vivo physiology studies, ex vivo experiments using acutely isolated cells and tissues, in vitro cell culture and molecular biology techniques, as well as in silico genetic analyses on several databases. The overarching goal of her translational research is to identify the interplay between genetic variation, risk factors, and lifestyle modification interventions that modulate the etiology and progression of cardiometabolic disease. A particular focus is to identify specific hormone-related genes, their encoded signaling molecules and the related pathways that contribute to cardiovascular and metabolic dysfunction. Recently, Dr. Pojoga's Group has identified that genetic variation in the caveolin-1 (Cav-1) gene associates with decreased Cav-1 expression and with perturbed cardiovascular and metabolic function, leading to a metabolic syndrome-like presentation in both humans and mice.

•*Sex and Cardiorenal Mechanisms of the Renin-Angiotensin-Aldosterone System Lab:* Dr. Jose R. Romero's research group characterizes the mechanisms by which aldosterone and angiotensin II regulate cardiovascular and renal function using state-of–the-art cellular and animal physiology techniques in rodent models of cardiovascular disease and ex vivo human tissue. Together with Dr. Luminita Pojoga, they led the discovery of striatin as a novel regulator of the rapid/nongenomic effects of aldosterone and its interaction with estrogen. These original studies led to the discovery of striatin as a novel regulator of salt-sensitivity of blood pressure in humans and, in one of the largest human studies of its kind, he documented important differences between women and men in aldosterone and blood pressure regulation. More recently, he identified a novel role for Endoplasmic Reticulum Aminopeptidase-1 in the regulation of the Renin-Angiotensin-Aldosterone System and salt-sensitivity of blood pressure.

•*Molecular and cellular adrenal Lab:* This lab, headed by Dr. Gordon Williams, is focused on understanding the regulation of steroids in the adrenal cortex. A variety of techniques are used: genetic modification from siRNA of cells to specific gene knockout; ex vivo single cell studies; superfusion of cells or organs; assessing steroid enzyme function in intact cells; single cell secretion and RNA sequencing; CRISPR/Cas9 gene editing. Studies of environmental factors that influence steroid secretion include the traditional (e.g., angiotensin II, potassium, ACTH, sodium and potassium intakes) and novel (e.g., mTOR1, sex steroids, kinins, NO, cGMP, natriuretic peptides). Of particular interest has been the effect of sex, aging and genetics on adrenal function. Current interest includes the epigenetic factor, lysine specific demethylase 1 (LSD1) whose genetic modification in humans leads to salt sensitive hypertension, and the identification of a novel ultrashort feedback loop modifying aldosterone secretion and cross talk between the zona glomerulosa and fasciculata of the adrenal cortex.

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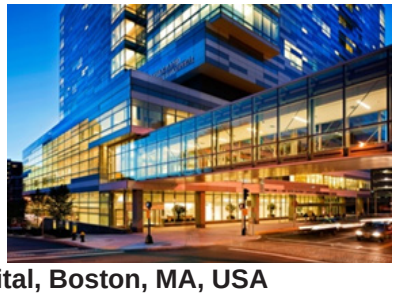

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**CEU Investigators from the CERG and HMCI:** (From left to right and top to bottom) Dr. Gordon Williams, Dr. Gail Adler, Dr. Ellen Seely, Dr. Naomi Fisher, Dr. Jonathan Williams, Dr. Rachel Blair, Dr. Andrea Haas, Dr. Anand Vaidya, Dr. Luminita Pojoga, Dr. Jose Romero.

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# INVITED PAPER

## May Measurement Month Update

NEIL POULTER

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One of the many casualties of COVID-19 was the May Measurement Month (MMM) campaign of 2020.Despite initial enthusiasm to continue with MMM20 from many MMM national leaders around the world, by March 2020 it had become abundantly clear that this years' campaign had to be deferred until 2021.

In the meantime the Global report of MMM19 was published in Hypertension[1] accompanied by a very supportive editorial[2].

The number of countries (92) and screenees involved (1,508,130) in MMM19 was marginally larger than in 2018 and a few new questions in the questionnaire generated some unique and novel findings. Surprisingly, about one third of screenees reported never having had their blood pressure (BP) measured before! We also discovered that over 500,000 screenees had hypertension (≥140/90 mmHg or on treatment for raised BP) of whom almost 60% were aware of their condition and half were on treatment. Importantly less than one half of those on treatment were receiving two or more anti-hypertensive agents. Consequently, only about 60% of treated patients had controlled BP (<140/90 mmHg) but less than 30% were controlled to <130/80 mmHg. Overall, the depressing message emerged that less than one in six patients with hypertension (as defined in this survey) were controlled to the contemporary target of 130/80mmHg.

Other data not evaluated in previous years showed a significant level of aspirin abuse amongst those

with hypertension by virtue of having uncontrolled BP levels and no history of cardiovascular disease.

The current activities in relation to these 2019 data include the analyses of the individual countries involved. Hitherto we have included the top recruiting countries in these national analyses by including only those countries where >2,500 adults had been screened.

The compilation of the 2017 and 2018 data in two European Heart Journal Supplements[3,4] have both been published and included 39 and 41 countries respectively.

However, in 2019, there will be over 50 countries eligible for inclusion. Whilst this will add to the expense of publishing the supplement, it provides a superb vehicle to feedback recognition of the hard work carried out by so many in each of the countries with sufficient screenees to make national analyses viable. Meanwhile, the countries with lesser numbers of screenees will be encouraged to collate their data across two or three years to generate their own national papers.

The central project management of MMM has now changed from Conference Collective to a company called Khanda supported by Dr Gaia Kiru who will add further scientific and administrative oversight. The handover of all relevant data from Conference Collective is currently in progress. Meanwhile, to add stability and consistency to the profile and scientific aspects of MMM a management board has been created and the composition of that board has been agreed by the ISH Executive.

Whilst it is by no means certain to take place in May 2021, funding is in place for MMM21 which is now in the planning stages. Clearly the safety of all involved must be the paramount consideration of any such planning and so the timing and methods used in the campaign may have to be modified from previous years. However, we very much hope that MMM21 will add to the more than 4.2 million adults screened by MMM to date during which time almost a million adults with untreated or uncontrolled hypertension were identified. Hopefully the MMM21 campaign will also generate unique global data relating to COVID-19.

We look forward to collaborating once again with the thousands of volunteers worldwide who have made MMM such a success to date.

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# INVITED PAPER
# HELLENIC SOCIETY OF HYPERTENSION

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DOI: 10.30824/2010-14

*The Hellenic Society of Hypertension (HSH)* was founded in 1973 and is among the oldest Societies in Hypertension in Europe. The HSH is very strong and active both in National and International levels, exhibiting substantial educational and research activities that strongly promote our vision for the constant improvement of hypertension management.

The HSH has 712 active members, mainly from three specialties (Internal Medicine, Cardiology and Nephrology), thus being one of the largest Societies in Greece. We have developed a multidimensional educational plan that aims to cover the need of continuing education in the Hypertension field:

a) **Annual National Hypertension Congress:** Takes place since 1973 and attended by more than 900 participants to discuss updated knowledge in hypertension presented by local but also international experts.

b) **Annual Educational seminars:** Held in the last 30 years attended by more than 200 physicians (mainly young). Each annual seminar take place in six Saturdays per year, simultaneously in Athens and Thessaloniki with interactive internet connection and speakers/audience from both cities. Each session is devoted to one or two main topics, focusing on the practical management of hypertension in real-life.

c) **Hypertension School:** During the last years we organized, an intensive, one-week, full-day, small group interactive training program. It takes place once or twice per year and covers the core knowledge in hypertension aiming to introducing the field to young doctors.

d) **Hypertension Day and ISH-MMM:** The HSH contributes to the global activities for improving the awareness and diagnosis of hypertension in the general population (Figures 1, 2). Six thousand adults were screened in 2019 and ten thousand are planned for the next MMM project.

e) **Three-day seminars:** These take place in several large cities across Greece, aiming to disseminate practical hypertension knowledge. Organized in collaboration with local medical associations, it usually achieves interaction with more than 100 doctors (Figure 3).

f) **Journal:** Official journal of the HSH is the "Arterial Hypertension", published in Greek every 3 months since 1992. It presents original research, review articles, case-reports, the activities or hypertension centers, and short timely reviews by distinguished International experts. It is distributed to all HSH members and primary care physicians interested in hypertension and is freely available online.

g) **Research:** The HSH members have impressive research activities covering the whole spectrum of hypertension research, from bench to bedside: pathophysiology, blood pressure monitoring, work-up, lifestyle and pharmacological management, resistant and secondary hypertension, and special populations. These research activities result in the publication of more than 300 papers in peer-reviewed journals each year, some of them in the

most prominent journals. Greece in consistently among the top 5 countries in accepted abstracts in the ISH and ESH congresses each year.

h) **Grants & Scholarships:** The HSH strongly supports research in hypertension by offering each year up to 10 grants of € 10,000 to fund research projects in hypertension, particularly focusing in supporting young investigators. So far, more than 50 young doctors have worked for a year in clinical research in hypertension with funding by HSH grants.

The HSH has a successful past, an active present, and a promising future. The longstanding and intense activities of the HSH are internationally acknowledged, as reflected by the establishment of 17 Excellence centers throughout Greece with 78 hypertension specialists, the large number of Greek lecturers in ISH and ESH congresses, the leadership of Working Groups by Greek experts, and the election as Board members in the ISH and the ESH. The current board continues and expands efforts to improve the care of hypertension in Greece and to further promote educational and research activities in cardiovascular medicine.

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Immediate Past President: G. Stergiou

*Figure 1*


*Figure 2*


*Figure 3*


George Stergiou - stergiougs@gmail.com

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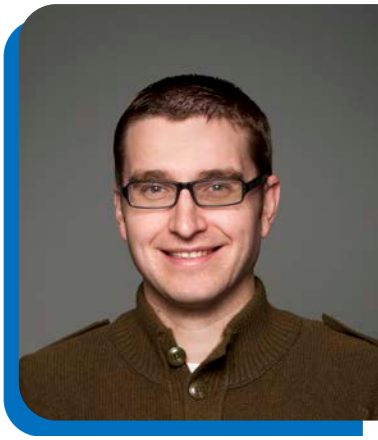
Find out more about the New Executive Council here

# REPORT ON 2020 ISH MEMBERSHIP SURVEY



DYLAN BURGER
Ottawa Hospital Research Institute
Ottawa, Canada

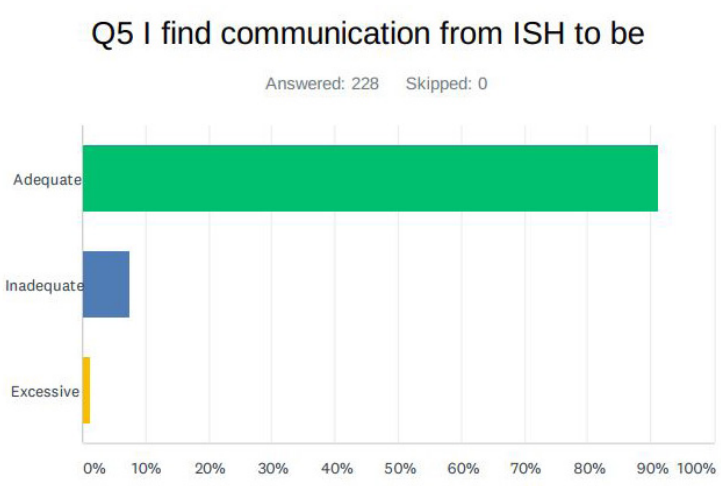
This summer, the ISH conducted a survey of membership for the first time in over ten years. The goal of the survey was to gain a better understanding of the demographics, satisfaction, perceptions, and needs of our members. The format prioritized convenience to members and consisted predominantly of multiple choice with the occasional open-ended question. All ISH Committees were provided the opportunity to submit questions and this was complimented a series of 5 optional questions related to the management of hypertension.

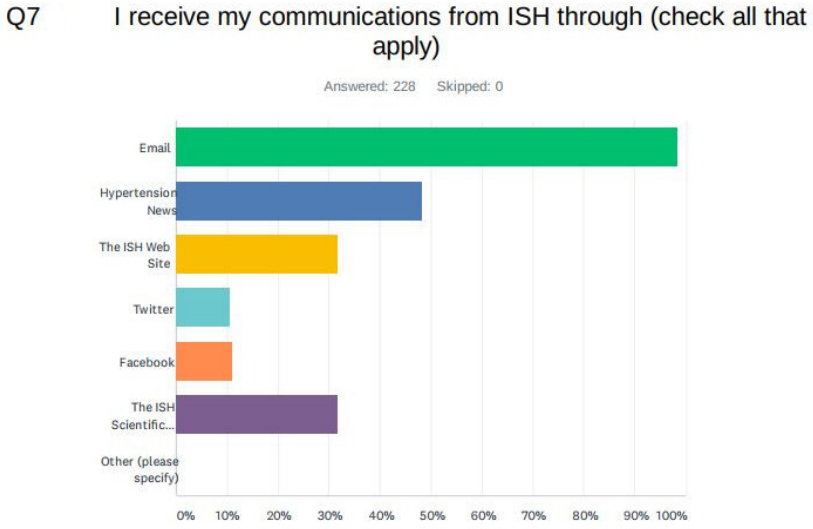
Response to the survey was strong with more than 220 members participating with good representation across regions, career stage, and discipline. A summary of findings from the multiple-choice component of the survey was assembled. While it was not possible to present all open-ended responses, several overarching themes were apparent:

- Members were broadly happy with the value of ISH membership and the strength of its communication
- Members would like to see more regional-specific communication
- Members would like more information on funding opportunities in hypertension
- Members are very interested in volunteering opportunities within ISH
- Certain members feel that their community and interests could be better represented in ISH leadership

In the coming months ISH Council will review the results of the survey and incorporate them into their decisions on the strategic directions for the ISH. If you wish to view the results of the survey then you may access them below.

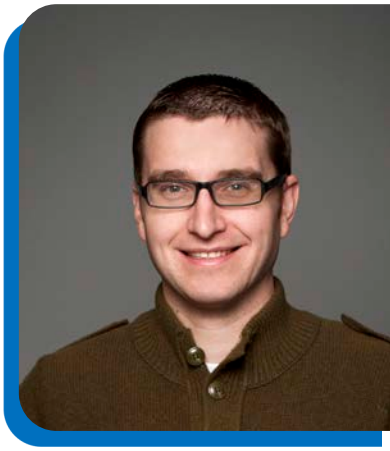
**VIEW SURVEY RESULTS**




Dylan Burger - dburger@uottawa.ca

# 2020 NEW BLOOD LEADERSHIP CAMPAIGN



DYLAN BURGER
Ottawa Hospital Research Institute
Ottawa, Canada

The "New Blood" campaign was an initiative to increase diversity of representation and reinvigorate ISH leadership through recruitment of new leaders to ISH committees. To achieve this goal, a digital media-driven campaign was designed in consultation with the membership committee and the incoming ISH president. Calls for expressions of interest were shared with ISH membership throughout August and September of this year, paired with regionally targeted calls to the broader cardiovascular research community. Promotional videos featuring several ISH leaders describing their experience with ISH committees were prepared and may be viewed on the ISH YouTube Channel. Response to the campaign was quite strong with more than 100 expressions of interest from more than 20 countries. In the coming months many of these individuals will be incorporated into ISH committees where they will add their voice and efforts to the global fight against raised blood pressure. We would like to thank all ISH membership who participated in the campaign or shared the call with their personal networks.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# How COVID-19 Has Affected My Career: The Power of Resilience and Mentorship

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DOI: 10.30824/2010-15

It was in February 2020 when I attended my last conference in person; an opportunity and memory that I cherish so much right now. In an afternoon session focusing on Early Career Researchers, it was unanimous that resilience was the word best defining the key skill for success. During dinner time, a group of colleagues and myself were discussing the word resilience again and wondering how far we have had developed this important skill and if it is even a skill to develop or something we needed to have as a gift. Little we knew what the future was holding for us in just a few weeks ahead.

If you search its definition, resilience is the capacity to recover quickly (or not so quickly) from difficulties. It is the process of adapting well in the face of adversity, trauma, tragedy, threats or significant sources of stress accordingly to the American Psychological Society (APS) (https://www.apa.org/topics/resilience). Before COVID-19, we all exercised it to bounce back from professional hurdles involving a rejected manuscript that you worked so hard to put together, that non-funded grant you worked on hours and days and the dream job or promotion you were also not the first option despite ticking all the boxes and sacrificing so much to be competitive for it.

COVID-19 is an insidious presence in our everyday lives now, affecting us not only in a professional level, but also on our personal lives. Lab closures, early career and other science related professionals on furlough schemes, social distancing, online teaching, school closures (and home-schooling) and the fear of losing loved ones were, between others, the many problems most of us, if not all of us, had to go through and deal with until now. You may be asking yourself if there is a piece of good news here. The answer is Yes! Resilience is a skill that you have been developing throughout your career. But now, the learning curve has made a steep turn and, while searching ways to strengthening my resilience, I found a few tips on how to further develop or learn the resilience skill that I would like to share with all ISH trainees.

It is imperative that we give priority to empathetic and understanding relationships, where the certainty of you are not alone is clear. Although we are currently social distancing, total isolation should not be the case. As we move to a more online approach in order to work and interact with our peers, try and learn the perks of online platforms for meetings, co-workers/collaborators/people engagement and social media. Exercise the full concept of community and be collegial more than ever. You must be proactive in facing your problems and enter the famous journey of self-discovery, learning from your small steps towards your goals but also from your vulnerability and mistakes. Make realistic plans and goals and move forward and towards them, no matter at what pace. Embrace the positivity around you by keeping things into perspective and avoiding drama, accepting the changes in your work life but still maintaining a positive outlook. I love this sentence from the article I read: “What is happening isn’t how your future will go. You can’t change an event, but you can change how to interpret it or respond to it” (David Palmiter and colleagues for the APA website) (for more detailed info visit: https://www.apa.org/topics/resilience).

Another must do tip is to seek help, in the form of mentorship. Prof Ruth Gotian published an interesting and helpful column in Nature (April 2020 - doi: 10.1038/d41586-020-01028-x) giving some notes on how mentors can create an excellent mentoring environment striving for a healthy relationship with your trainee, while keeping a productive and focused career progress.

In the article, she suggests that mentors should: (1) maintain check-in conversations (via emails, texts or video-calls); (2) draft a to do list containing activities that are not lab centric but still develop important skills, such as performing literature reviews, preparing a manuscript outline, reading papers often left for later, preparing/planning fellowship applications or small grants (or even grants in general) between others; (3) listen more and accept that you can't fix your trainees problems; (4) have lower expectations without demanding a high level of productivity or flawless work and finally; (5) focus on important tasks or activities that will contribute to a healthy physical, emotional and psychological state.

But this is not only for mentees with mentors in their lives, as many of our ECRs may not have a mentor or be part of a programme that foster their professional growth. This is where we from the Mentorship and Training Committee (ISH-MTC) come into play and can help you. We have an outstanding mentorship programme where we pair you with an internationally recognized mentor willing to guide you through the highs and lows of the scientific path. Our work is also only getting better, so keep in touch and an eye open for this space, as we plan many more exciting initiatives for all ISH ECRs. We would also love to hear from you about your experiences and needs, so please, don't hesitate to contact us and share your stories.

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# ISH mentoring program experience

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DOI: 10.30824/2010-16

The year of 2020 has impacted our lives in many ways. As a fresh PhD graduate, I started my early career postdoc journey in 2020 with curiosity and enthusiasm. However, for a long period, my mind was flushed with negative news about increased COVID-19 numbers, death, lock down and job insecurity. One of the most valuable experience I have had during such time is to be part of the ISH mentoring program. I am very fortunate to have Professor Rhian Touyz as my mentor, since she is a very successful researcher whom I admire greatly. Although we have never met in person since the commencement of our mentoring program, Rhian is not only willing to share her career journey with me but, also, she is very happy to share her personal story. Her sotry has inspired me in many ways. For example, I have learnt from her to have a positive mind and work hard to achieve my goals rather than being influenced by the negative news around me. Although it is only the start of the ISH program, I have been enjoying every meeting, after which I reflect on our discussions and start looking forward to our next meeting! When I asked Rhian "why does she still want to be a mentor to someone she has never met when she has already had a super-busy schedule", her answer was very simple: to support and help. Through our conversations, I can always experience the supportive and friendly international environment for young scientists. Finally, I'd like to show my appreciation by thanking the ISH committee for providing such a valuable experience for young scientists and such a great opportunity to learn from experts who can provide an international perspective on science and career advice to young scientists at the start of their journey.

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# Starting a PhD during a pandemic


## CHUDAN XU

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DOI: 10.30824/2010-17

In 2015, I migrated from Argentina to Australia to study Bachelor of Biomedical Sciences. I have recently finished my honours degree during the early outbreak of the SARS-CoV-2 pandemic. I have not seen my family in three years and a half, so I had initially planned to have a break and visit them before I started my PhD. However, due to COVID-19, the shutdown of the Australian boarder, states lockdown and many other restrictions, I decided to start my PhD earlier than I had planned. In addition, I was lucky that the university made some exceptions for the application process, allowing me to fast-track my study. Foremost, my supervisor, Associate Professor Francine Marques, has been tremendously supportive and helpful in both of my academic and personal life. I am so grateful that I had the opportunity to start my PhD journey during this challenging time.

I may say almost everyone around me has never experienced living in a pandemic. It is the first time that we are working and studying from home for such a long period, where everything is virtual. I always believe that all things have both sides. Staying at home means not hanging out with my friends and colleagues, restricted outdoor activities, and most importantly, postponed lab work. However, working from home allows me to wake up later, save time from commuting, and join international conferences without hours of travelling and jet lag.

Working from home is not a big challenge for me. I have my own quiet space that I am used to study in. I like to keep my working-desk clean and organized, which makes me feel pleasant to sit and work. Although being at home, I like to wear outdoor clothing. Personally speaking, wearing pyjamas increases the chance of lying on a couch, bed or somewhere else comfortable at home. Besides, it is a good way to separate my work and personal lives. Since everyone is different, I will say that you should try different routines to find out which one suits you better and makes you most comfortable and efficient, then stick to it.

There are two things that help me a lot during this time. Firstly, accept the fact that sometimes I can be less productive and have little progress. I used to be very anxious when I had unproductive days, and the anxiety made me even less efficient. It was a vicious cycle. Now, when I encounter this type of situation, I will walk outside, sunbathe or do something I enjoy. Then, I will try to have a fresh start for the next day. Secondly, I practice gratitude. I write down three or more things that I feel grateful for each day. This is more powerful than I thought it would be. In my gratitude journey, I learned that "in daily life, we must see that it is not happiness that makes us grateful, but gratefulness that makes us happy" – David Steindl-Rast.

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# Juggling COVID, work and family

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DOI: 10.30824/2010-18

If I could send a message to my pre-2020 self, I would say: Everything is not perfect, but these are great times, enjoy!

When I got the email in mid-march from my children's school that in-person instruction was immediately suspended until further notice, I shrugged and thought "oh well, that will give me a little break from getting up at 5:00 am every day to prepare breakfast, make the lunch my children will take to school and get them to the bus stop by 6:37 am". Fast forward 7 months later, research and participant recruitment have resumed on campus, but there is still no clear plan for when my children's school will resume in-person instruction. What a break!

For an early career scientist with no nanny, doing human research, who does not have the luxury of running experiments in the evening or at night, I find myself with the dilemma of prioritizing my research and work or prioritizing my children's instruction during this COVID-19 pandemic. In previous years, I believed that if I could work from home one or two days a week, I would be more productive. However, in 2020, I spent months working solely from home and yet struggled to stay productive. With the constant distraction of my children's instructional, nutritional and health needs, on top of their need for attention, it is hard to focus and complete any task requiring more than minimum brain cells. Juggling the daily zoom meetings while taking care of my children meant that the daytime work productivity was almost nil. Therefore, nighttime became the appointed time for serious and uninterrupted work. When I wasn't too exhausted and was able to be productive during those late hours, I paid the price of sleep deprivation the next day. As many parents, I normalized sleep deprivation over the years despite knowing its health consequences; but staying home because of COVID-19 created an additional anxiety-induced sleep deprivation. I am nevertheless privileged that my husband and I remain employed and are able to work from home and be present for our children during this pandemic. I don't take that for granted!

I learned a few things while juggling family and working from home because of COVID; some things that I wish I applied and some that I did. In retrospect, I realize that I didn't have to cook dinner every day. A few take out dinners a week could have freed some time for work or self-care. My house didn't have to be tidy all the time. Nobody was visiting anyway! However, I was able to get my children to pick up chores and help with cleaning, dishes, laundry and more. I want to stress that every parent should find out and do what works best for their family in a situation like this. At the end of the day, it is better to have a sane mind and a messy house than an insane mind and a tidy house. A silver lining during this pandemic is how supportive and understanding students, colleagues, mentors and collaborators were (and still are) of the various interruptions and zoom bombing by children; who always happen to need something in a middle of a zoom meeting. I am truly grateful to the non-parents who have not made me feel incompetent or unprofessional during these unusual times we are still living in.

One particular challenge that parents like me who typically work outside the home have been facing, and for which we weren't prepared was the sudden fusion of three spaces that are normally separate in our daily life: the work space, the school space and the domestic space. Daily activities that take place in each space were suddenly all brought together to collide into the home/domestic space. I realized that finding a way to structure the house space and the routine, in order to minimize this fusion of spaces was very helpful. Depending on the size of your home, setting a separate space for kids' school and one for your work could minimize interferences and help improve productivity for all. To be honest, it didn't always work for us.

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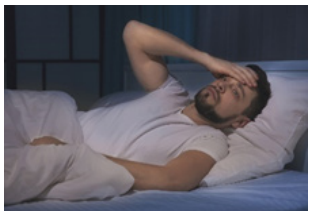
# OMRON ACADEMY

## New course on OMRON Academy Online: Nocturnal blood pressure



Nocturnal hypertension is a significant risk factor for cardiovascular diseases. Patients with an optimal blood pressure during the day can still be at risk for cardiovascular events if their blood pressure is elevated at night. However, there are still many uncertainties regarding the mechanisms of nocturnal hypertension.

Learn more today about the cardiovascular risk, pathogenesis and measurement of nocturnal blood pressure and stay in the know for more courses on nocturnal hypertension and sleep.

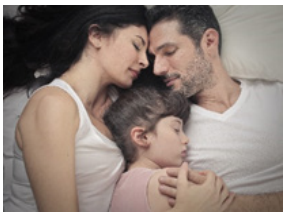
[Preview course link: https://omron.platform.co.nl/#/share/Hypertension/Sleep_&_Nocturnal/Nocturnal_blood_pressure/7a8c667e-c74e-4f56-a150-75661b8d611d/1]

## New course on OMRON Academy Online: Obstructive Sleep Apnea

Obstructive Sleep Apnea is considered a global issue with significant implications on global health and quality of life. It is characterized by recurrent episodes of upper airway obstruction occurring during sleep. There is also a linear association with obesity and hypertension. Learn more about the diagnosis and treatment in the new course and continue earning your CME points with OMRON Academy Online.

Preview course link: https://omron.platform.co.nl/#/share/Hypertension/Sleep_&_Nocturnal/Obstructive_Sleep_Apnea/13f684a9-ee60-489a-b5c1-73603d87eec7/1]

## New course on OMRON Academy Online: Sleep



Do you know that one-third of a human life is spent sleeping? Sleep is characterized by a complex biological state of behaviors, physiological and electrophysiological parameters. It is regulated by internal clocks. It is well known that during sleep the body recovers, but how much sleep is actually needed and what happens with a lack of sleep? Find out more about the importance of sleep in this new course.

Preview course link: https://omron.platform.co.nl/#/share/Hypertension/Sleep_&_Nocturnal/Sleep/0dafc0a4-5a75-4907-8374-76ad357f4b07/1]

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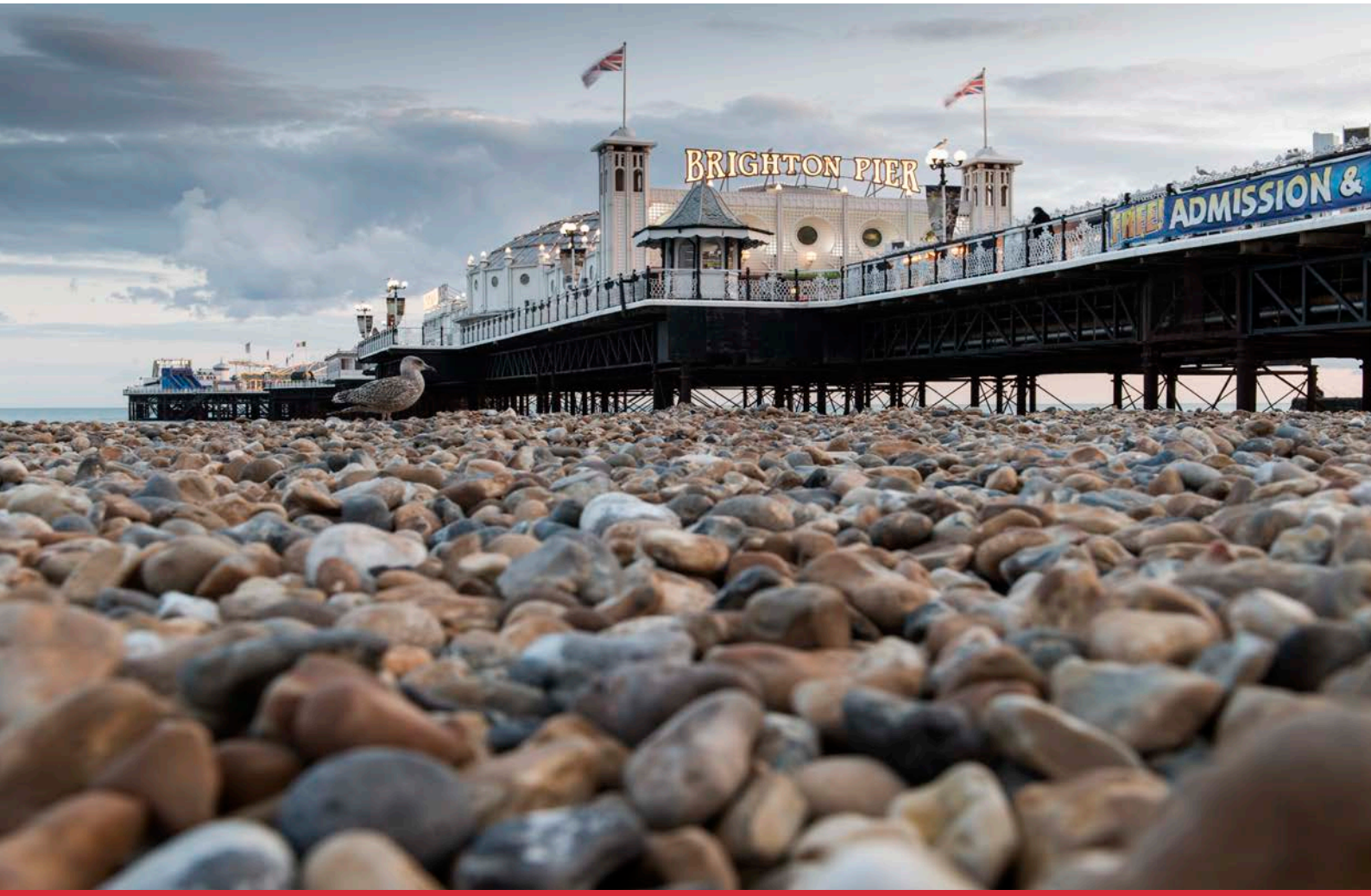


# British and Irish Hypertension Society Annual Scientific Meeting 2021

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**Medtronic.com/hypertension**

**35%**

of treated hypertension patients remain uncontrolled.[1,2]

**50%**

Nearly 50% of patients become non-adherent to therapy within one year.[3]

**2x**

Non-adherence levels double when patients move from 2 to 3 drugs.[4-6]

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**References**

[1] CDC. Vital Signs, 2012;61(35):703-709. Available at: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm6135a3.htm. Accessed May 22, 2019.
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