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IN THIS ISSUE

FROM THE EDITOR

NEW BLOOD - A recruitment strategy of new, highly motivated ISH members to enhance the Society's future leadership

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Editor

Dear member,

Again, it is my pleasure to present a new issue of Hypertension News – said to be one of the flagships of the Society. We are delighted that the previous issue, (Opus 63), published in October 2020, was accessed by 9,115 readers in three months, the second highest number so far.

Today's Newsletter has a new cover and more space has been given to five early-career scientists under the banner of "New Blood" (pages 28 - 36). To make this possible, we have shortened the reports from the ISH Executive. For those who want a more detailed update on ISH matters, I recommend the monthly ISH Bulletin. Moreover, in this issue you will also find two excellent reports from the Chairs of the New Investigator Committee (page 37) and the Women and Hypertension Research Committee (page 39), written by Brandi Wynne and Ulrike Muscha Steckelings respectively, on where they want to take their committees in the coming years.

The "Learning the Ropes" section (pages 6 - 18) is on pulmonary hypertension with four excellent papers written by distinguished and internationally well-known authors with focus on: genetics, pathophysiology, old and new treatment, and "the clinic". The topic was chosen since many of us know little about this difficult condition caused by a heterogenous group of diseases, where treatment should be directed at its primary cause(s). Prognosis is poor with a short-expected survival of 2-3 years from the time of diagnosis. With modern therapy, however, some improvements have been seen.

May Measurement Month (MMM), ISH's, global campaign to raise awareness of the need for people to get their blood pressure checked will be back in 2021. After three successful years, 4.2 million people have been screened in about 100 countries, and almost 1 million people have been identified with untreated or inadequately treated high blood pressure. This year, the timing of screening has been extended to run at any time between May and November due to the current Covid-19 pandemic. Neil Poulter gives a report on page 41, entitled "Sleeves up, Risk Down", on how this is planned and we can just wish him and his co-workers good luck with their important undertaking, another flagship of the Society.

The Institute Focus in this issue is written by Iris Jaffe from the Molecular Cardiology Research Institute at Tufts Medical Centre in Boston, MA (page 42). I strongly recommend you to read this well written paper on advancing our understanding of molecular mechanisms of CVD and translating these discoveries into improvements in patient care.

I hope you agree with me that there is a nice mix in this issue of a combination of younger members with enthusiasm and vigor (New Blood) and older members with experience giving us hope for the future and longevity of the Society.

Finally, many thank to my outstanding team special welcome to Charlotte Mills, representing the early career scientists on the team and special thanks to Araceli for her administrative work.

Have a good read!

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NEWS FROM THE CHAIRMAN OF THE ISH COMMUNICATION COMMITTEE

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ISH Officers and Committees 2020-2022

The ISH Officers and Committees for the current presidential term have been finalized. The committee structure has been expanded and committees feature many new leaders identified through the recent New Blood campaign.

The current ISH Council can be viewed on the ISH website

The full list of ISH Committees and Chairs can be viewed on the ISH website

ISH Live: Inaugural event to be held on 25th March

The ISH New Investigator Committee has launched a new networking initiative called "#ISHLIVE"

These virtual events will be home to panel discussions, webinars, scientific discourse and social activities, all focused on helping trainee to early career investigators (pre-tenure) move their careers forward. The first event "Discovering the ISH" will be held on March 25th. More details can be found in Brandi Wynne's feature on p 37

Women in Hypertension Research Network

The ISH Women in Hypertension Research Committee will soon by launching a new research network to encourage, support and inspire women in science and medicine in the field of hypertension. For more information on the ***Women in Hypertension Research Network*** sure to check out the feature from Prof Muscha Steckelings on p 39.

New ISH website:

The ISH is currently undergoing a major redesign of our web site. We aim to launch next month and look forward to feedback from members.

ISH branded merchandise now available through Zazzle

Do you wish to show your support for the ISH? Do you simply love the logo? ISH branded coffee mugs, shirts, and other merchandise are now available through our online store. A portion of sales goes to support the ISH.

Store: https://www.zazzle.ca/store/ish_online_store

Save the Date: World Hypertension Day

A reminder to ISH Members that World Hypertension Day will return this year on May 17th. The theme for the 2021 campaign, which is led by our partners the World Hypertension League is "Measure Your Blood Pressure Accurately, Control It, Live Longer". For more information visit the WHL website

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HOT OFF THE PRESS: CLINICAL

Bibliometric information to study trends in hypertension research

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Research on hypertension can go in different directions. When these efforts can be brought together successfully (today sometimes described as translational research), this will help research move forward. In this context, a recent publication on how bibliometric information can be used to study trends in hypertension research is of interest. Bibliometric analyses provide objective information on scientific output within a defined area (such as hypertension, vascular medicine or cardiovascular disease) or in general terms, and can be used to compare and evaluate activity. Alas, this is commonly used for scientific ranking, for giving priority to recourses, and for political decision making.

Devos and Ménard[1] recently published interesting findings from bibliometric analyses on more than 90 000 published original articles concerning hypertension during 1999 through 2018, complementing their earlier publication on trends in published hypertension research in Europe[2]. Among the 20 countries contributing the most hypertension related articles, most work comes from the United States (30%), followed by Japan (11%), China (9%), United Kingdom (7%), Germany (6%), Italy (6%), Canada (5%), France (4%), Australia (4%), and Brazil (4%); while all European countries among these 20 taken together represent 39%. However, temporal trends show a different pattern. Here, China shows the greatest increase in number of publications, followed by South Korea, Poland, Brazil, and Turkey; while France and Japan show a (small) decrease in number of articles over time. Of note, the increase in published work in hypertension during this study (43%) was less than the increase observed for cardiovascular (64%) or biomedicine (96%). The authors further studied spatial trends for international collaborations and show that during 1999-2003 there were three clusters: the European Union; the Nordic countries; and the United States, Germany, and United Kingdom. This changed towards the end of the study (2014-2018), where two clusters were observed: The United States, United Kingdom, Canada, and China; and Germany, Italy, the Netherlands, and France. Finally, the authors show that only four out of the 20 countries (i.e., United Kingdom, Denmark, Taiwan, and Poland) increased hypertension specific research performance more than research as a whole, as based on bibliometric data.

Thus, the number of publications in hypertension increases over time, but less than other areas within cardiovascular medicine and biomedicine. This should call for action. Time trends for countries and clusters show changes, suggesting that the way researchers collaborate is changing. This may be important for hypertension research to reach out globally. Finally, whether these findings should prompt researchers, journals and publishers to adopt the way of collaborating and publishing hypertension research, to the benefit of our patients, warrants further discussion.

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HOT OFF THE PRESS: BASIC

Let's AIM2 find treatments for vascular dementia

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Vascular dementia is responsible for up to 30% of dementia cases, and is described as cognitive impairment arising from cerebrovascular disease leading to impaired blood flow to the brain[1]. However, vascular complications are evident in other forms of dementia, and many patients are diagnosed with mixed dementia where they have both a neurodegenerative disorder such as Alzheimer's disease and cerebrovascular disease[1]. At present, there are no disease-modifying therapies available for vascular dementia and current treatments can target symptoms only as the underlying mechanisms are not well understood.

Inflammation is emerging as a potential key player in the pathophysiology of dementia. Sustained inflammation appears to have detrimental effects in the brain and can promote cerebrovascular dysfunction, oxidative stress, white matter injury and blood brain barrier (BBB) breakdown – all processes currently thought to contribute to the pathophysiology of vascular dementia[1]. Inflammatory responses are initiated through the inflammasome, a multiprotein complex that produces mature IL-1β and/or IL-18. Inflammasome complexes comprise a pattern recognition receptor (PRR), an apoptosis-associated speck-like protein containing a caspase recruitment domain (ASC) and caspase-1. Different inflammasomes are characterised by their PRR such as nucleotide-binding domain and leucine-rich repeat containing family pyrin domain containing 3 (NLRP3) and absent in melanoma 2 (AIM2)[2].

A recent paper by Poh L et al in Molecular Psychiatry has added to our understanding of the role of inflammation in vascular dementia. This elegant study demonstrated that the AIM2 inflammasome contributes to the pathophysiology of bilateral carotid artery stenosis (BCAS), a mouse model of vascular dementia[2]. Chronic cerebral hypoperfusion – which is caused by experimental BCAS – is a major cause of vascular dementia due to chronic cerebral hypoperfusion-induced brain injury[2]. Using this model, Poh et al found upregulation of the inflammasome receptors including AIM2 in the cerebral cortex and hippocampus – regions that play a critical role in cognitive function. The products of inflammasome activation, IL-1β and IL-18, were also found to be increased in the cerebral cortex and hippocampus of BCAS mice specifically in a spatial and temporal manner. There was also evidence for brain injury including elevated apoptosis, pyroptosis, glial-cell activation, white matter lesions, myelin breakdown and hippocampal neuronal loss in BCAS mice. Interestingly, double stranded DNA – the only known agonist of the AIM2 inflammasome receptor – was increased in the serum of BCAS mice. Involvement of the AIM2 inflammasome in BCAS-induced brain injury was confirmed using AIM2-deficient mice in which there was blunted BCAS-induced inflammasome activation, IL-1β and IL-18 levels and brain injury.

Importantly, AIM2-deficiency also reduced BCAS-induced cognitive decline.

Inflammasome activity has been implicated in the pathophysiology of major cardiovascular risk

factors for vascular dementia, such as hypertension and stroke. Specifically, the AIM2 inflammasome has been now also shown to contribute to brain injury and cognitive impairment following stroke[3].

Many stroke patients go on to develop cognitive deficits, and approximately 30% of patients that survive a severe stroke develop dementia within 1 year[1]. Hence, the study by Poh et al is consistent with the concept that AIM2 inflammasome antagonists may have therapeutic potential to reduce the risk of developing vascular dementia after stroke, or indeed to treat overt vascular dementia. Currently, there are no drugs available that specifically target the AIM2 inflammasome but there are commercially available drugs which target its inflammasome partner, caspase-1. Importantly, VX-765, a caspase-1 inhibitor, has been shown to reverse cognitive deficits and brain inflammation in a mouse model of Alzheimer's disease[4]. Alternatively, interleukin products of inflammasome activation in vascular dementia could be targeted with clinically available antagonists for IL-1β and its receptor (IL-1 receptor) drugs which are currently used to treat several forms of arthritis[5].

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LEARNING THE ROPES: PULMONARY HYPERTENSION

Introduction

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Pulmonary hypertension is defined as an invasively measured mean pulmonary arterial pressure (mPAP) of more than 20-25 mm Hg at rest (normal values are 12±2 mm Hg) or more than 30 mm Hg during exercise. Non-invasive measurements by echocardiography provide estimated systolic pulmonary arterial pressures (sPAP), and are considered normal if below 35-40 mm Hg. Pulmonary hypertension may appear spontaneously, with no known underlying disease, or it can occur in connection with other conditions. While pulmonary arterial hypertension (previously known as primary pulmonary hypertension) has a relatively low prevalence (approximately 10-15 cases per 1 000 000 people), connections to other diseases such as pulmonary thromboembolism, chronic lung diseases including fibrosis, hypertensive heart disease, and chronic heart failure are more frequent. The most common cause of pulmonary hypertension, however, is chronic obstructive pulmonary disease (COPD).

Patients (mostly women) with pulmonary hypertension have an insidious onset of exertional dyspnoea and their condition often comes to attention of the doctor late in the course of the illness or when symptoms and signs of right ventricular heart failure develop.

Since pulmonary hypertension is a condition caused by a heterogenous group of diseases, treatment should be directed at its primary cause(s). Patients who have symptoms resulting in a limitation of physical activity and those who have symptoms at rest used to have a poor prognosis, with a short (2-3 years) survival from the time of diagnosis. With modern therapy the prognosis has improved. The cause of death is usually acute right ventricular heart failure or sudden death.

Below, we have invited a group of distinguished authors to discuss pulmonary hypertension with a focus on genetics, pathophysiology, treatment (now and in the years to come) and clinic. Have a good read of four excellent papers on a topic many of us know little about!

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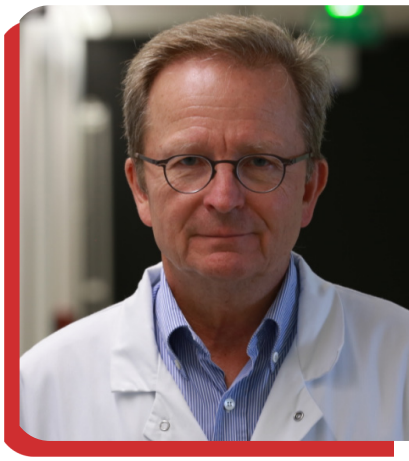
LEARNING THE ROPES: PULMONARY HYPERTENSION

Genetic architecture of pulmonary hypertension: From gene discovery to genetic counseling



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The genetic architecture of group 1 pulmonary hypertension (PH), including pulmonary arterial hypertension (PAH) and pulmonary veno-occlusive disease (PVOD) has deeply changed during the last 20 years. BMPR2 (coding for bone morphogenetic protein receptor type-2), the first and major gene linked to heritable PAH, was identified in 2000 through genetic linkage studies in several large multiplex families[1]. Whole exome and whole genome sequencing in affected families or in large populations of cases and control subjects allowed identification of a few predisposing genes involved less frequently in heritable PAH.

The BMP (bone morphogenetic protein) pathway genes are the major genetic actors of non-syndromic heritable PAH since pathogenic loss-of-function variants were identified at the heterozygous state in affected PAH patients, confirming that heritable PAH is transmitted as an autosomal dominant disease with incomplete penetrance (i.e. % of mutation carriers developing the disease), because only 14% of male mutant carriers and 42% of female carriers will develop the disease[2] BMPR2 is a type II receptor of BMP ligands and dimerizes with ALK1 (Activin receptor-like kinase 1) and the co-receptor endoglin in endothelial cells, and the complex activates intracellular signaling and nuclear transcription of target genes though signaling intermediates that are Smad1/5/8 and the coreceptor Smad 4[3]. Indeed, pathogenic variants of *Smad9*, encoding Smad8, were also rarely reported in PAH cases[4,5]. Rendu-Osler disease (hereditary hemorrhagic telangiectasia, HHT), a hereditary vascular disease presenting with telangiectasias, epistaxis and visceral arterio-venous malformations, was shown to be linked to two major genes, *Endoglin* and *ACVRL1* (encoding ALK1)[6,7]. PH can develop in HHT patients by arteriovenous malformations causing left-to-right shunts and high-throughput heart failure, but precapillary PAH can also develop with histological remodeling similar to idiopathic PAH. In this latter case ACVRL1 was identified as the gene of PAH complicated HHT[8]. Other genes of the BMP pathway have been involved in heritable PAH such as Smad9 in which rare pathogenic variants were found in PAH families[4]. Heterozygous loss-of-function (LOF) variants of GDF2 encoding BMP9 (Bone morphogenetic protein 9) were initially described as responsible for a particular form of HHT and a homozygous child carrying a LOF variant of this gene was reported with severe PAH[9,10]. Finally, GDF2 heterozygous pathogenic variants were shown to be associated with PAH in a large whole genome sequence-based association study[11]. These results were subsequently confirmed in European and Asian patients[5,12]. A close paralog of GDF2, BMP10, was also investigated as a candidate gene and found mutated in rare cases in two studies[5,13].

The systematic search for gene mutations, has shown the presence of pathogenic variants in approximately 20% of sporadic PAH whereas this proportion reaches 80% in familial cases, mainly represented by BMPR2[5,14]. *BMPR2* and *ACVRL1* mutation carriers develop PAH at an earlier age than mutation non-carriers in both sexes, and the age at death is also younger, both parameters varying among studies and the genes involved[15]. A follow-up study showed that in a quarter of asymptomatic BMPR2 mutation carriers, mild or exercise-induced pulmonary hypertension could be detected and additional cases were detected during follow-up, yielding a PAH yearly incidence of 2.3%[16].

Another group of heritable PAH is due to LOF mutations occurring in three genes important for lung development. These genes are *TBX4, SOX17*, and *KDR* (coding for VEGFR2/FLK1). The *TBX4* gene encodes a transcription factor important for lung and bone development, T-box transcription factor TBX4. Heterozygous LOF mutations lead to the small patella syndrome, an autosomal dominant skeletal syndrome[17]. In a small proportion of TBX4 mutation carriers, PAH develops at various ages of onset, from neonates to adult patients[18–20]. Clinical presentation, hemodynamic parameters and histological lesions are similar to idiopathic PAH. Some elements suggest a parenchymal lung involvement of developmental origin in affected patients, such as abnormal distal lung development, small size of the lung, and low diffusing capacity for carbon monoxide adjusted for hemoglobin ($D_{LCO}c$), although some TBX4 mutation carriers seem to have an exclusive vascular involvement[20].

The *SOX17* gene, coding for the transcription factor SOX-17, was identified as a PAH gene through a whole genome sequencing (WGS) gene-based association study and a single nucleotide polymorphism based genome wide association study[11,21]. A whole exome sequencing (WES) study in PAH associated with congenital heart diseases clearly indicated the involvement of this gene[11]. Indeed, *SOX17* is expressed in arterial endothelial cells of the embryonic vasculature and conditional deletion of *Sox17* in mesenchymal progenitor cells demonstrates that *Sox17* is required for normal vasculature morphogenesis and normal cardiac morphogenesis.

Preliminary evidence for a responsibility of the *KDR* gene encoding VEGFR2, the main receptor for vascular endothelial growth factor A (VEGF-A) was initially suggested by a WGS-based association study[11]. Subsequently, two *KDR* pathogenic variants were found in a prospective study in PAH patients from two different families[22]. In both families, affected mutation-carriers had a reduced $D_{LCO}c$, from 19 to 35%, consistent with parenchymal lung involvement observed on high-resolution CT scan. A reduced $D_{LCO}c$ is also observed but to a lesser extent in non-affected mutation carriers. This parameter can therefore be used as a biomarker of the disease in the context of this genetic predisposition[22]. A subsequent association study based on WES showed additional KDR pathogenic variants in PAH[23]. Since expression of KDR is high in human embryonic endothelial cells, and VEGF signaling has a major role for proper blood vessel and epithelium-capillary bilayer formation and maintenance, it is likely that defect in VEGF signaling resulting from KDR haploinsufficiency might impair lung vasculature development and alveolar maintenance during postnatal life (reviewed in [22]).

Exome sequencing of a large family has identified a likely pathogenic variant of the *KCNK3* gene encoding a pH-sensitive potassium channel, and segregating in all affected cases of the family[24]. The functional effects of the *KCNK3* variants found in a few PAH families were tested in vitro, showing a decreased function of the mutated channel. The pulmonary expression of the channel was also shown to be reduced in human PAH and experimental model of PAH in rats[25]. Homozygous deficient rats for Kcnk3, showed more severe PAH when challenged by hypoxia or monocrotaline[26]. A severe and early PAH was observed in a child homozygous for a *KCNK3* likely pathogenic variant from a highly consanguineous family[27] . However, from clinical testing data, *KCNK3* seems very rarely involved in PAH.

More genes were identified through WES or WGS gene-based association studies. These genes are aquaporin (*AQP1*), encoding a water channel protein, *ATP13A3* encoding a protein involved in cation transport across membranes[11] and *ABCC8* encoding an ABC protein transporting molecules across cellular membranes[28]. The *FBLN2* and *PDGFD* genes were also identified through the same strategy in various forms of PAH[23].

Pulmonary veno-occlusive disease (PVOD) is either sporadic, mainly due to tobacco exposure or chemotherapy by alkylating agents, or hereditary (hPVOD) linked to biallelic loss of function mutations of the *EIF2AK4* gene[29]. This lung vascular disease belongs to group 1.6 of PAH, that includes PAH with overt features of venous/capillaries involvement[30]. Clinically, PVOD can be misdiagnosed as PAH because there is no hemodynamic difference. Some clues come from abnormal chest imaging ground glass opacities, septal lines and lymphadenopathy and from a decreased $D_{LCO}c$[31]. hPVOD, is transmitted as an autosomal recessive disease and age at onset is far younger that in sporadic forms (26 vs 60 yrs)[32]. Genetic analysis showing biallelic *EIF2AK4* mutations is able to correct the diagnosis. Vascular remodeling predominates on veins and veinules with intimal fibrosis and medial hypertrophy, muscular hyperplasia of interlobular septal veins, but arterial remodeling and microvascular muscularization are also observed[33]. Capillary hemangiomatosis (PCH)-like foci are also observed and explain the term pulmonary capillary hemangiomatosis that also designates the disease also linked to *EIF2AK4* mutations in its hereditary form[34]. The evolution is extremely severe, and treatment used in PAH are contraindicated because of severe adverse effects.

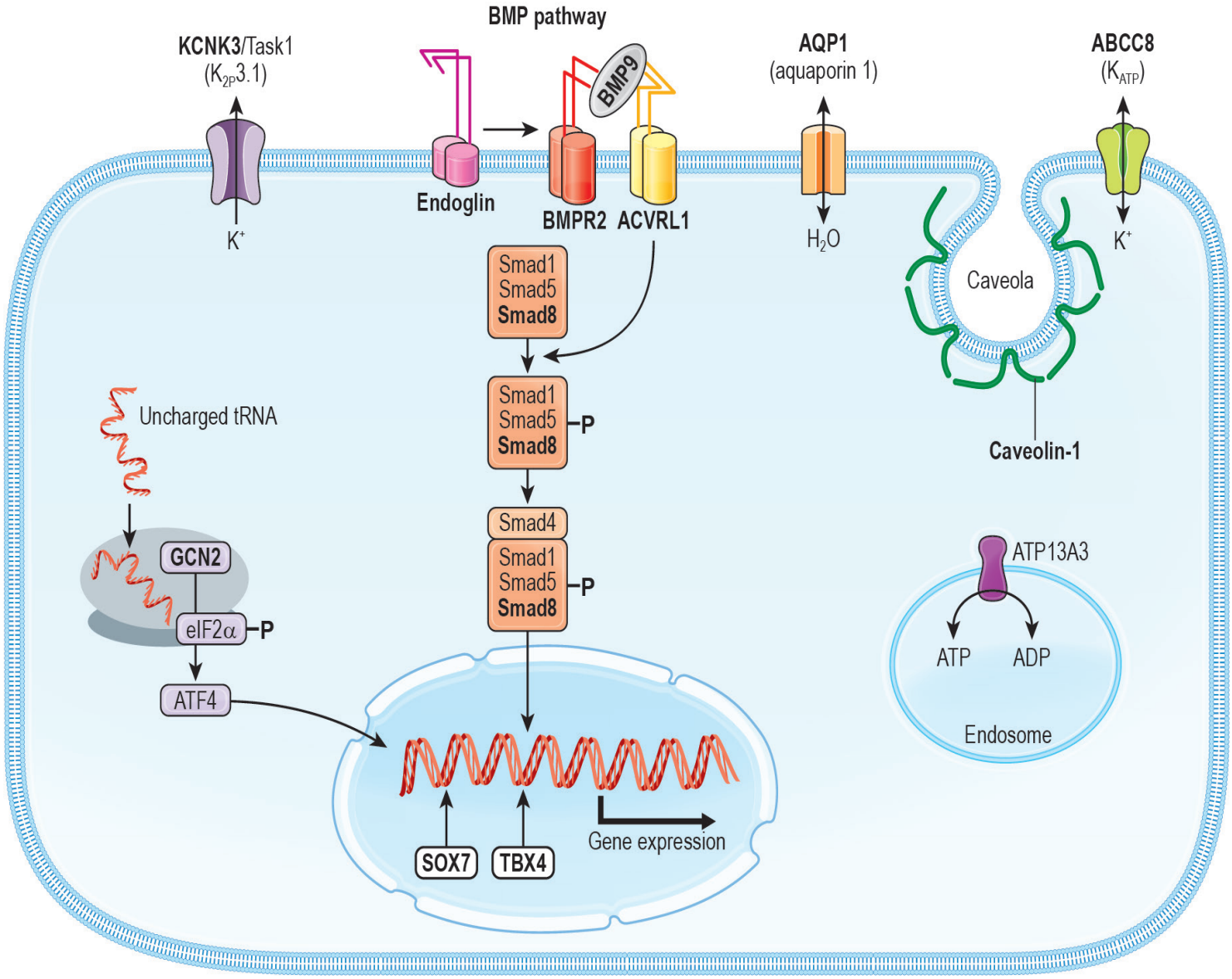
Genetic counselling is a major contribution of gene identification in the care and support of carrier patients. Preimplantatory diagnosis (PID) can be proposed to parents when there is a risk for the fetus to carry a mutation leading to a severe and intractable disease and if feasible, is preferred to prenatal diagnosis, especially if the mother is affected. The best example is hereditary PVOD because the penetrance is high, the disease very severe and one fourth of the offspring from two heterozygous parents will carry mutations on both alleles. PID was also performed in a case of BMPR2 linked severe familial PAH[35].

Although some unexplained familial cases are likely linked to deep intronic mutations in known and sequenced genes, it is likely that new genes will be identified in extremely rare cases. The current important challenge is understanding the incomplete and sexually differentiated penetrance of PAH, the variable age of onset of the disease. A putative second hit of unknown nature remains to be identified.

Figure: Schematic representation of the genes involved in heritable pulmonary arterial hypertension and hereditary pulmonary veno-occlusive disease.

Only genes in bold characters are directly involved. The main components of the BMP pathway are depicted. Smad 8 is encoded by the SMAD9 gene. BMP9 is encoded by GDF2. GCN2 (encoded by EIF2AK4) is involved in pulmonary veno-occlusive disease. Both the gene name and the protein name (between parentheses) are indicated when different. ATP13A3 is a member of the P-type ATPase family of proteins that transport a variety of cations across membranes. ABCC8 is a member of the superfamily of ATP-binding cassette (ABC) transporters. Aquaporin 1 is a small integral membrane protein that functions as a water channel protein.

Figure: Schematic representation of the genes involved in heritable pulmonary arterial hypertension and hereditary pulmonary veno-occlusive disease.



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LEARNING THE ROPES: PULMONARY HYPERTENSION

Novel concepts in the endothelial pathobiology of pulmonary arterial hypertension: Piecing the puzzle together

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Pulmonary hypertension (PH) is defined as mean pulmonary arterial pressures >20mmHg, assessed by right heart catherization[1]. Based on the underlying etiology, PH can be further sub classified into 5 categories, whereby Group 1 PH, or pulmonary arterial hypertension (PAH), results from progressive pruning of the lung arteriolar bed leading to increases in pulmonary vascular resistance (PVR) and pulmonary arterial pressures. Hallmarks of PAH include intimal and medial pulmonary arterial thickening and the formation of obliterative 'plexiform' arterial lesions[2]. Although there has been considerable progress in the elucidation of the mechanisms that lead to vascular abnormalities in PAH over the last 3 decades, there is still no consensus on a unified pathway from initial endothelial injury to the development of advanced disease. Current PAH therapies address only symptoms, delaying but not preventing disease progression; therefore, it is of the utmost importance that a more complete, end-to-end understanding of the pathobiology of PAH be established to guide the development of potentially curative treatments. In this brief review we will outline three major paradigms for the endothelial pathobiology of PAH which we will attempt to reconcile into a cohesive conceptual framework for the pathophysiology of this devastating disease.

Endothelial dysfunction in PAH

The concept of endothelial dysfunction as a major mechanism in the pathogenesis of PAH emerged in the late 1980s and early 90s with the discovery that endothelial cells (EC) play a critical role in the regulation of vascular tone and structure[3]. Nitric oxide, prostacyclin, and endothelin-1 are potent endothelial-derived vasomotor factors, the levels of which are profoundly altered in PAH. Endothelial dysfunction is characterized by decreased levels of endothelial nitric oxide synthase (eNOS) and prostacyclin synthase in pulmonary vessels, and increased levels of the potent vasoconstrictor, endothelin-1 which contribute to increased vasoconstriction as well as smooth muscle cell proliferation and medial thickening resulting in narrowing of lung arteries[1,3]. Currently approved PAH-specific therapies seek to mitigate the hemodynamic consequences of endothelial dysfunction using medications that target each of these three pathways, including prostanoids (parenteral, inhaled and oral), endothelin receptor blockers, and PDE5 inhibitors or soluble guanylate cyclase stimulators[4] . While current therapies have been beneficial in improving symptoms and outcomes for PAH patients, the 5-year mortality remains high (~50%)[4] suggesting that targeting endothelial dysfunction alone is not sufficient to reverse the underlying vascular pathology in this disease.

Endothelial apoptosis leading to dysregulated vascular cell growth: the proliferative hypothesis

Many of the manifestations of severe PAH, including the formation of complex plexiform lesions, can be reproduced in a rat model of PAH in which EC apoptosis is induced by inhibition of VEGF signaling with SU5416 (SU), combined with a 3-week exposure to hypoxia (Hx)[5]. In this model, the appearance of growth dysregulated, cancer-like vascular cells is thought to drive the formation of complex arterial lesions which can obliterate the arterial lumen thus contributing to increased vascular resistance and disease progression. This paradigm has garnered considerable interest and has generated a plethora of possible mechanisms mediating dysregulated vascular cell growth as potential therapeutic targets[2,6], some of which are now in the early stages of clinical development.

However, there are aspects of the pathogenesis of PAH that are not well explained by the proliferative paradigm, particularly relating to the early phases of the disease in which pulmonary arterial pressures may be elevated even preceding the appearance of obliterative arteriopathy. In particular, a recent study using the rat SU-Hx model of PAH has demonstrated that reducing pulmonary blood flow by banding one pulmonary artery can reverse obliterative arterial remodeling in the banded lung, suggesting that perturbation in pulmonary hemodynamics related to increased intimal shear stress is a prerequisite for the development of complex arterial remodeling[7]. In other words, occlusive arteriopathy maybe a consequence but not the cause of the hemodynamic abnormalities in PAH, which begs the question of what mechanisms underlies the initial development of this disease.

Endothelial injury leading to arteriolar 'drop-out': the degenerative hypothesis

We have argued that the initial onset of hemodynamic abnormalities in PAH can occur as a direct result of EC injury and apoptosis[8]. In this paradigm, EC loss leads to 'drop out' of fragile precapillary arterioles, which consist of little more than endothelial tubes with occasional mural cells. This results in functional pruning of the distal lung arterial circulation which directly increases arterial resistance and pressure, creating the hemodynamic conditions that can give rise to proliferative arterial remodeling. With the progressive loss of lung arterial area, the remaining microvascular bed needs to accommodate the cardiac output which results in marked increases in intimal shear stress[9]. Indeed, this recapitulates the hemodynamic abnormalities which underly the development of PAH in patients with congenital heart disease (CHD) and a large left to right shunt in which pathological intimal shear forces are thought to cause ongoing endothelial injury leading to progressive pulmonary arterial remodeling[5].

Persistent cycle of endothelial injury and failed repair in PAH: the final piece of the puzzle?

Thus far, we have connected three of the puzzle pieces in the pathophysiology of PAH (Figure): 1) Endothelial dysfunction increases pulmonary arterial tone and medial thickness contributing to early increases in arterial resistance; 2) Endothelial apoptosis leads to drop-out of fragile precapillary vessels, arteriolar pruning and the worsening lung hemodynamic abnormalities, which in turn perpetuate EC injury through pathological levels of intimal shear stress and; 3) Persistent hemodynamic abnormalities lead to the development of proliferative arterial remodeling and occlusive arteriopathy. However, the link between EC loss and the emergence of growth dysregulated vascular cells remains unclear. It is likely that EC proliferation, which is apparent even in the early stages of the SU-hypoxia model, represents an attempt to repair the endothelial damage and restore the lung microvasculature. But endothelial repair may be overwhelmed by ongoing EC loss caused by protracted intimal injury. Over time, this cycle of ongoing injury and repair could lead to exhaustion and senescence of regenerative cells, amplifying proliferative and inflammatory signaling through the senescence associated secretory phenotype. Indeed, Van der Fenn et al. have recently demonstrated that reversibility of arterial remodeling may be time-limited in a model of CHD associated PAH induced by monocrotaline combined with the creation of a surgical aortocaval shunt. They showed that the reversal of complex arterial remodeling after transplantation of a PAH lung into a normal host was lost after 21 days, which coincided with the appearance of markers of EC senescence[10]. Thus, these data are consistent with the concept of a vicious cycle of ongoing EC injury and repair during the development of PAH which eventually leads to exhaustion of reparative mechanisms (Figure). Therefore, targeting EC repair and senescence may represent another potential therapeutic target for PAH.

These paradigms provide a conceptual framework for understanding the complex pathobiology of PAH and suggest new opportunities to develop novel therapies for this devastating disease. Ultimately, the validity and relative importance of

each of these concepts will be established by the effectiveness of therapeutic strategies developed to target these interrelated mechanisms. After many decades and intensive research, it is only by embracing these new ideas that a curative therapy for PAH may one day be found.

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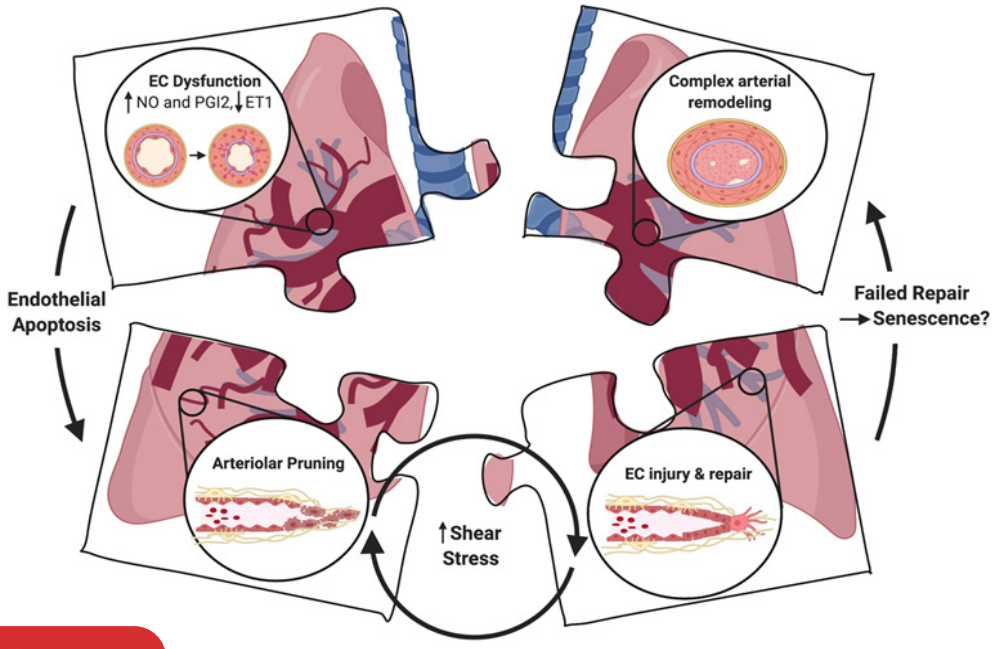

Figure: Piecing together the paradigms of endothelial pathobiology of PAH. Endothelial dysfunction results in increased vascular tone and narrowing, while endothelial cell (EC) apoptosis leads to arteriolar pruning. The resultant perturbed hemodynamics and increased intimal shear stress contributes to a cycle of persistent injury and endothelial repair. Failed arteriolar repair and EC senescence contribute to emergence of hyper-proliferation and complex arteriolar remodeling. Created with BioRender.com

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LEARNING THE ROPES: PULMONARY HYPERTENSION

Actual and novel treatments for pulmonary hypertension

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The current management of pulmonary arterial hypertension (PAH) consists of a **combination of pharmacological and non-pharmacological measures**. In contrast to the treatment of systemic arterial hypertension, treatment success is quite limited as PAH is a progressive, incurable disease which is extremely difficult to approach therapeutically. Thus, treatment goals are, among others, usually defined as a 6-minute walking distance (6MWD) of >380 to >500 m with >440 m currently accepted as standard by the most recent ESC/ERS guidelines of 2016[1]. Here, only general therapeutic strategies are dealt with. For special cases of PAH such as PAH in children, congenital heart disease, connective tissue disease, portal hypertension or HIV please refer to respective guidelines[1,2].

Current Drug treatment of PAH follows the "traditional" concepts of PAH pathophysiology. According to these, the disease process is governed by an imbalance of endogenous vasoactive agents in lung vessels: increased activity of endothelial vasoconstrictors such as endothelin and thromboxane, reduced activity of vasodilators such as nitic oxide (NO) and prostacyclin. Current treatment strategies aim to restore the balance at least to a certain extent.

According to the ESC/ERS guidelines[1] (a new edition is underway but not yet published), **the treatment strategy** can be divided in three steps:

1) General measures including physical activity, psychosocial support, supportive therapy (oral anticoagulants, diuretics, O_2, digoxin), referral to an expert center and acute vasoreactivity testing for the indication of chronic therapy with calcium channel blockers (CCB).

2) Initial therapy with high-dose CCB in vasoreactive patients or with drugs approved for PAH in non-vasoreactive patients.

3) If the response to initial therapies is insufficient, combination of approved drugs and lung transplantation follow, if drug treatment is unsuccessful.

Approval of **drugs for the treatment of PAH** is based on their effects in evidence-generating studies in patients with different forms of PAH[1,2]. Due to the specific characteristics of lung vessels featuring some vasodynamic deviations from the systemic circulation, these drugs are lung-specific and not in use for the treatment of systemic arterial hypertension.

Drug monotherapy can be begun with members of the following drug classes:

- **Endothelin receptor antagonists** to block the actions of the vasoconstrictor endothelin: *Ambrisentan, Bosentan, Macitentan,*

- **Phosphodiesterase type 5 inhibitors** to block the degradation of thecyclic Guanosine-Monophosphate (cGMP) which generates the vasodilator NO: *Sildenafil, Tadalafil, Vardenafil*,

- **Guanylate cyclase "stimulators"** activating the enzyme soluble Guanylatcyclase (sGC) to generate cGMP which in turn induces vasodilation via further signaling steps: *Riociguat,*

• **Prostacyclin analogues** which replace/mimic the vasodilator prostacyclin: *Epoprostenol, Iloprost, Treprostinil, Beraprost*. These drugs cannot be applied orally with the exception of *Treprostinil and Beraprost* (used mainly in Asia),

• **IP receptor agonists** to selectively stimulate the prostacyclin (IP) receptor leading to vasodilation: *Selexipag (oral)*.

Similar to the drug treatment of systemic arterial hypertension, **initial combination therapy** has gained increasing attention as an attractive option to simultaneously address the different pathophysiological pathways of PAH. Recommended combinations include:

• Endothelin receptor antagonist (ERA) *Ambrisentan* + Phosphodiesterase 5 inhibitor (PDE-5i) *Tadalafil* [3],

• *Bosentan* (ERA) + *Sildenafil* (PDE-5i) + *Eprostenol* i.v. (Prostacyclin analogue)[4],

• *Bosentan* + *Eprostenol* i.v.[5],

• ERA or PDE-5i + other i.v. prostacyclin analogue.

An alternative to initial combination therapy is **sequential combination therapy**. Evidence has been generated for numerous dual and triple combinations between the different drug classes[1,2] with the exception of the combination of the CGMP stimulator *Riociguat* with PDE-5i (hypotension, safety issues)[6].

New and more efficient drugs for PAH remain a major unmet medical need. A better understanding of pathomechanisms leading to vascular remodelling and to the cancer-like phenotype of pulmonary vascular cells is the basis for many new drug targets[7,8] .

A search on www.clinicaltrials.gov on January 24th, 2021, for clinical trials in PAH revealed 103 Phase I, II or III trials within the last 5 years, which are either "completed", "recruiting", "not yet recruiting" or "active, but not recruiting".

The following provides an overview about drugs targeting novel targets in PAH and their current status in clinical/preclinical drug development for PAH.

Drugs targeting genetic or epigenetic changes:

The best characterized genetic defect in PAH are mutations leading to an impairment of bone morphogenetic protein receptor type II (BMPR2) signalling thus promoting vascular remodelling. The following drugs target impaired BMPR2 signalling.

• **Gene therapy**: Adenoviral BMPR2 gene delivery. **Status**: Preclinical.

• **Chloroquine**: Prevents lysosomal degradation of BMPR2. **Status**: Preclinical.

• **Tacrolimus (FK506)**: Identified by high-throughput screening of 3.756 FDA-approved drugs to activate BMP signalling. **Status**: Improved 6-min walk distance (6MWD) and increased BMPR2 expression in a Phase II trial, but only in a subgroup of patients. No Phase III study initiated.

• **Sotatercept**: Recombinant activin receptor IIA (ActRIIA) ligand trap. Improves BMP/TGFbeta signalling. **Status**: Successfully tested in Phase II trial. Ongoing Phase III study.

• **Etanercept**: TNFalpha inhibitor. Anti-inflammatory and prevents TNFalpha-mediated repression of BMPR2 synthesis. **Status**: Preclinical.

Drugs targeting reversible, epigenetic abnormalities are thought to prevent the hyperproliferative phenotype, inflammation and fibrosis in PAH.

• **HDAC-inhibitors**. **Status**: Preclinical.

•**Apabetalone**: Inhibits epigenetic mechanisms involving bromodomain and extra-terminal motif (BET) proteins. **Status**: Ongoing Phase Ib trial.

Drugs targeting inflammation:

Pulmonary perivascular inflammation is a hallmark of PAH. There have been many attempts to repurpose anti-inflammatory drugs.

• **Rituximab**: Depletes B cells. **Status**: Significantly improved 6MWD after 24 weeks of treatment in a Phase II trial in PAH associated with systemic sclerosis, but this effect was lost by week 48. Currently not continued.

• **Tocilizumab**: IL-6 receptor antagonist. **Status:** Unsuccessful Phase II "TRANSFORM-UK" trial.

• **Anakinra**: Recombinant IL-1 receptor antagonist. **Status**: Pilot study showed improvement of CRP levels, heart failure, IL-6 levels and quality of life. Phase III trial expected.

Drugs targeting mitochondrial dysfunction and oxidative stress:

Oxidative stress/reactive oxygen species are increased in PAH. They are caused by and trigger inflammation, which makes them an interesting drug target.

• **Bardoxolone methyl**: Orally active NF-kappaB inhibitor and Nrf2 inducer. Promotes synthesis of antioxidant molecules. **Status**: Successful Phase II trial with significant increase in 6MWD (LARIAT). Phase III trial (CATALYST) initiated, but terminated early because of COVID-19 pandemic.

Drugs targeting metabolic and hormonal disturbances:

The renin-angiotensin system (RAS) is overactivated in PAH, but conventional RAS blockade is ineffective. New drugs target the protective arm of the RAS.

• **Human recombinant ACE2** (*hrACE2; GSK2586881; APN01*): Catalytic synthesis of the protective RAS hormone angiotensin-(1-7). **Status**: Completed pilot and Phase II studies showing improvement of pulmonary hemodynamics. Development of *GSK2586881* for PAH has discontinued for strategic reasons.

• **C21**: Angiotensin AT2-receptor agonist. Status: Ongoing Phase II trial in idiopathic pulmonary fibrosis.

A role of oestrogens in PAH has been suspected because of higher prevalence in women and increased oestrogen levels in males with PAH.

• **Tamoxifen**: Oestrogen receptor modulator. **Status**: Ongoing Phase II trials.

• **Anastrozole**: Aromatase inhibitor preventing formation of oestrogens from androgens. **Status**: Ongoing Phase II trials.

Drugs improving insulin resistance are tested, because insulin resistance is a risk factor for PAH.

• **Metformin**: Promotes insulin sensitivity, endothelial NO synthesis and inhibits VSMC proliferation. **Status**: Three ongoing Phase Ib/II trials.

Drugs targeting proliferation:

Targeting proliferation in PAH mainly aims at reducing vascular remodelling. Several anti-cancer drugs are tested for repurposing.

• **Imatinib**: Tyrosine kinase inhibitor. Status: Five active trials. Improved 6MWD and reduced pulmonary vascular resistance in Phase III trial, but severe side effects (subdural hematoma) prevented approval.

• **Seralutinib**: Inhaled kinase inhibitor. **Status**: Ongoing Phase Ib trial.

• **Elafin**: Endogenous elastase inhibitor and tumour suppressor. **Status**: Phase I trial.

• **Olaparib**: PARP inhibitor. Promotes cell death by preventing DNA repair. **Status**: Phase Ib trial.

New drugs for vasodilation:

•**Getagozumab (GMA301)**: Humanised, monoclonal, inhibitory endothelin ET_A receptor antibody. **Status**: Ongoing Phase Ib trial.

•**Pemziviptadil**: Recombinant fusion protein with sustained release of vasoactive intestinal peptide for once/week s.c. application. **Status**: Ongoing Phase II trial.

• **Zamicastat**: Dopamine β-hydroxylase inhibitor. Reduces sympathetic tone. **Status**: Ongoing Phase II trial.

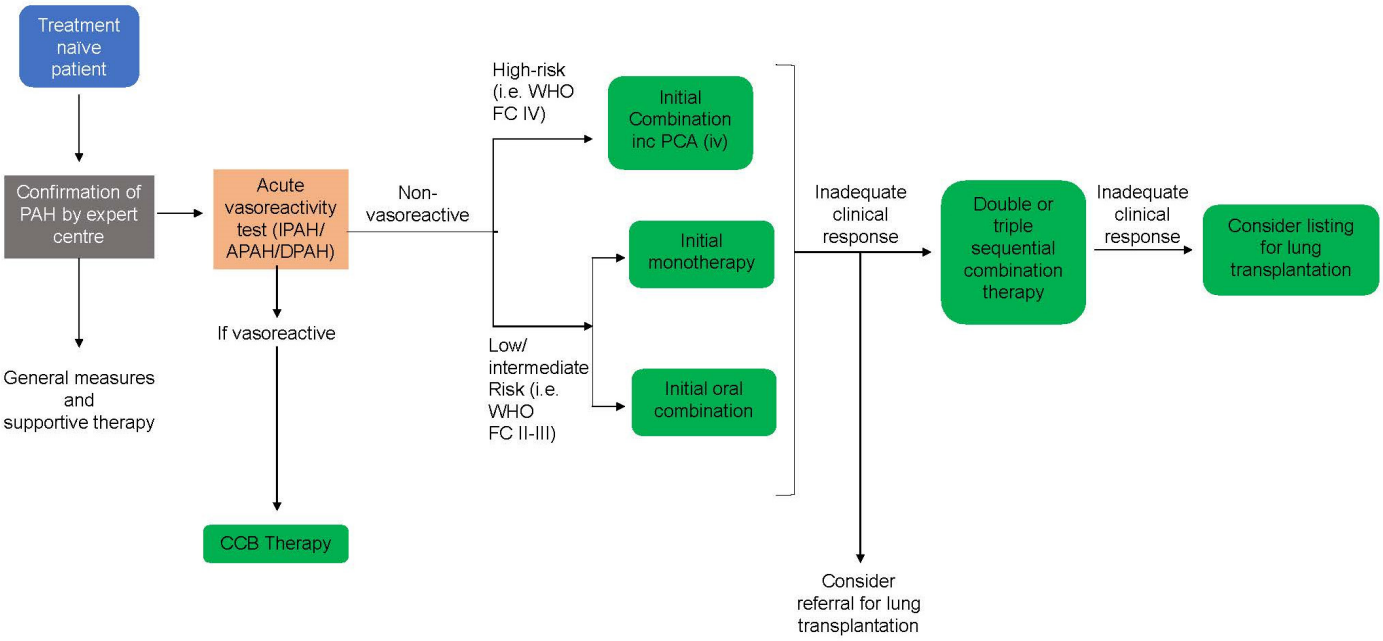
Future will tell whether one or more of these novel treatment approaches will become a breakthrough in PAH drug treatment which is desperately hoped for in view of the currently limited therapeutic perspectives.

In summary:

The management of PAH, a difficult-to-treat condition, consists of drug- and non-drug strategies. Referral to an expert center is crucial whenever possible. Following general measures like physical activity, oral coagulants, diuretics, or O2 administration, specific drug treatment follows conventional concepts about PAH pathophysiology trying to restore the disturbed balance between vasoconstrictor and vasodilating principles in pulmonary arteries. Due to specific features of the lung circulation, PAH drugs differ from those used in systemic arterial hypertension. High dose calcium channel blockers (CCB) are first-line in vasoreactive patients. Non-vasoreactive

patients receive either monotherapy or, more frequently, combined drug treatment right from the beginning or in sequential order. Drugs used are endothelin receptor antagonists, phosphodiesterase type 5 inhibitors, guanylate cyclase stimulators, prostacyclin analogues, and IP (prostacyclin) receptor agonists. The search for novel, more potent, drugs has revealed new targets including genetic or epigenetic changes, inflammation, mitochondrial dysfunction and oxidative stress, metabolic and hormonal disturbances, proliferation, and vasodilation. More than one-hundred clinical trials are underway with these new approaches, and a breakthrough with one or more of these is eagerly awaited.

Figure 1: Treatment algorithm in PAH Modified from 1) with permission



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LEARNING THE ROPES: PULMONARY HYPERTENSION

Pulmonary hypertension clinical presentation and relevance



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Pulmonary hypertension (PH) is a hemodynamic condition affecting approximately 1% of the world population, and the prevalence in adults >65 years is about 10%[1]. Incidence and prevalence are related to the underlying cause, PH associated with left heart diseases and/or chronic lung diseases representing the most common forms[1].

Based on the underlying etiology and clinical presentation, the updated clinical classification of PH categorizes five groups [2]: 1. Pulmonary arterial hypertension (PAH); 2. Pulmonary hypertension due to left heart disease; 3. Pulmonary hypertension due to lung disease and/ or hypoxia; 4. Pulmonary hypertension due to pulmonary artery obstruction; 5. Pulmonary hypertension with unclear and/or multifactorial mechanisms (**Table 1**). Despite the differing etiology, all forms of PH are linked to progressive clinical symptoms and associated with excess mortality[3]. In fact, even moderate elevations of pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) are associated with increased mortality[4,5].

PAH is a relatively rare disease of the small pulmonary resistance vessels that may affect younger individuals, and – if left untreated – leads to right heart failure and death[6]. As the disease is slowly progressing, clinical signs and symptoms usually develop gradually over time and at initial stages are often unspecific, PAH is usually diagnosed with a significant delay. The clinical picture resembles exertional dyspnea, reduced exercise capacity, bendopnoe, and fatigue. Advanced stages are characterized by signs of right heart failure such as venous congestion, peripheral edema, and ascites, along with states of exhaustion and syncope (during or after physical effort)[3,6]. Progressive right ventricular dysfunction may lead to episodes of cardiac decompensation that are associated with a high mortality risk.

Impaired right ventricular function results in backward failure and systemic congestion, but also in diminished left ventricular filling and reduced systemic output, at rest and during exercise. The combination of the two triggers systemic inflammatory reactions and inter-organ crosstalk, affecting multiple organ systems (**Figure 1**)[7] .These systemic consequences of P(A)H place additional burden on patients and may represent treatable traits in addition to targeted therapy of PH and underlying causes[7].

The diagnostic work-up in patients with suspected PH follows a diagnostic algorithm, aiming at establishing a precise diagnosis and classification of PH[8]. This is of utmost importance, as the

therapeutic consequences differ substantially between the distinct forms of PH. In addition to physical examination, non-invasive tools and findings include ECG-signs of right heart strain, reduced exercise capacity (assessed by cardiopulmonary exercise testing [CPET] and the 6 minute walk distance [6MWD]), and elevated N-terminal fragment of brain natriuretic peptide (NTproBNP) serum levels[8]. Echocardiography is of particular importance, as it may show elevations of the estimated systolic pulmonary arterial pressure (PASP), and pathological changes of right heart dimensions and function[8]. More recently, cardiac MRI has also been established to accurately assess RV size, morphology and function, and allows non-invasive measurement of stroke volume, cardiac output (CO) as well as pulmonary arterial flow. Nevertheless, the diagnosis of PH can only be confirmed by right heart catheterization (RHC). PH is defined by an elevation of the mean pulmonary arterial pressure (mPAP) ≥25 mmHg at rest, although lowering the threshold to >20 mmHg has recently been proposed[2]. The hemodynamic definition sub-classifies PH into a pre- and post-capillary form, depending on the pulmonary arterial wedge pressure (PAWP). The hemodynamic profile in PAH is characterized by pre-capillary PH, defined by a PAPm ≥25 mmHg, a PAWP ≤15 mmHg, and a PVR >3 WU[3,8].

Among patients with PAH, there appear to be distinct clinical phenotypes. While idiopathic PAH was originally recognized as a disease of younger patients with a female predominance, who had no or few comorbidities, recent registry analyses have shown that PAH is now increasingly diagnosed in elderly patients that may have multiple comorbidities. Those patients meet the hemodynamic criteria of PAH (pre-capillary PH), but disease characteristics, pathophysiology, and the distinction from group 2 PH are more complex and challenging. In addition, response to targeted therapy and the tolerability of PAH drugs are less well studied. To better describe the distinct phenotypes, the terms "typical" or "classical" PAH (younger patients with few comorbidities) and "atypical PAH" or "PAH with comorbidities" (elderly patients with multiple comorbidities) have been introduced[9]. Although the evidence for the safety and efficacy of PAH medications was mainly derived from patients with "classical PAH", recent analyses indicated that the group of "PAH with comorbidities" also benefits from targeted therapy[10,11].

Consistent with the distinction of PAH phenotypes, a recent cluster analysis of patients with idiopathic PAH from the COMPERA registry which was based on age, sex, DLCO (diffusing capacity of the lungs for carbon monoxide) , smoking status and the presence of comorbidities (obesity, hypertension, CHD, diabetes mellitus) identified distinct patient clusters, which differed in clinical presentation, response to therapy, and survival[12]. Specifically, a cluster of younger age and without comorbidities had a better response to PAH treatment and better outcome when compared to clusters of elderly patients with comorbidities, lower DLCO, and smoking history. However, there were also differences in the treatment patterns with less combination therapies in the latter groups.

In order to predict outcome and inform treatment decisions, the current ESC/ERS guidelines recommend a risk assessment strategy for patients with PAH[8]. Based on a multimodal approach considering various clinical measures, patients are categorized as "low risk", "intermediate risk", or "high risk". This strategy was recently validated independently in 3 large registries, which consistently proved its validity both at the time of diagnosis and during follow-up. According to these studies, risk assessment in patients with PAH provides accurate mortality estimates, with mortality rates in low, intermediate, and high risk patients of <5%, 5-10%, and >10%, respectively. Furthermore, a simplified risk assessment strategy quantifying the number of low-risk criteria accurately predicted transplant-free survival, and patients with key non-invasive variables (WHO-FC, 6MWD, NTproBNP) in the low-risk category had an excellent 5-year survival. Hence, an important treatment goal is to achieve a low-risk profile, i.e. a high number of low-risk criteria.

It should be acknowledged, however, that risk assessment has been validated primarily for patients with "classical PAH", whereas it has to be further evaluated in "PAH with comorbidities". Moreover, the efficacy and safety of targeted PAH therapies, as well as treatment strategies, must be further assessed in the latter group in randomized controlled trials.

Figure 1. Systemic consequences of P(A)H and right-sided heart failure: Interdependent mechanisms, systemic inflammation, and interorgan cross-talk[7] *Republished with permission from AHA.*

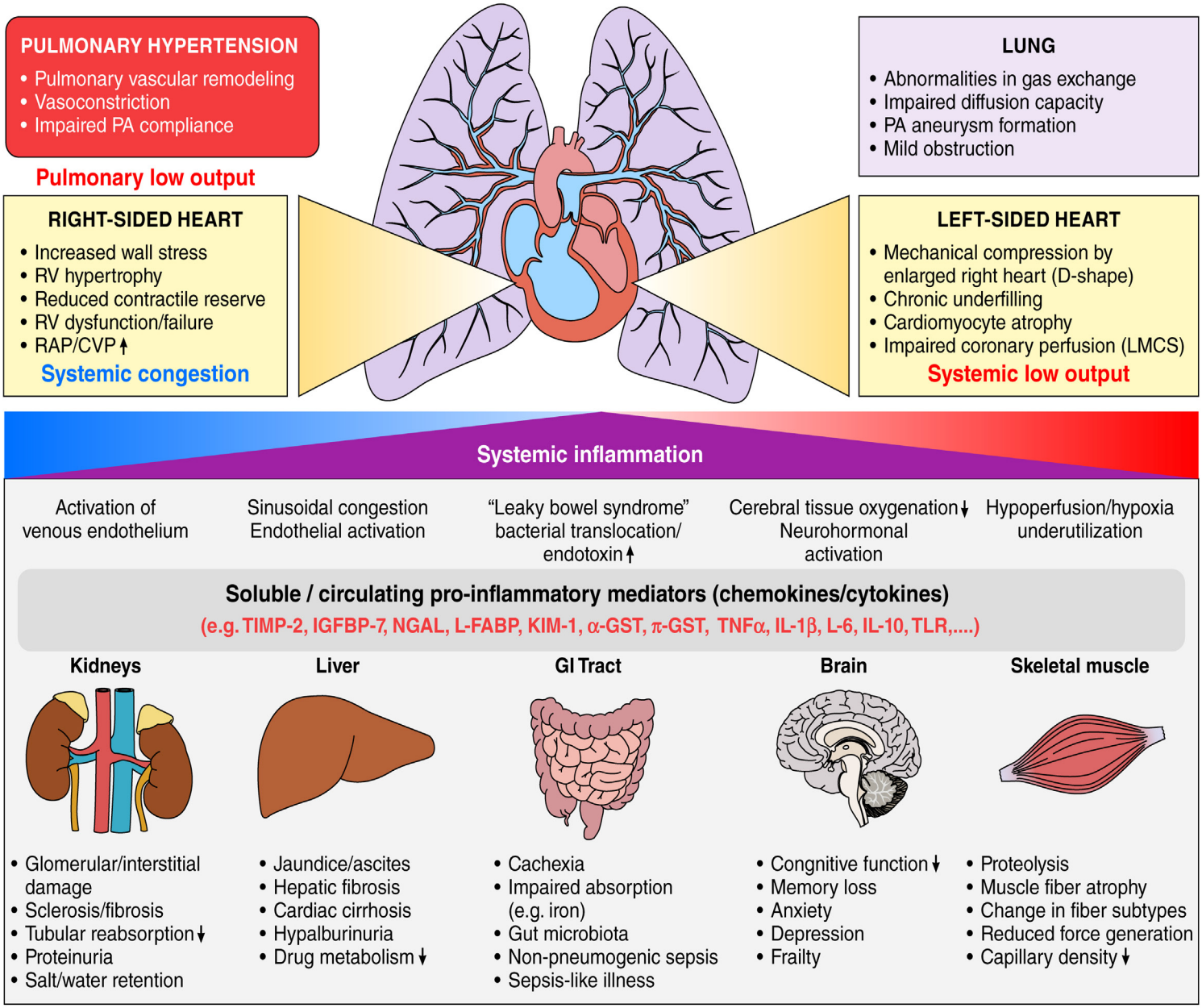

Table 1. Updated clinical classification of pulmonary hypertension (PH); according to the 6th World Symposium on Pulmonary Hypertension[2]

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH
1.2 Heritable PAH
1.3 Drug- and toxin-induced PAH
1.4 PAH associated with:
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5 Schistosomiasis
1.5 PAH long-term responders to calcium channel blockers
1.6 PAH with overt features of venous/capillaries (PVOD/PCH) involvement
1.7 Persistent PH of the newborn syndrome
2. PH due to left heart disease
2.1 PH due to heart failure with preserved LVEF
2.2 PH due to heart failure with reduced LVEF
2.3 Valvular heart disease
2.4 Congenital/acquired cardiovascular conditions leading to post-capillary PH

3. PH due to lung diseases and/or hypoxia
3.1 Obstructive lung disease
3.2 Restrictive lung disease
3.3 Other lung disease with mixed restrictive/obstructive pattern
3.4 Hypoxia without lung disease
3.5 Developmental lung disorders
4. PH due to pulmonary artery obstructions
4.1 Chronic thromboembolic PH
4.2 Other pulmonary artery obstructions
5. PH with unclear and/or multifactorial mechanisms
5.1 Haematological disorders
5.2 Systemic and metabolic disorders
5.3 Others
5.4 Complex congenital heart disease

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INVITED PAPER

An ISH-led prospective meta-analysis on RCTs of RAAS inhibitors in COVID-19 patients: A call for collaboration

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With 2020 came COVID-19. Already early on in the pandemic the go-to antihypertensive therapy, namely renin-angiotensin aldosterone system (RAAS) inhibitors, came under fire. This includes angiotensin-converting enzyme inhibitors (ACEi) and angiotensin II receptor blockers (ARB). The COVID-19 pandemic has drawn attention to these first line therapies due to the fact that the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infects respiratory epithelial cells via attachment to the angiotensin-converting enzyme 2 (ACE2) receptor. With millions of patients using ACEi/ARB therapy on a daily basis, there was overall anxiety on whether therapy should be continued, initiated or ceased in patients with COVID-19.

Animal studies: These studies have shown that ACEi/ARB therapy may upregulate ACE2 receptor expression and produce increased cardiac ACE2 mRNA levels.[1,2] Upregulated expression of surface ACE2 receptors has been postulated to promote viral cell invasion, increase the risk of SARS-CoV-2 infection and increase disease severity, with consequent life-threatening complications.[3,4] At the same time, other animal studies suggest that increased ACE2 expression secondary to ACEi/ARB use might have protective effects on cardiac, kidney and pulmonary function and thus reduce the severity of COVID-19.[5]

Observational retrospective human studies: Observational studies in humans and meta-analyses of these studies suggest that there is no adverse effect of RAS blockade on COVID-19 severity and outcome[6], but there may be possible protective benefits including reduced rates of mortality,[7] critical disease[8] and admission to intensive care.[9] Observational studies can still have multiple sources of bias, and RCTs are needed to mitigate this risk.

Randomised controlled trials: To date reliable data from large robust RCTs are unavailable to guide clinical decision-making. Preliminary results from the BRACE-CORONA randomised trial[10] presented at the European Society of Cardiology conference 2020 suggested that all-cause mortality at 30 days was equivalent in those continuing ACEi/ARBs compared to those who had therapy suspended (HR 0.97, 95%CI 0.38-2.52, p=0.95). However, the trial did not assess benefit in those acutely initiated on ACEi/ARBs, nor did it assess longer-term outcomes. There are multiple other RCTs in process, which will better inform clinical decision making rather than relying on observational human studies and inconsistent animal data. Most of the RCTs under way are small to moderate in size. It is still difficult to know whether these trials are powered to answer questions regarding subgroup populations, including whether there is utility of ACEi/ARB therapy in patients with COVID-19 with concomitant hypertension, cardiovascular or kidney disease.

Current recommendations: International hypertension and cardiovascular societies have recommended that patients continue ACEi/ARB therapy during the COVID-19 pandemic, on the

basis of the strong and well-documented evidence on their protective cardiovascular effects, but identified a need for more reliable human data.[11, 12, 13,14]

A prospective meta-analysis of RCTs: Given the uncertainty of ACEi/ARB use in those with COVID-19, several RCTs started ACEi/ARB therapy for possible benefit, while other trials are stopping the same therapy due to concerns about harm. A prospective meta-analysis led by the *International Society of Hypertension* will therefore be an ideal approach to address these limitations, as well as promoting international collaboration. This approach entails studies to be identified, evaluated, and determined to be eligible before the results of any included studies are known or published, thereby avoiding some of the potential biases inherent in standard, retrospective meta-analyses.

The ISH will therefore be leading a prospective meta-analysis pooling data from RCTs to investigate the safety and efficacy of these RAAS inhibitors.

We are including RCTs recruiting patients with COVID-19 to assess the safety and efficacy of ACEi/ARB therapy compared to those not on ACEi/ARBs. As primary outcome, pooled data will be used to assess all-cause mortality associated with ACEi/ARB therapy compared to those not on ACEi/ARBs stratified by age, co-morbidity, sex, ethnicity, and trial characteristics.

A detailed protocol of our approach has been published in BMJ Open.[15]

For clinical trials to be eligible for inclusion, the trials must meet the criteria listed in **Box 1**.

Box 1: Eligibility Criteria for Meta-Analysis

- RCTs recruiting between March 2020 and March 2021
- Aged ≥18 years
- Laboratory confirmed SARS-CoV-2 infection
- Comparison of patients randomised to ACEi/ARB versus no ACEi/ARB therapy
- Findings reported in English
- Trial duration ≥14 days
- Oral administration of ACEi/ARB therapies

We will include trials that investigate continuation versus cessation of ACEi/ARB among patients currently treated with ACEi/ARB; and trials that report initiation of ACEi/ARB versus control in those not currently treated with such therapies. The exclusion criteria will be at the discretion of each individual trial.

The primary outcome will be all-cause mortality at ≤30 days. Secondary outcomes will include mechanical ventilation at ≤30 days; admission to intensive care at ≤30 days; myocardial infarction at ≤30 days, revascularisation at ≤30 days, congestive cardiac failure at ≤30 days; pulmonary embolism and/or deep vein thrombosis at ≤30 days, hospitalisation at ≤30 days and acute kidney injury at ≤30 days; all-cause mortality at >1 month follow-up. Standardised grouped tabular de-identified data will be requested from triallists/sponsors for both short-term (≤30 days) and longer term (>1 month) follow up, where available. Individual identifiable patient data will not be requested.

An electronic search of **ClinicalTrials.gov** was performed to identify potential ongoing trials for inclusion in the meta-analysis. This search will be continuously updated, and investigators of newly reported and eligible trials will be invited to join the collaboration. Electronic searches of MEDLINE (1996–present), EMBASE (1996–present) and the Cochrane Central Register of Controlled Trials will also be performed to identify any other RCTs that meet inclusion criteria in March 2021. We emailed invitations including details about the study protocol, offer of authorship, identification of the time for data retrieval and confirmation of data security. Thus far, the following trials have already agreed to be involved in the meta-analysis, including sites in the United States of America, Austria, Brazil, Denmark, France, Germany and the Netherlands:

- Stopping ACE-inhibitors in COVID 19 (ACEi-COVID): Innsbruck, Austria; Munich, Germany.
- Austrian CoronaVirus Adaptive Clinical Trial (ACOVACT): Innsbruck and Vienna, Austria.
- Outpatient Treatment of Elderly People with Symptomatic SARS-CoV-2 Infection: a Multi-arm, Multi-stage RCT to Assess the Efficacy and Safety of Several Experimental Treatments to Decrease the Risk of Hospitalization or Death (COVERAGE): Bordeaux, France.

- A Double blind, Placebo-controlled RCT with Valsartan for Prevention of Acute Respiratory distress Syndrome in hospitalised patients with SARS-COV-2 Infection Disease (PRAETORIAN-COVID): 's-Hertogenbosch, Arnhem, Nijmegen, Roermond, Rotterdam, the Netherlands.

- Effects of Discontinuing Renin-angiotensin System Inhibitors in Patients With COVID-19 (RASCOVID-19): Copenhagen, Denmark.

- RCT of Losartan for Patients With COVID-19 requiring Hospitalization: Minnesota, USA.

- RCT of Losartan for Patients With COVID-19 not requiring Hospitalization: Minnesota, USA.

- RCT of ACEIs in Treatment of COVID-19: Tanta, Egypt.

- Elimination or Prolongation of ACE Inhibitors and ARB in Coronavirus Disease 2019 (REPLACECOVID): Pennsylvania, USA.

- Pilot Clinical Trial of the Safety and Efficacy of Telmisartan for the Mitigation of Pulmonary and Cardiac Complications in COVID-19 Patients: Hawaii, USA.

- Switch of Renin-Angiotensin System Inhibitors in Patients With Covid-19 (SWITCH-COVID): São Paulo, Brazil.

Given the widespread use of RAAS inhibitors worldwide, clear guidance based on evidence from RCTs on the use of ACEi/ARBs in adults with COVID-19 is still outstanding. We trust that this international collaboration will give clear direction to inform public health policy and clinical decision making on RAAS inhibition therapy in COVID-19 patients.

We continue to openly invite other eligible trialists to collaborate with us. Please get in touch at a.schutte@unsw.edu.au

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Full reference list

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INVITED PAPER

JOIN ESH-ISH 2021 ON-AIR

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The ESH-ISH 2021 Congress will take place on April 11-14, 2021 and be conducted as a fully virtual meeting.

The European and International Society of Hypertension meetings are the largest scientific events in hypertension worldwide, attracting a significant number of participants from around the world. Most participants are mainly or exclusively involved in hypertension and cardiovascular prevention, ranging from family medicine and general practitioners to specialists such cardiologists, nephrologists, endocrinologists, and internists as well as diabetologists, lipidologists, pharmacologists, and those involved in basic research aspects (physiologists, bioengineers, molecular biologists, and geneticists).

It is only every six years that both societies come together for their Joint Meeting providing a rare and important opportunity for the entire hypertension community to be connected and able to interact and network with well-known experts and opinion leaders.

For this reason, we have developed an outstanding scientific programme for ESH-ISH 2021, including State-of-the-Art Lectures and Debates on issues of current interest or controversy. The programme also includes sessions dedicated to the practical aspects of the management of hypertension via Teaching, How-to, Meet the Expert and Clinical Case sessions. Finally, an important contribution will also come from specific sessions organised by industry.

ESH-ISH 2021 is delighted to have secured the following excellent Keynote Speakers:

Professor Bina Joe – "Microbes and Metabolites: What is the Pressure?" Tuesday13th April at 16.00 CEST

Professor Victor Dzau - "Future of Hypertension: Time for Transformation" Sunday 11th April at 11.40 CEST

Professor Donna Arnett – "Personalized Approaches to Hypertension: Opportunities and Obstacles" Tuesday 13th April at 16.42 CEST

Professor Rory Collins – "Blood pressure and cardiovascular risk: a population-based perspective" Wednesday 14th April at 11.42 CEST

Professor George Davey Smith – "Mendelian Randomization in hypertension research: what can it add?" Wednesday 14th April at 13.00 CEST

Doctor Richard Horton – "Where Medicine went wrong" Tuesday 13th April at 15.0 CEST

Doctor Costantino Iadecola – "Hypertension, salt and dementia: towards a molecular understanding" Monday 12th April at 13.00 CEST

Professor Susanne Oparil – "The SPRINT Marathon: The Race Goes On" Monday 12th April at 16.43 CEST

Professor K. Srinath Reddy – "Hypertension Control in the SDG Era" Monday 12th April at 14.00 CEST

As in previous ESH-ISH Joint Meetings, a significant portion of the scientific programme will be devoted to original scientific data via oral and poster presentations of abstracts selected by peer review. More than 1300 abstracts have been accepted and divided in oral and poster presentations. As a global meeting, abstracts have been submitted from from around the world.

Sessions on COVID-19 and including late-breakers with the most up to date research from abstracts submitted are also scheduled during the meeting.

The platform which will host the ESH-ISH 2021 ON-AIR Joint Meeting will be a "real" virtual venue to optimise the experience of each delegate, providing tools and spaces to interact, opportunity to attend live sessions switching from one meeting room to the other, and availability of all the congress content in the on-demand area for three months. This will enable all participants to take full advantage of the extensive scientific programme the Societies have brought together.

All sessions will be transmitted "live" throughout the congress, respecting the time and (virtual) room, and will then be available in the on-demand section of the platform, thus offering delegates across different time zones the opportunity to access all lectures.

Please visit the congress website: www.hypertension2021.org for further information and to register for the meeting:

Registration Fees	
	NO DEADLINES
ESH/ISH/BIHS MEMBER	€ 99,00
ESH/ISH/BIHS NON-MEMBER	€ 120,00
LOW- AND MIDDLE-INCOME COUNTRIES	€ 50,00
GENERAL PRACTIONERS, NURSES	€ 50,00
YOUNGER THAN 35	free

We look forward to welcoming a global audience
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We look forward to connecting with you in April 2021. Meantime, we wish you and your families good health and resilience during these difficult times.

A.F. Dominiczak

ESH ISH 2021 President

“DDD” DYLAN’S DISTRIBUTION DATA

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The October edition of Hypertension News continued to draw strong interest and ended up being our second most viewed edition to date (9115 total downloads). There were strong contributions throughout the issue. As always the Learning the Ropes feature on Secondary Hypertension was heavily viewed, notably the feature on Primary Aldosteronism by Maria-Christina Zennaro. Other features of interest were the interviews with then incoming ISH president Maciej Tomaszewski and the interview with Dame Anna Dominiczak on the ESH-ISH virtual meeting. As always the Hypertension News editorial board is grateful for the support and interest of our loyal readers.

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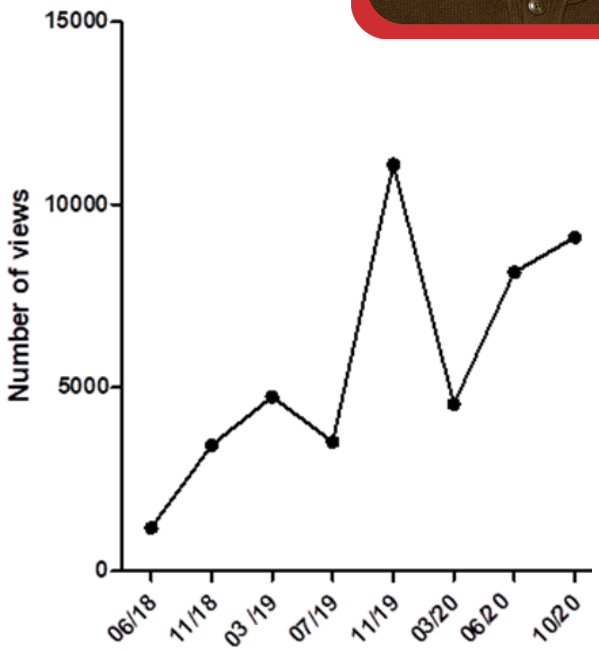

A silver lining from previous times "The pudding" clip from Lancet 1961

She was a charming old lady of eighty-seven, whose proximal colon was obstructed. In the X ray two metallic objects, plus one like a faint ghost of the others, were visible in the terminal ileum. I asked her if she had ever swallowed a button. “ Young man,” she bridled, showing scant respect for my grey hairs, “ what do you take me for: why should I want to swallow buttons? Besides, I have a very small swallow and even an aspirin has to be crushed for me.” When further pressed she did remember that her dear brother Albert—“ such a joker he was, poor man ”—told her that on Christmas day ten years back he had put a threepenny bit in her pudding and then vowed that it had disappeared. “ Quite impossible. I could never swallow such a thing.” In due course she had to have a re-section, and there in the last foot of the ileum, thickly encrusted with deposit, lay not only the threepenny piece but a sixpence and the kernel of a nut. When scraped, the silver shone brightly out at us. Later I went over to the laboratory to discuss the slide with the pathologist, who knew nothing of this story. “ I think it’s a carcinoid, probably an argentaffinoma,” he said; “ we are just about to try staining it with silver.” “ Don’t worry,” I told him, “ she’s been trying to do just that for ten years.”

* * *

FEBRUARY 4, 1961 THE LANCET

MEANWHILE IN ‘HYPERTENSION MEWS’...

Holding hands is allowed in Sweden when one lives in the same bubble

Photo by Li Winther (from the Lindholm family)

NEW BLOOD

Introduction

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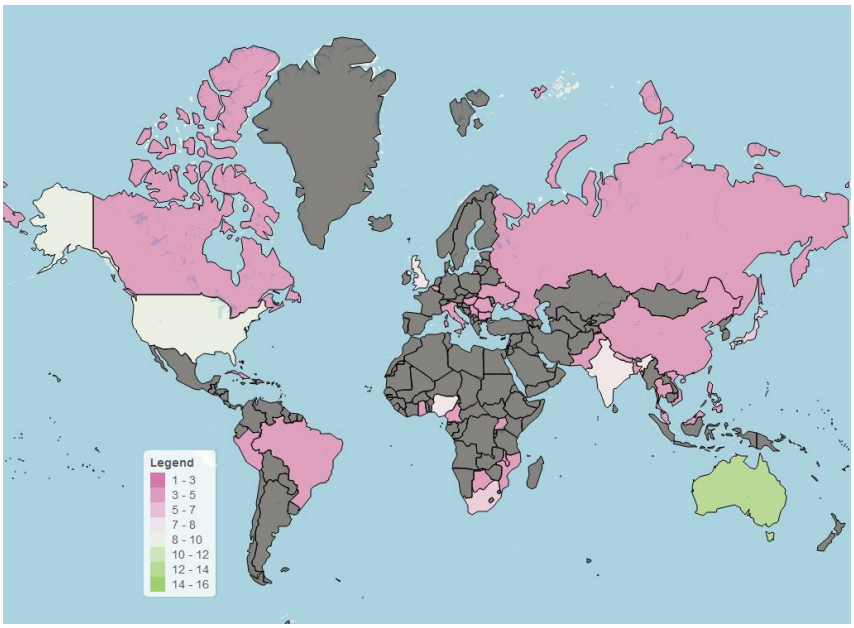
As a global society the ISH can only grow through the recruitment of a new, highly engaged membership which brings fresh energy and creativity to its initiatives. The "New Blood" campaign was developed in recognition of this with the goal of expanding and diversifying leadership.

> *"We would like to recruit ambitious, driven, talented people of diverse age, gender, ethnicity and experience to enhance our leadership".*
>
> **--ISH President Maciej Tomaszewski on the goal of the New Blood Campaign--**

The campaign was initiated by ISH President Maciej Tomaszewski in partnership with the ISH Communications and Membership committees. A digital-heavy strategy focused on reaching individuals mostly likely to have interest in engagement was developed including recruitment videos and graphic-rich social media messaging. The campaign, which ran over approximately 4 weeks, asked individuals to self-declare interest, outline the reason for interest, and identify possible fits within the ISH. Prospective candidates then met with committee chairs to optimize placement and ensure balance across committees. If a strong candidate was not yet an ISH member then an expedited application process was carried out.

By any measure the New Blood campaign has been an overwhelming success. The society has identified numerous fresh faces to support ISH committees and increase global representation. Below you will see a heatmap showing the location of individuals recruited through the New Blood campaign.

As you can see the campaign recruited new leaders from all five continents. While regions where ISH has been historically strong (such as Australia) were well represented, there was also an encouraging level of recruitment in under-represented areas (i.e. South America and Africa). In total, more than 70 new leaders from 43 different countries were recruited through the New Blood campaign and they are quickly becoming actively involved in ISH committees and regional advisory groups.



Hypertension News will have a new feature "New Blood" which will introduce new leaders and provide them with the opportunity to share their thoughts on hypertension with the ISH community. This is done in cooperation with Brandi Wynne, Chair of the Young Investigator Committee who introduces her committee on page 37. This month (see below) Charlotte Mills, Adeyanju Oluwaseun Aremu, Praew Kontruchin, Elizabeth Muxfeldt share their thoughts. Stay tuned in future issues for further contributions from our New Blood!

Another key aspect of growing the ISH is mentoring of the next generation of leaders. Francine Marques, Chair of the ISH Mentoring and Training Committee discusses the topic mentorship on p 35. Be sure to check out this article with insights from several of the excellent ISH Mentorship podcasts.

Members recruited to ISH Committees and Groups (2020-2022) via the New Blood Campaign

•1st row from left to right: Anne Monique Nuyt (Canada), Tazeen Jafar (Singapore), Niamh Chapman (Australia), Jafar Alsaid (Bahrain), Audrey Adji (Australia), Abiodun Adeoye (Nigeria), Fady Hannah Shmouni (USA), Xin Joy Wang (UK)

•2nd row from left to right: Henry Ndhlovu (Malawi), Philippe Delmotte (Belgium), Heddwen Brooks (USA), Erwinanto Erwinanto (Indonesia), Elizabeth Muxfeldt (Brazil), Satoko Nakamura (Japan), Daniel Piskorz (Argentina), Abdullah Shehab (UAE)

•3rd row from left to right: Diego Lucumi (Colombia), Joseph Flynn (USA), Alice Veronika Lamwaka (Uganda), Rana El-Bikai (Lebanon), Swapnil Hiremath (Canada), Augustine Odili (Nigeria), Erika Jones (South Africa), Eun Joo Cho (South Korea).

•4th row from left to right: Charlotte Mills (UK), Mohammad Ishaq (Pakistan), Neusa Jessen (Mozambique), Siska Danny (Indonesia), Kazutoshi Miyashita (Japan), Vikas Kapil (UK), Tshewang Gyeltshen (Bhutan), Evi Christofidou (UK)

•5th row from left to right: Adrian Stanley (UAE), Manja Zec (Serbia/USA), Tatuso Shimosawa (Japan), Lebo Gafane-Matemane (South Africa), Dinesh Neupane (Nepal / USA), Kei Asayama (Japan), Ayodipupo Oguntade (Nigeria), Karla Neves (Brazil / UK)

•5th row from left to right: Praew Kotruchin (Thailand), Dagmara Hering (Poland), Adam Greenstein (UK), Mariane Bertagnolli (Canada), Chloé Landry (Canada), Yook-Chin Chia (Malaysia), Shariful Islam (Australia), David Cardona Muller (Mexico)

•6th row from left to right: Chukwuemeka, Nwokocha (Jamaica), Pablo Ortiz (USA), Lingkan Barua (Bangladesh), Nicolás Renna (Argentina), Akira Nishiyama (Japan), Tawfik Albassam (Saudi Arabia), Lizzy Brewster (Netherlands), Udaya Ralapanawa (Sri Lanka)

•7th row from left to right: Abid Amin Khan (Pakistan), Rikeish Muralitharan (Australia), Carina Mels (South Africa), Tiny Masupe (Botswana), Quynh Nhu Dinh (Australia), Yuqing Zhang (China), Betty Twumasi-Ankrah (Ghana), Hae-Young Lee (South Korea)

•8th row from left to right: Zhiyi Ma (China), Matias Gabriel Zanuzzi (Argentina), Priscilla Prestes (Australia), James Eales (UK), Pensee Wu (UK), Mirakhmadjon Mirmaksudov (Uzbekistan), Juliana Kagura (South Africa), Abhinav Gupta (India)

•9th row from left to right: Praveen Veerabhadrappa (USA), Colin Sumners (USA), Ghazi Haji (Iraq), Rodrigo Maranon (Argentina), Lance Dworkin (USA), Débora Simões de Almeida Colombari (Brazil), Stefano Taddei (Italy)

• Not pictured: Ana Barrientos (Honduras) and Sheila Patel (Australia)

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NEW INVESTIGATOR PAPER

'Superfoods' and the antioxidant fallacy: The impact of (poly)phenols on cardiovascular health

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'Let food be thy medicine and medicine be thy food' is attributed to Hippocrates and is still a pertinent message in today's society. The general population are fascinated by the impact of food on health and the media frequently report on the next dietary trend. The term 'superfood' is commonplace in modern day vocabulary. According to the Oxford English Dictionary it is used to describe 'food considered especially nutritious or otherwise beneficial to health and well-being'; arguably almost all foods could be defined in this way, making the term somewhat redundant. Nonetheless, berries, green tea and cocoa are commonly referenced as 'top superfoods' and one thing these foods have in common is high quantity of (poly)phenols; a class of secondary plant metabolites ubiquitous in the foods we eat suggested to reduce risk of many non-communicable diseases. (Poly)phenol classification with example foods is shown in Figure 1.

Evidence for cardio-protection

Interest in the association between (poly)phenols and cardio-protection stemmed partially from observation of the Kuna Indians. Kuna Indians inhabit islands off the coast of Panama but have much lower blood pressure and incidence of cardiovascular diseases than their Panamanian neighbours; one notable feature of their diets is their high intake of a cocoa drink high in (poly) phenols. (Poly)phenols have since been attributed to explaining the French Paradox; a phenomenon whereby the French have a low incidence of cardiovascular disease despite their high saturated fat intake. Epidemiological data for flavonoids (the most researched class), demonstrates reduction of cardiovascular disease risk[1]. Many randomised controlled trials have attempted to prove causality between (poly)phenols and reduction in cardiovascular disease risk factors with evidence for improved vascular function[2]; however, the trials are relatively small scale and short term. The results of the COSMOS trial, a 22,000 participant, 5-year intervention with cocoa flavanols focusing on cardiovascular events are due this year and are hotly anticipated.

Mechanism of action

(Poly)phenols in foods exhibit strong antioxidant capacity *in vitro*, for this reason it was long (and is still frequently) reported that the benefits associated with (poly)phenols are due to antioxidant mechanisms. However, we now know that these compounds are extensively metabolised *in vivo* yielding metabolites which are found in circulation in very low levels (nM-μ M) and have a much lower antioxidant capacity, hence this is highly unlikely. So much so after the USDA (United States Department of Agriculture) has removed their antioxidant database (ORAC Database) from its website acknowledging that the data cannot always be extrapolated to human health.

A definitive mechanism driving (poly)phenols' vascular effects is still yet to be proven, however, we have recently confirmed that it is the metabolites (rather than the native compounds) that play a crucial role in mediating vascular function[3]. One potential mechanism is that they increase circulating nitric oxide. Despite the structural differences, different (poly)phenol classes yield many similar metabolites, an example of this is the production of ferulic acid and associated sulphates and glucuronides. Ferulic acid is structurally very similar to apocynin (an established NADPH-oxidase inhibitor), hence it is quite possible that (poly) phenols may act in a similar way, inhibiting NADPH oxidase and hence formation of reactive oxygen species, thus increasing nitric oxide bioavailability.

Dietary approaches to managing cardiovascular disease are becoming accepted by both

patients and medical professionals, but a better understanding of the benefits of different food components is essential. (Poly)phenol rich foods offer promise for the treatment and prevention of cardiovascular disease.

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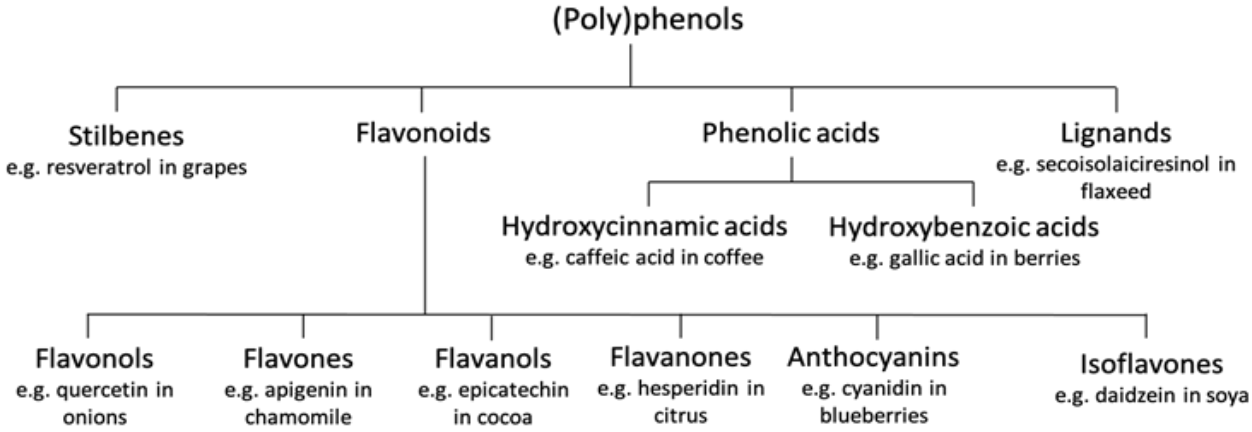
Figure 1: (Poly)phenol classification



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NEW INVESTIGATOR PAPER

Cinderella called MR: Low dose spironolactone as therapeutic target against cardiometabolic disorder induced by estrogen deficiency

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Globally, cardiometabolic disorder is assuming an increasing role as a major cause of morbidity and mortality. Cardiometabolic disorder identifies a cluster of metabolic disorders that occur together; affected individuals have up to 2 times higher risk of a major cardiovascular event, 3 times higher risk of chronic renal insufficiency, more than 4 times higher danger of developing type 2 diabetes mellitus, incidence of congestive heart failure and cardiovascular mortality. Sex differences seem to have a say in the development of cardiometabolic disorder; a women's risk increases sharply during menopause, a state of estrogen deficiency. The fact is this: many women will spend the second half of their lives in a state of estrogen deficiency. Thus, the contribution of estrogen deficiency in the pathobiology of multiple chronic diseases in women is a conceivable therapeutic challenge of the 21st century and worth looking into. This made me have a keen interest in this aspect of science as

there is the need to address this growing problem and the only way is improved understanding of how estrogen deficiency contributes to cardiometabolic disorder. This promises to open a novel therapeutic application for an increasing large segment of the female population.

The mineralocorticoid receptor is a member of the steroid receptor family and is the effector of mineralocorticoid's cellular response. The mineralocorticoid receptor is referred to as the 'Cinderella' of the steroid receptors due to the fact that not much attention was given to it until it was identified that its activation was involved in cardiovascular disease[1], hence, prompting me to join this 'new wagon' of interests.

I joined the HOPE cardiometabolic research unit of the Department of Physiology, University of Ilorin, Nigeria under the joint supervision of Professors Soladoye and Olatunji to explore and see if there is a connection between the activation of the mineralocorticoid receptor and challenges that comes with estrogen deficiency, and to see if blocking of the mineralocorticoid receptor can proffer solution to this challenge. Before I joined the unit, my supervisors had worked for some time on combined oral contraceptives and going by their previous findings, combined oral contraceptives can create estrogen deficient state, hence, giving me one model to suppress the estrogen functions of ovaries. I found that combined oral contraceptives effectively induced estrogen deficiency and with it, noticeable cardiometabolic disorder; this was reversed with the treatment of low dose spironolactone. Whilst mineralocorticoid receptor blockers work through the aldosterone pathway, I found that the therapeutic potential of the low dose spironolactone can be independent of aldosterone-pathway but through a corticosterone – dependent pathway[2]. I decided to create an experimental surgical rat model by totally removing the ovaries and treating with or without combined oral contraceptives to mimic a postmenopausal status. Removal of the ovaries activated the mineralocorticoid receptor and induced cardiometabolic disorder[3]. Treatment with low dose spironolactone however, effectively replenished the depleted estrogen and reversed the cardiometabolic disorder induced by estrogen deficiency, also through corticosterone dependent pathway. The interesting thing here is this, low dose spironolactone could actually be used as hormone replacement therapy. More so, combined oral contraceptives seemed to effectively reverse the cardiometabolic disorder induced by surgical removal of the ovaries, however, combination of the combined oral contraceptives with the low dose spironolactone in a state of estrogen deficiency works more effectively[3]. With further curiosity, I went ahead and decided to look at the effectiveness of the low dose spironolactone in an experimental model of polycystic ovarian syndrome, one of the major causes of infertility in women of reproductive age! The low dose spironolactone completely blocked the activation of the mineralocorticoid receptor and improved the cardiometabolic disorder induced by polycystic ovay syndrome[4,5]. This indeed shows that the mineralocorticoid receptor has its 'Cinderella' in low dose spironolactone.

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NEW INVESTIGATOR PAPER

Hypertensive emergencies; Clinical, treatment, and outcomes in the Southeast Asians

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Hypertension is a well-known modifiable risk factor of major cardiovascular events[1]. However, despite the availability of treatment choices, only a minimal improvement in the hypertension control rate has been reported worldwide.[1]

Patients with uncontrolled hypertension can develop hypertensive crises, which can be classified under 1) hypertensive emergencies or 2) hypertensive urgencies, according to the presence or absence of acute target organ damage[2].In cases of hypertensive emergencies, intensive blood pressure (BP) control should be carried out over a designated time frame to limit the extension of target organ damage.[2]

The prevalence rate of hypertensive crises in Asia was varied according to different cut-off BP level, in Thai population, the prevalence was 64/100000 patients-year.[3] However, there was limited information about the clinical presentation, treatment, and outcomes of hypertensive emergencies in the Southeast Asians. Therefore, we conducted a longitudinal study that ran from 2016-2019.[4] The results showed that the prevalence rate of hypertensive emergencies was 2.2%. The mean age of the patients was 66 years old. Both the prevalence rate and the mean age were higher than that found in the European populations.[2] Interestingly, more than half of the patients were known to have hypertension (64%), moreover, 20% of the patients once had prior strokes. This was partly due to poor adherence and compliance to antihypertensive treatments.

Most of the patients in our study suffered from strokes (63%). The second most common type of target organ damage was cardiovascular disease; 19.3%, 6.5%, and 2.5% presented with acute heart failure, acute coronary syndromes, and acute aortic diseases, respectively. Regarding treatments in the emergency room (ER), only 42% of the patients were prescribed IV antihypertensive medications. Since the most common target organ damage was attributable to strokes, a higher BP target was generally accepted to maintain the autoregulation of the intracerebral blood flow (up to 180/105 mm Hg in the patients who were prescribed thrombolysis and up to 220/120 mm Hg in those who were not given thrombolysis). Therefore, IV antihypertensive medication was not prescribed immediately. This could explain the lower rate of IV antihypertensive medication prescriptions given in our study. The outcomes of ER treatment were favorable with a lower than 1% mortality rate. While the hospital admission rate was relatively high (80%). The in-hospital mortality rate in our study was 1.6%, which was lower than that found in an American study (3-4.5%).[5]

Hypertensive emergencies are burdens in the ER, causing ER crowding, consuming time, manpower, and cost of treatments. Asians tended to have differential characters compared with Caucasians. Poor adherence of treatments in the known hypertensive patients was one of the risk factors for developing hypertensive emergencies. Doctors should provide their efforts for giving health education and should encourage patients to adhere with antihypertensive treatments and healthy lifestyles.

Finally, the attempt to find for a correct diagnosis and give appropriate treatment are very important for the favorable outcome in hypertensive emergency patients. Since the target organ damage is a determinant of the choice of treatment, the time frame, and the target BP.

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NEW INVESTIGATOR PAPER

Refractory hypertension: A new phenotype?

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Refractory hypertension is not a continuum of resistance to blood pressure treatment, but a new phenotype that demands anticipation and priority. In fact, we are talking about two sides of the same disease.

Refractory hypertension was recently described, and its definition is still being developed.[1] Initially, it was described as an extreme phenotype of resistant hypertension – a continuum of severity – based on the premise that the evolution of hypertension is a cycle in which high blood pressure (BP) causes more endothelial dysfunction and consequently a higher increase in BP, that is, higher resistance to treatment. Currently defined as uncontrolled BP despite the use of 5 or more drugs, including a long-acting thiazide diuretic and a mineralocorticoid receptor antagonist, refractoriness deserves to be better discussed and investigated.[2,3]

For over 20 years, I have been following a large cohort of resistant hypertensives and it was possible back then to distinguish a more severe clinical presentation, frequently associated to younger patients. That situation did not seem to be related to a progressive worsening of a disease caused by endothelial dysfunction since it was less prevalent in individuals with resistant hypertension for many years. Actually, it was noticed mainly in those ones with hypertension of early beginning.

From this initial definition, several studies were developed analyzing the pathophysiology of refractory hypertension and it looks better elucidated nowadays. These findings point out that sympathetic hyperactivity is related to refractoriness while resistant hypertension would be more associated to volume component and hyperaldosteronism status with a good response to diuretics and mineralocorticoid receptor

antagonists, reinforcing the hypothesis that these are two distinct clinical conditions.[2,3]

Another point that still needs to be better defined is whether refractoriness should be based on the absence of office BP control or ABPM/HBPM. Since ABPM is mandatory in resistant hypertension clinical follow-up, I believe that refractory hypertension should also be based on uncontrolled out of office BP without the need of using the distinctive term true refractory hypertension.[4]

In different populations described so far, refractory patients are more frequently women, younger, obese, diabetic and have metabolic syndrome.[5,6] Most of the studies have described a high prevalence of asymptomatic hypertension-mediated organ damage.[3,5] Being a historical cohort, in our recently published study6 we were able to divide refractory patients between pre- and post-spironolactone eras. Surprisingly, we identified that, despite the lack of BP control when using 5 or more drugs, the introduction of spironolactone showed an improvement in the cardiovascular risk profile with less aortic stiffness and decrease in left ventricular mass. Still, further robust longitudinal studies are needed to let us know the actual prognosis of refractory hypertension.

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NEW BLOOD

Mentoring: a priceless relationship

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Priceless. Crucial. Helpful. Opportunity. Network. Satisfying. These were the words the six senior members of our research community used to describe their mentoring experience when interviewed for the ISH Podcast in 2020. Professor Rhian Touyz, the first female president of the ISH as well as the first mentor we interviewed, said *"Mentorship is important because I feel one can always learn from others".* Professor Stephen Harrap, also a past ISH president, spoke about mentoring providing *"an objective independent view to the mentee".* Professor Maciej Tomaszewski, current president of the ISH, adds "*You need someone who you can look up to because that makes your life much easier and you can benefit enormously".*

It was inspiring to hear the many ways our interviewees have helped their mentees. Examples included guiding them on career choices after training or how to climb the professional ladder,

serving as referees for job applications or awards, introducing mentees to leaders in the field, promoting their work, and stimulating their passion about research. Professor Xin-Hua Zhang, president of the World Hypertension League, says *"Mentors can share their knowledge and network"*, and by many different ways support mentees to achieve their goals. Associate Professor Dylan Burger, chair of the ISH Communications Committee, adds "*It all starts by having a conversation with the person and finding what they want to get out of the relationship (...), and working with them to do what you can to help".*

Who needs a mentor, and when?

From the interviews, the unanimous comment was that everybody benefits from mentoring. Professor Alta Schutte, the second female president of the ISH, mentions that a great time to start a mentoring relationship is early during PhD training. She mentions that many PhD students do not plan ahead their careers. By inviting her mentees to have a discussing about it she could inspired them to identify and follow their ambitions. Professor Touyz added: *"The earlier you can engage with a mentor the better it is",* but as Professor Zhang states *"At every stage of your life you need a mentor".*

How many mentors one needs?

A recent survey of 508 American College of Cardiology cardiologists identified that those with a team of 3 or more mentors external to their institution had higher satisfaction with their mentoring experience.[1] This satisfaction was association with their perceptions of achieving their career goals.[1] Indeed, Associate Professor Burger says during his career he has had many mentors, who have been fundamental for his career progress. He added *"Don't think of mentoring as a single match of one mentor and one mentee, but look for many mentors that are going to help you in various areas of your career development".*

What makes a great mentee?

Many of our interviewees said that great mentees are open-minded. Professor Harrap explains *"Opportunities would appear out of the blue and even thou you have a plan in your mind if you don't deviate (...) you might miss a really excellent opportunity"*. Professor Schutte comments that a great mentee gets out of their comfort zone and has the *"willingness and ability to reach out despite the fact that it is daunting to do so".* Indeed, Professor Touyz says that it is crucial for mentees to be comfortable to share their concerns with their mentors, so they can help. Professor Tomaszewski adds that great mentees are ambitious, driven, curious and passionate about research.

In times where uncertainty is the norm, turning to mentors for support is crucial, especially for early- and mid-career researchers.[2] Professor Tomaszewski says that in the past mentoring relationships happened organically, without a structured system such as a mentoring program. This meant, however, many would miss out on the opportunity to have a mentor. Professor Tomaszewski says that *"we were one of the first societies to put such a strong emphasis on the new generation".* While earlier versions of the program existed, the ISH Mentoring Scheme as we know now was launched in the 2014 Athens congress. The scheme continues to support our community today – everyone is welcome to apply to be matched with a mentor. If you would like to be matched with one of our senior members, all you need to do is to complete this form. We learned much during the interviews and hope all our members enjoy listening and learning about maximizing their mentoring experience. We welcome new nominations of interviewees, both leaders and emerging leaders within the ISH.

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COMMITEE REPORT

New Investigator Committee chair update

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Welcome everyone to 2021! To say that this past year has been one of the most difficult in memory, is an understatement. This is especially true for early career researchers, who have had to juggle new and unfamiliar territory- not only in our careers but family, friends and society. As your New Investigator Committee (NIC), we hear your concerns and have initiatives that we hope will help to invigorate new investigators.

First, I'd like to introduce you to ***your*** NIC. Everyone is beyond excited to develop programs we hope will aid your career. This new committee is comprised of three separate arms- Outreach, Communications and Advancement & Promotion- which also broadly defines our goals. I serve this team as chair, and couldn't be more excited about our momentum. I am a predominantly basic science/discovery researcher based in Salt Lake City Utah (US) and an Assistant Professor of Internal Medicine in the Division of Nephrology & Hypertension at the University of Utah. I obtained my PhD at the Medical College of Georgia and then completed my postdoctoral training at Emory University (Atlanta GA). A physiologist by training, my research focuses on the intersection of hypertension and inflammation, with a strong focus on the contribution of both the cardiovascular and renal systems to hypertension. The other members of the committee are as diverse as the greater hypertension community; from nutrition and metabolism to microbiome, clinical and discovery.

As a committee, we recognize that new investigators have a choice in the societies they choose to speak for them, and our goal is to better serve the new investigator community. To do so, we have formed three main 'arms' of the NIC, each with goals and new initiatives. In the coming weeks, old members will notice we have also kept some of the popular initiatives, so please be sure to check the website, mailers and ISH e-bulletins to keep up-to-date. This is our first 'arm': Communications. With the COVID-19 pandemic, we all recognize the importance of maintaining a network. The NIC would like you to become part of our greater network. We will be launching several new hashtags to help keep you informed on social media/twitter, making it easier for you to access information. Additionally, with the help of the editorial team at Hypertension News, we will be promoting new investigators (trainee to junior faculty level) in every issue. Below, you'll also notice that the NIC has a new email address, a direct line. We hope that you'll use this to connect with us.

Our second 'arm' is: Advancement & Promotion, with the sole goal to help promote and advance your career. We wish to highlight you and your work in the popular New Investigator Spotlight and re-vamped Our Fellows Work, starting this month. Coming soon, a new 'advice column' is also debuting- Words of Wisdom. This initiative will highlight specific scientific knowledge or advice, aimed to answer precise questions by ISH early career researchers (rolling out, March 2021). We encourage the membership to submit nominations, questions or concerns, and the NIC will solicit advice from experts. This is your place for answers, so don't be shy. And lastly, this subcommittee has been working with other ISH committees to develop programs and webinars. More details to follow soon, but we hope to see you there!

Our last 'arm' is: Outreach. The Outreach subcommittee was formed with two main goals

in mind; exploring ways to better serve current members, and reaching out to new members. This subcommittee will be communicating with you in the near future to determine how we can improve. We want to know what your needs are, and how we can help. This subcommittee is committed to ensuring representation, and has a special interest in regions and populations that are underserved by the NIC. One new initiative starting this month (March, 2021), will be the interactive and virtual ISHLive series. The first of these events will be an "Introduction to ISH". This first #ISHLive event will showcase what ISH has to offer and will feature ISH President, Professor Maciej Tomaszewski.

We are excited about the future of the NIC, and hope these events help you during these uncertain times. We encourage your participation, and look forward to 'seeing' you soon. Please feel free to contact me if you have any suggestions.

NIC Advance - Promotion Working Group

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NIC Communications Working Group

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COMMITEE REPORT

Women in Hypertension Research Committee: Goals and Launch of the WiHR Network

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The Women in Hypertension Research Committee (WiHRC) was founded in 2016 by ISH Past-President Rhian Touyz with the mission to encourage, support and inspire women in science and medicine in the field of hypertension and related cardiovascular diseases.

The recent New Blood Recruitment Campaign of ISH has once again revealed the huge interest within ISH membership in the work of the WiHRC. In an attempt to respond to this interest and to actively involve as many ISH members as possible into the work of the WiHRC, the committee has grown significantly with the start of the new presidential term and now consists of 19 members and 2 advisers from 5 continents and 21 countries.

ISH Women in Hypertension Research

WiHRC members, advisors and ambassadors (from top left to bottom right): U. Muscha Steckelings (Denmark/Germany, Chair), Audrey Adji (Australia), Hindh Beheiry (Sudan), Lizzy Brewster (Netherlands/ Suriname), Heddwen Brooks (USA/UK), Niamh Chapman (Australia/Ireland), Eun Joo Cho (South Korea), Siska Danny (Indonesia), Alexandra Konradi (Russia), Ruan Kruger (South Africa), Satoko Nakamura (Japan), Marisol Fernandez-Alfonso (Spain), Karla Neves (UK/Brazil), Anne Monique Nuyt (Canada), Mansi Patil (India), Mariane Bertagnoli (Canada/ Brazil; NIC ambassador), Alta Schutte (Australia/ South Africa), Ching Siew Mooi (Malaysia), Rhian Touyz (UK), Betty Twumasi-Ankrah (Ghana), Pensée Wu (UK/Taiwan), Yan Li (China), Augusto Montezano (UK/Brazil; MTC ambassasdor), Anastasia Mihailidou (Australia; Communication Com. ambassador); Picture courtesy of Anastasia Mihailidou

As during the last presidential term, the committee is chaired by Ulrike Muscha Steckelings, who is also a member of the ISH Council and of the ISH Executive Committee. Muscha is an MD by training, holds a specialisation in dermatology and is currently a Professor of Cardiovascular Pharmacology at the University of Southern Denmark. She has been working for more than 25 years in cardiovascular pharmacology with a research focus on the renin-angiotensin system, in particular the angiotensin AT2-receptor and the development of a first-in-class, orally active angiotensin AT2-receptor agonist.

With 19 members, the WiHRC has now for the first time been divided into 4 working groups. These working groups are responsible for "Communication", "Mentoring", "Science" and "Outreach". To better coordinate collaborations with other ISH committees, the working groups on "Communication", "Mentoring" and "Outreach" are joined by so called "ambassadors", which are members of the ISH Communications Committee, the Mentoring and Training Committee and the New Investigators Committee, respectively.

The overall goal of the work of the WiHRC is to fulfil its mission to encourage, support and inspire women in hypertension research. This will include offering mentoring opportunities for young researchers, to promote science on hypertension in women, and to respond to the great interest in WiHRC by improving our communication with interested ISH members, with other hypertension societies and generally with colleagues interested in our work.

Specific activities, which the WiHRC is currently planning or conducting are

-Publication of a comprehensive review article on Hypertension in Women

-Face-to-face mentoring meetings between junior and senior ISH members

-WiHRC supported ISH Live events addressing topics on Hypertension in Women

-WiHRC supported ISH School events on career development

-Intensifying collaborations with other ISH committees and RAGs

-Partnering with scientific conferences all over the globe

-WiHRC supported science and career development sessions and awards for female researchers at the main ISH meetings 2020 and 2022

In an attempt to specifically respond to the great interest in the WiHRC, the WiHRC is happy to announce the

Launch of the Women in Hypertension Research Network on April 1st 2021.

All ISH members interested in the work of the WiHRC and in creating a WiHRC community are welcome to register their interest with the ISH secretariat: WiHRC@ish-world.com

The WiHRC will then communicate more closely with network members, plan events and meet at the ISH scientific meetings.

Contact:

Follow us on Twitter: #WiHypertenRes

Webpage: https://ish-world.com/women-in-hypertension/about-us.htm

Email: WiHRC@ish-world.com

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Sleeves up, Risk Down: May Measurement Month Returns in 2021

NEIL POULTER

Imperial Clinical Trials Unit, Imperial College London, London, UK

May Measurement Month (MMM), ISH's global campaign to raise awareness of the need for people to get their blood pressure (BP) checked, will be back in 2021. MMM builds on the WHL's established World Hypertension Day — held on 17 May each year - with volunteer health professionals offering free BP measurement at local screening sites across the world.

After three successful years, and over 4.2 million people screened in almost 100 countries, and almost 1 million people identified with untreated or inadequately treated hypertension, MMM was naturally forced to pause in 2020, but is returning in 2021, albeit with a staggered start depending on local conditions, which we are monitoring carefully over the coming months.

83 countries have signed up to participate in MMM this year, but the timing of screening and submitting results has been extended to run at any time between May to November to support the numerous and varying restrictions on access for participants due to the current Covid-19 pandemic. For these countries or sites where the usual MMM screening programme is not possible, even in the extended screening period, we are working with Omron and others, to identify possible alternative ways of BP screening using home BP monitoring.

The new campaign to promote MMM, Sleeves Up, Risk Down, encourages participants to 'roll their sleeves up' and help to tackle the issue and awareness around hypertension, and the 10.8 million deaths due to raised BP that could be prevented each year. It is a positive message of a small action leading to significant change, using the symbol of a rolled-up sleeve as an easy to identify, international symbol of 'getting to work'.

The campaign will be launched with global PR support, local marketing kits for each country, a new website and a social media campaign featuring high-profile ambassadors 'rolling their sleeves up for MMM' encouraging people who have been tested to do the same, and publicly share their support. This awareness raising will be complemented with educational, easy to digest information around BP, what it means, the associated risks and optimal management.

In 2021, the short questionnaire completed by each MMM screenee includes new questions relating to COVID, adherence, birthweight and exercise. We are also planning a collaboration with CDC in the US, to investigate the association between BP and atmospheric pollution as a sub-study of MMM in cities from several countries in the Far East. Other research projects including one on pregnancy associated hypertension, using the MMM database both prospectively and retrospectively are in planning.

Meanwhile, the MMM team has been strengthened by the addition of three mentees from among the ISH membership and of six external luminaries from around the world.

Finally, we are delighted to report that the third MMM supplement including 47 national publications from 2019 is currently in press with the European Heart Journal Supplements.

It is important to remember that even with increased threats to public health due to COVID over the last year, raised BP remains the biggest single contributing risk factor to global death causing about 30,000 deaths per day. It is therefore important that MMM continues to increase public understanding of the importance of BP measurement, and helps to save lives that need not be lost.

For more information about how you can support, contact Harsha at harsha@maymeasure.org.

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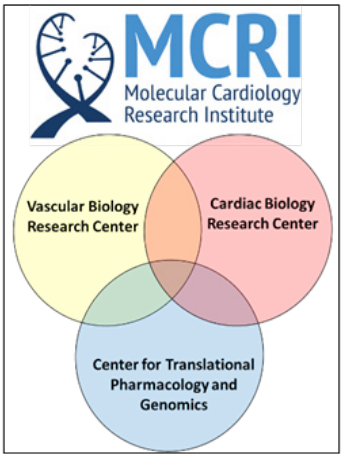
INSTITUTE FOCUS

Molecular Cardiology Research Institute at Tufts Medical Center, Boston, MA

Iris Jaffe

Molecular Cardiology Research Institute at Tufts Medical Center, Boston, U.S.A.

The Molecular Cardiology Research Institute (MCRI) was established in 1998 at Tufts Medical Center in Boston with a tripartite mission of: (1) *advancing our understanding of molecular mechanisms of cardiovascular disease;* (2) *translating these discoveries into improvements in patient care*; and (3) *training the next generation of cardiovascular researchers*. The MCRI was founded and originally directed by Michael Mendelsohn MD from 1998-2010, followed by Richard Karas MD/PhD from 2010-2016, and Iris Jaffe MD/PhD became the third Executive Director in 2016. As of 2021, the MCRI is comprised of 13 Principal Investigators, an intentional combination of PhD scientists and Cardiologist physician-scientists, teamed with 40-50 highly-trained staff and engaged trainees. The MCRI is organized into three collaborative centers: Vascular Biology Research Center (VBRC); Cardiac Biology Research Center (CBRC); and Center for Translational Pharmacology and Genomics (CTPG).



The MCRI is part of Tufts Medical Center, a 415 bed academic medical center and principle teaching hospital for Tufts University School of Medicine, located in downtown Boston. To translate basic discovery into advanced in patient care, the MCRI collaborates extensively with the Tufts Cardiovascular Center, which cares for some of the most complex cardiovascular patients in the area. The Tufts Medical Center Heart Failure and Transplant program is the highest volume program in New England and ranks in the top 10 in the USA. Tufts Medical Center is also a Center of Excellence for care of patients with Hypertrophic Cardiomyopathy (HCM) and the coordinating center for the International Cardiogenic Shock Working Group Registry.

Molecular Cardiology Reserach Institute Annual Retreat, Poster Session
Woods Hole, Massachusetts, September 2019

Historical MCRI Contributions to Vascular Mechanisms of Blood Pressure Regulation:

MCRI Discovers Basic Mechanisms of Vascular Control of Blood Pressure:

While it is established that blood pressure is controlled by regulation of sodium and water balance in the kidney, two decades of MCRI discoveries contributed substantially to the growing appreciation of the vasculature as an additional major contributor to blood pressure control. In 1999, Drs. Mendelsohn and Surks published in Science (Surks HK et. al.) the novel mechanism by which protein kinase G-1 (PKG1) in human vascular smooth muscle cells is targeted to the myosin binding subunit of protein phosophatase-1 to control vasodilation. This interaction assembles a multi-enzyme complex targeted to stress fibers where dephosphorylation of myosin induces vasodilation. This is the critical step regulating smooth muscle cell relaxation in response to nitric oxide. They further determined that phosphorylation of regulator of G-protein signaling-2 (RGS2) by PKG1 is necessary to prevent vessel constriction and hence, RGS2 knockout mice develop hypertension (Tang M. et. al., Nature Medicine, 2003). Indeed, a mouse with point mutations that prevent PKG1 binding to its substrates develops high blood pressure with preserved renal sodium handling, further supporting a vascular mechanism of hypertension (Michael S et. al., PNAS, 2008).

MCRI Insights into Hormonal Mechanisms Controlling Vasomotor Function and Blood Pressure:

MCRI investigators have a long history of studying hormonal regulation of vascular function and the impact on blood pressure control. The Mendelsohn and Karas teams demonstrated that human vascular smooth muscle cells and endothelial cells express functional estrogen receptors that respond by genomic (transcriptional) and non-genomic (rapid signaling) mechanisms to protect the vasculature from injury. They found that estrogen receptor is tethered to the membrane by the scaffolding protein striatin to form a complex that mediates rapid signaling to activate nitric oxide and induces vasodilation (Lu Q et. al., PNAS, 2004). Indeed, Yan Zhu and colleagues demonstrated that mice lacking estrogen receptor beta have enhanced vasoconstriction and hypertension *(Science, 2002*). These discoveries contribute to our growing understanding of how premenopausal women are protected from cardiovascular disease and hypertension relative to age-matched men.

MCRI Determines a Role for Mineralocorticoid Receptors in Smooth Muscle in Aging-Associated Blood Pressure Elevation:

Mineralocorticoid hormones and the mineralocorticoid receptor (MR) are critical regulators of blood pressure by controlling renal sodium and potassium channels in the distal nephron. The Jaffe lab demonstrated that MR expressed in human vascular smooth muscle and endothelial cells can respond directly to aldosterone or be activated by hormone-independent mechanisms by angiotensin II (Jaffe and Mendelsohn, Circulation Research, 2005). In 2012, McCurley and colleagues showed that mice with MR deleted specifically from smooth muscle are protected from rising blood pressure with age (McCurley AM et. al. Nature Medicine, 2012). Further studies revealed that, as in the kidney, MR in vessels controls ion channels and that by regulating the L-type calcium channel, MR in smooth muscle contributes to vascular tone and vasoconstriction.

Akiko Hata while in the MCRI, discovered how non-coding micro-RNAs mature in vascular cells to regulate vessel function (Davis BN et al, Nature, 2008). More recently, microRNA155 was identified as a miR that declines in the aging vasculature and contributes to aging vessel constriction (Dupont JJ et al, *JCI Insight, 2016*). Essential hypertension is a disorder of aging, affecting 60% of people over the age of 65, a population in which hypertension is poorly controlled thus, understanding mechanisms for rising blood pressure with age can improve future hypertension management.

Current Research in the MCRI:

The investigators in the MCRI centers work collaboratively to understand how genetics, traditional risk factors and other exposures affect cardiac and vascular function leading to common disorders including heart attack, stroke, heart failure and arrhythmia. The current MCRI investigators and their areas of focus are summarized in the figure.

Molecular Cardiology Research Institute Centers

Vascular Biology Research Center

Investigators:
Iris Jaffe, MD/PhD, Director
Jennifer Dupont, PhD
Mary Wallingford, PhD
Miranda Good, PhD
Basak Icli, PhD

Expertise/Areas of interest:
Mechanisms of hypertension
Vascular cell biology
Vascular injury/remodeling
Atherosclerosis
Aging /Epigenetics
Microvascular function
Sex differences/Women's Health
Wound Healing
Obesity/diabetes complications
Cerebral vessels and stroke
MicroRNAs

Cardiac Biology Research Center

Investigators:
Navin Kapur, MD, Director
Robert Blanton, MD
Howard Chen, PhD
Jonas Galper, MD/PhD
Michael Chin MD/PhD

Expertise/Areas of interest:
Mechanisms of Heart Failure
Mechanisms of Cardiac Fibrosis
Autonomic Dysfn & Arrhythmia
Hypertrophic cardiomyopathy
Cardiac Energetics
Cardiac Device Development
Animal Models of Heart Failure
Invasive Hemodynamics
Nanoparticles for In Vivo Imaging

Center for Translational Pharmacology and Genomics

Investigators:
Gordon Huggins, MD, Director
Isabelle Draper, PhD
Lakshmi Pulakat, PhD

Expertise/Areas of interest:
Genetics
Genomics/Transcriptomics
Pharmacokinetics/Dynamics
Drosophila Genetics
G-protein coupled receptors
Drug Screening in Flies and in Human Cells
Novel drug delivery methods

Cardiac Biology Research Center: investigators explore mechanisms driving heart failure and arrhythmia. The Blanton and Kapur labs are investigating the molecular underpinnings by which pressure overload leads to cardiac fibrosis and heart failure, focusing on targets including PKG1 and endoglin. The Chin lab is using human samples collected by the MCRI biobank from the Hypertrophic Cardiomyopathy (HCM) Center at Tufts Medical Center, to identify novel drug targets for HCM that can be interrogated in the CTPG. The Galper lab studies how diabetes effects the autonomic nervous system to contribute to cardiac arrhythmia and the Chen lab uses nanoparticles to image cardiac damage induced by new cancer therapies. The MCRI also has a track record of innovation in device development for heart failure and PreCardia, a company founded on MCRI technology developed by Drs. Karas and Kapur, recently received breakthrough device designation from the US FDA for a novel catheter-based heart failure therapy.

Vascular Biology Research Center: investigators are interrogating how risk factors including diabetes, hypertension, and obesity contribute to microvascular dysfunction, atherosclerosis and stroke with a focus on sex differences and age-specific mechanisms. The Jaffe lab continues exploring MR roles in vascular disease having recently identified sexually dimorphic mechanisms by which endothelial MR regulates adhesion molecule expression and nitric oxide production to contribute to sex-differences in atherosclerosis and obesity outcomes. Her lab is also examining the impact of novel cancer therapies on vascular function and collaborating with the Tufts Veterinary School to test innovations in clinical trials to protect pet dogs with cancer from cardiovascular toxicity. The Dupont lab studies sex differences in the vascular impact of aging and obesity in humans using laser Doppler flowmetry coupled to intradermal microdialysis. The Wallingford lab is exploring the impact of placental vascular phosphate transport on mother and fetus during and after pregnancy. The Good lab studies the role of cerebrovascular ion channels in stroke outcomes and the Icli lab continues the MCRI journey studying microRNAs in the vasculature, now exploring the impact on wound healing in obesity and diabetes.

Center for Translational Pharmacology and Genomics: investigators work independently and collaboratively with all MCRI investigators to translate discovery into improvements in human health. Gordon Huggins leads the biobank with his own work focused on genetics of HCM and dilated cardiomyopathy. Dr. Pulakat leads drug screening efforts in cells and is developing novel devices to improve drug delivery with her own program focused on angiotensin type-2 receptor agonists to prevent diabetes complications. Dr. Draper directs the drosophila drug screening lab with her own focus on RNA splicing mechanisms as novel drug targets.

MCRI Trainees Present at National and International Meetings

2019 International Aldosterone Conference, New Orleans, LA, USA

2019 APS: Aldosterone and ENaC Conference, Estes Park, CO, USA

Iris Jaffe - ijaffe@tuftsmedicalcenter.org

LET'S REDUCE DISPARITIES IN THE MANAGEMENT OF HYPERTENSION.

Hypertension remains the leading global cause of cardiovascular disease and preventable death.[1] Low- and middle-income countries have more people with hypertension than high-income countries and lower rates of blood pressure control.[2]

These disparities vary significantly according to ethnicity and genetic differences, and are accompanied by lower levels of awareness, treatment, and control.[3]

Read the **2020 International Society of Hypertension Global Hypertension Practice Guidelines** to learn how to start addressing the needs of hypertensive patients worldwide.

ish-world.com

References

[1] Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. *Lancet* 2020; 396:1223-1249.

[2] Mills KT, Stefanescu A, He J. The global epidemiology of hypertension. *Nat Rev Nephrol.* 2020 Apr;16(4):223-237. doi: 10.1038/s41581-019-0244-2. Epub 2020 Feb 5. PMID: 32024986.

[3] Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. *J Hypertens.* 2020 Jun;38(6):982-1004. doi: 10.1097/HJH.0000000000002453. PMID: 32371787.

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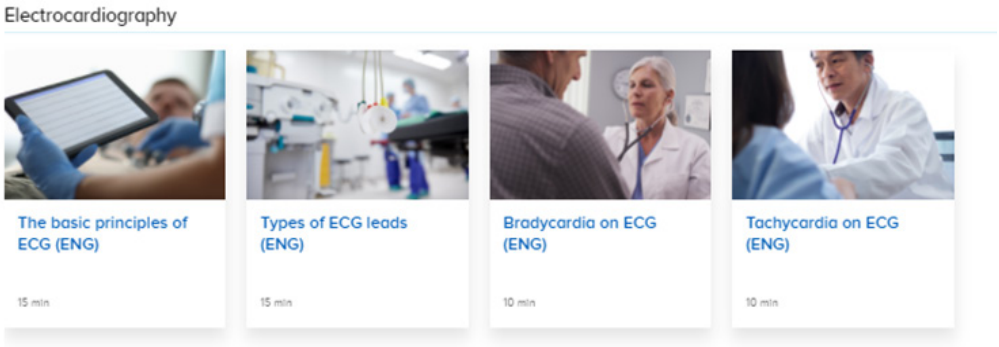
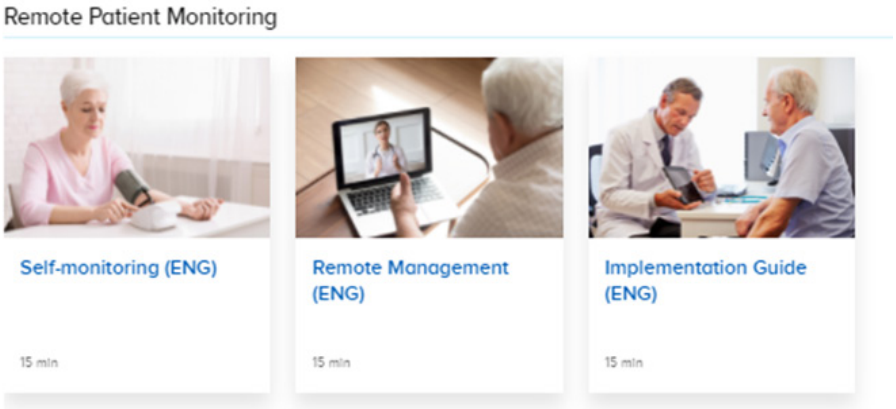
New courses on OMRON Academy Online:

ECG is a fundamental part of cardiovascular assessment and an essential tool for investigating cardiac arrhythmias. Knowing how to read an ECG is of importance for most medical professionals since an early detection of a cardiac disorder can save lives. Learn more on OMRON Academy Online about the basic principles of ECG, the different types of leads and how to assess a bradycardia and tachycardia on an ECG.



Next to this, you will also find the new Remote Patient Monitoring courses. Find out more on the effectiveness of remote management in the new courses about self-monitoring, remote management and guidelines to help implement an approach to hypertension benefitting both patients and health care professional.



Click here to sign-up today and unlock the latest courses related to hypertension!

ESH-ISH 2021

Interested to know more about OMRON Academy from the experts? You can find us at the ESH-ISH 2021 Joint Meeting during our workshop Innovation in the online education of cardiovascular disorders in collaboration with the ESH with prof. Gianfranco Parati and prof. Roland Asmar. Join the workshop to learn more about why the leading medical societies endorse OMRON Academy Online and see it for yourself during a live demonstration. Click here for the full program

15 PhD Fellowships within H2020 Marie Curie programme MINDSHIFT

Would you like to increase our knowledge in understanding the dynamic interactions between vascular and endocrine pathways in hypertension and boost European innovation in future health science and industry towards more effective prevention of and cure for hypertension? Would you like to start your career in a European training network of leading research universities and professionals from the industry? Would you like to be part of a unique training programme focussed on personal development leading to a joint or double doctorate?

MINDSHIFT offers a top-level interdisciplinary research programme to bridge the gap in understanding the dynamic interactions between vascular and endocrine pathways in hypertension, using an integrative framework approach fed by new data and insights from cutting-edge experimental and clinical studies.

MINDSHIFT is an EU funded PhD network coordinated by CARIM, School for Cardiovascular Diseases of Maastricht University, The Netherlands. MINDSHIFT brings together six university partners from across Europe to recruit a group of 15 of the best early stage researchers. The doctoral researchers will work together with senior researchers from across the network. Each candidate will be employed at one of the six universities and enrolled in a local PhD programme, while at the same time being part of an integrated research team and research project at network level.

We invite applications for 3-year PhD fellowships to start between May 2021 and October 2021 to work with one of the host organisations. The Fellows will benefit from secondments in academia and industry, training and transferable-skills courses and active participation in workshops and conferences. You will be offered a salary plus mobility allowance and family allowance (if applicable) in line with the Marie Sklodowska-Curie Horizon 2020 requirements for Early Stage Researchers. For more information on Marie Skłodowska-Curie Innovative Training Networks (ITNs), please see: http://ec.europa.eu/mariecurieactions.

Applicants must satisfy the following eligibility requirements: at the time of the recruitment by the host organisations, the candidates 1) must not have resided in the host country for more than 12 months in the last 3 years, and 2) must be in the first four years of his/her research career and not have a doctoral degree. The fellowship is offered in conjunction with a PhD position, subject to the fellow satisfying the host University's admissions requirements for PhD study.

This Network is formed by 6 internationally recognised research institutions:

- Maastricht University
- University of Glasgow
- Université de Paris
- Universita Degli Studi Padova
- Universidad Autónoma de Madrid
- Universidad Complutense de Madrid

This Network is complemented by 9 partner organisations that will contribute to the research training and personal development programme:

- Attoquant Diagnostics GmbH
- Intelligent Imaging Innovations GmbH
- TMC Data Science b.v.
- Microlife AGv
- Withings
- The Recess College
- Bioscientifica Ltd.
- Tech2Market sp.o.o.
- Quipu

Project details and institutions, indicative starting dates of the positions, application and eligibility criteria and contact persons are available on the MINDSHIFT website. Applications can only be submitted via the vacancy form on the MINDSHIFT website.

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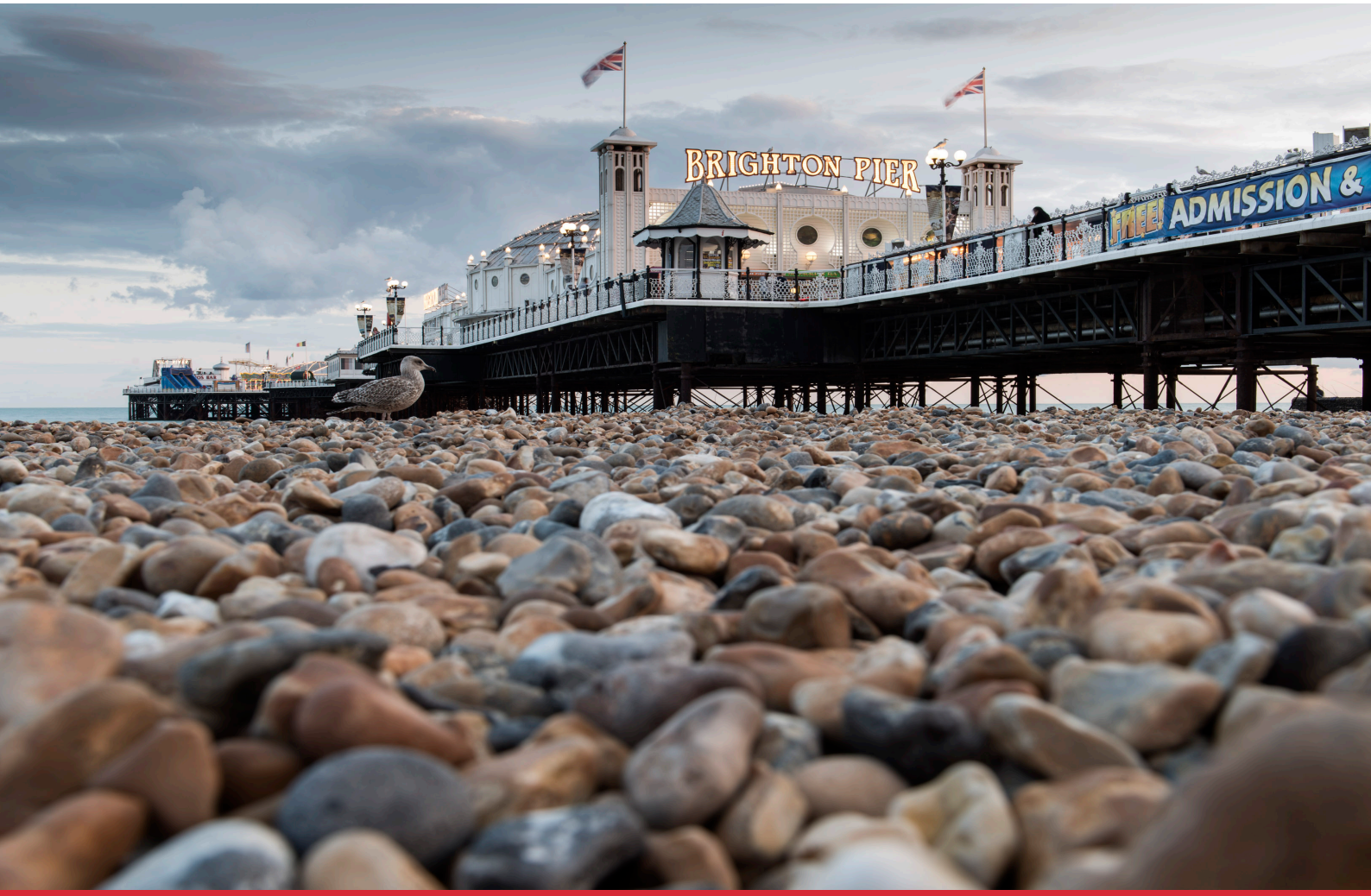

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Activity of the Japanese Society of Hypertension (JSH)

JSH Plan for the Future
Good Blood Pressure for Lively 100 Years

Reduce hypertensive patients by 7 million in 10 years, and Expand the healthy life expectancy
Through…

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

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