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Controversies in hypertension management: target blood pressure, renal nerve ablation, ARNIs, and NSAIDs medication

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Blood pressure has already been assumed to be 'essential' for the perfusion of the organs of our body by William Harvey in his seminal work '*De motu cordis*'.[1] It took another 200 years, however, until the Reverend Stephen Hales for the first time measured it in a conscious horse[2]—an experiment that today would not pass any ethical review board. Although at the turn of the 20th century Riva-Rocci[3] and later Korotkoff[4] provided a simple way to measure blood pressure in humans, it had few clinical implications at that point. Until the 1950s, during the last century, high blood pressure was considered 'essential' in the proper sense of the word, i.e. a normal counter-regulation of the body to ensure proper perfusion in damaged organs. Only after the Second World War did we realize that high blood pressure was actually associated with myocardial infarction, stroke, and premature death. It took another two decades until anti-hypertensive therapy became an accepted approach to prevent these events. Over the next three decades, the recommended target levels of blood pressure in hypertensive patients changed continuously, as did age as a factor for decision-making.

In this Focus Issue on Hypertension, the most recent developments inspired by the publication of the SPRINT Trial are discussed in two position papers taking completely opposite standpoints. Following an introduction by myself to set the stage,[5] Sverre E. Kjeldsen from the Oslo Universitets Sykehus Ulleval in Oslo, Norway provides his opinion in '**A critical review of the Systolic Blood Pressure Intervention Trial (SPRINT)**'. He reminds us that 'SPRINT' was stopped early because of a statistically significant reduction in cardiovascular morbidity and mortality by lowering systolic blood pressure to below 120 mmHg—as is common practice today.[6] He questions the clinical relevance, and criticizes the unconventional method used to measure blood pressure in this trial; therefore >100 years after Riva-Rocci, the discussion on the right way to measure blood pressure continues![7] He claims further that a target blood pressure in regular practice below 120 mmHg might be harmful, particularly in the elderly and those with high entry blood pressure. Vasilios Papademetriou from Washington DC on the other hand counters these arguments with a large body of evidence and supports the notion that this trial will change practice and guidelines in the near future in this opinion piece entitled '**SPRINT is a landmark trial: results should be adopted in clinical practice**.'[8]

Another controversy in hypertension management is the use and value of renal nerve ablation.[9] While the unblinded Symplicity-HTN-2 trial was positive, the sham-controlled Symplicity-HTN-3 was neutral,[10] although a subanalysis showed that with >12 ablations, a similar blood pressure-lowering effect was obtained.[11] Later the French DEBNERHTN trial, although not sham controlled, raised new hope,[12] but Prague-15 was again a bit disappointing.[13] At this year's ESC in Barcelona, the SPYRAL-HTN OFF-MED trial in untreated hypertensives was presented and published.[14] In their *Viewpoint* '**Renal denervation: will the Phoenix rise from the ashes?**'[15], Sripal Bangalore and Franz H. Messerli from the New York University School of Medicine put the results into perspective and compare them with the blood pressure-lowering effects of commonly used anti-hypertensive drugs.

This issue continues with another *Current Opinion* entitled '**Proceedings from the 2nd European Clinical Consensus Conference for device-based therapies for hypertension: state of the art and considerations for the future**' by Felix Mahfoud and colleagues from the University Hospital Saarland in Homburg, Germany.[16] The authors remind us that a substantial proportion of hypertensives remain inadequately controlled,[17] and this has prompted the development of interventional approaches.[18] Several devices have been developed and tested. Even though based on strong pathophysiological rationale, catheter-based renal denervation has not conclusively demonstrated its value for the treatment of

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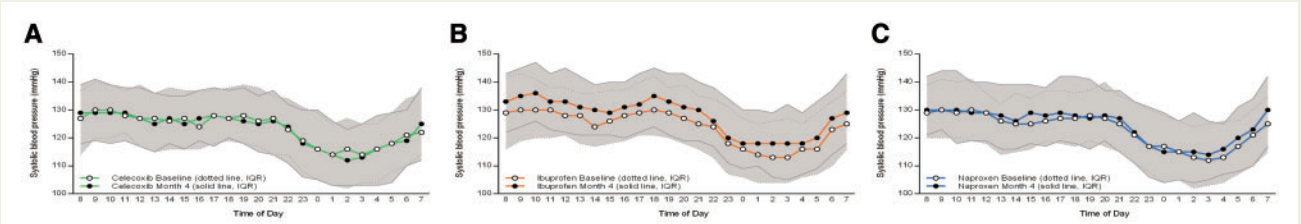

Figure 1 The hourly ambulatory SBP curves over 24 h (median and first and third quartiles) at baseline and at month 4 for the three treatment groups (*P* for change in 24-h SBP for ibuprofen <0.001; for celecoxib and naproxen *P* = 0.801 and 0.117, respectively) (from Ruschitzka F, Borer J-S, Krum H, Flammer A-J, Yeomans N-D, Libby P, Lüscher T-F, Solomon D-H, Elaine Husni M, Graham D-Y, Davey D-D, Wisniewski L-M, Menon V, Fayyad R, Beckerman B, Iorga D, Michael Lincoff A, Nissen S-E. Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective 5 Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) Trial. See pages 3282–3292).

resistant hypertension, and its place in the therapeutic armamentarium remains uncertain. Other device-based approaches under investigation include the creation of a central iliac arteriovenous anastomosis with a coupler, stimulation of the carotid sinus, ablation of the carotid body, and stent-based expansion of the carotid bulb. The expert group reviews the current evidence and its implications for future clinical trials.

Non-steroidal anti-inflammatory drugs, both non-selective and selective cyclooxygenase-2 (COX-2) inhibitors, are among the most widely prescribed drugs, but have been associated with increased blood pressure[19] and adverse cardiovascular events.[20–22] In their *FAST TRACK* '**Differential blood pressure effects of ibuprofen, naproxen, and celecoxib in patients with arthritis: the PRECISION-ABPM (Prospective Randomized Evaluation of Celecoxib Integrated Safety Versus Ibuprofen or Naproxen Ambulatory Blood Pressure Measurement) trial**', Frank Ruschitzka and colleagues from the University Heart Center Zurich in Switzerland report the results of PRECISION-ABPM, a substudy of the large PRECISION trial, which was conducted at 60 sites, to determine blood pressure effects of the selective COX-2 inhibitor celecoxib vs. the non-selective non-steroidal anti-inflammatory drugs naproxen and ibuprofen.[23] In this double-blind, randomized, multicentre non-inferiority cardiovascular safety trial, 444 patients mainly with osteoarthritis and to a lesser extent with rheumatoid arthritis and evidence of or at increased risk for coronary artery disease received either celecoxib 100–200 mg bid, ibuprofen 600–800 mg tid, or naproxen 375–500 mg bid in a 1:1:1 allocation. After 4 months, changes in blood pressure were assessed using 24-h ambulatory blood pressure monitoring. Celecoxib reduced the mean 24-h systolic blood pressure by –0.3 mmHg, while ibuprofen and naproxen increased it by 3.7 and 1.6 mmHg, respectively (*Figure 1*). These changes resulted in a difference of 3.9 mmHg between celecoxib and ibuprofen, of 1.8 mmHg between celecoxib and naproxen, and of 2.1 mmHg between naproxen and ibuprofen. The percentage of patients who developed hypertension was 23.2% for ibuprofen, 19.0% for naproxen, but only 10.3% for celecoxib. The authors conclude that the non-selective non-steroidal anti-inflammatory drug ibuprofen, compared with the selective COX-2 inhibitor celecoxib, was associated with a significant increase of systolic blood pressure, and a higher incidence of new-onset hypertension. These clinically relevant findings are further discussed in a comprehensive **Editorial** by William S. Weintraub from the Christiana Care Health Services in Newark, Delaware, USA.[24]

The value of 24-h blood pressure recording used in the previous study is evaluated in a research paper entitled '**Office blood pressure or ambulatory blood pressure for the prediction of cardiovascular events**' by Christian Torp-Pedersen and colleagues from the Aalborg University and Aalborg University Hospital in Denmark. They sought to determine the added value of 24-h ambulatory blood pressure relative to office blood pressure, and night-time ambulatory blood pressure relative to daytime ambulatory blood pressure for 10-year person-specific absolute risks of fatal and non-fatal cardiovascular events in a cohort of 7927 individuals.[25] No differences in predicted risks were observed when comparing office blood pressure and ambulatory blood pressure. When comparing daytime and night-time blood pressure, the median difference in 10-year risks was also minimal for cardiovascular mortality and events. Thus, 10-year predictions obtained from ambulatory blood pressure were similar to those derived from office blood pressure (*Figure 2*). Night-time blood pressure did not improve 10-year predictions obtained by daytime measurements. As such, in healthy individuals, office blood pressure provides sufficient prognostic accuracy of cardiovascular risks. These practically relevant findings are put into context in a balanced **Editorial** by Thierry Gillebert from Ghent University in Boechout, Belgium.[26]

Important target organ damage of high blood pressure is progressive aortic stiffening,[27] left ventricular hypertrophy,[28] and heart failure.[29] Thus, the reversibility of these changes in cardiovascular function and structure is an important therapeutic aim. Although established anti-hypertensive agents reverse this to some extent, the novel angiotensin receptor/neprelysin inhibitors or ARNIs that showed impressive effects in heart failure[30,31] have not been tested yet. In their clinical research article '**The effect of sacubitril/valsartan compared with olmesartan on cardiovascular remodelling in subjects with essential hypertension: the results of a randomized, double-blind, active-controlled study**', Roland E. Schmieder and colleagues from the Friedrich-Alexander-Universität Erlangen-Nürnberg in Germany investigated the effects of LCZ696, a dual-action angiotensin receptor blocker and neprilysin inhibitor compared with olmesartan, on arterial stiffness and left ventricular remodelling in a randomized, multicentre, double-blind trial involving 114 hypertensives with elevated pulse pressure.[32]

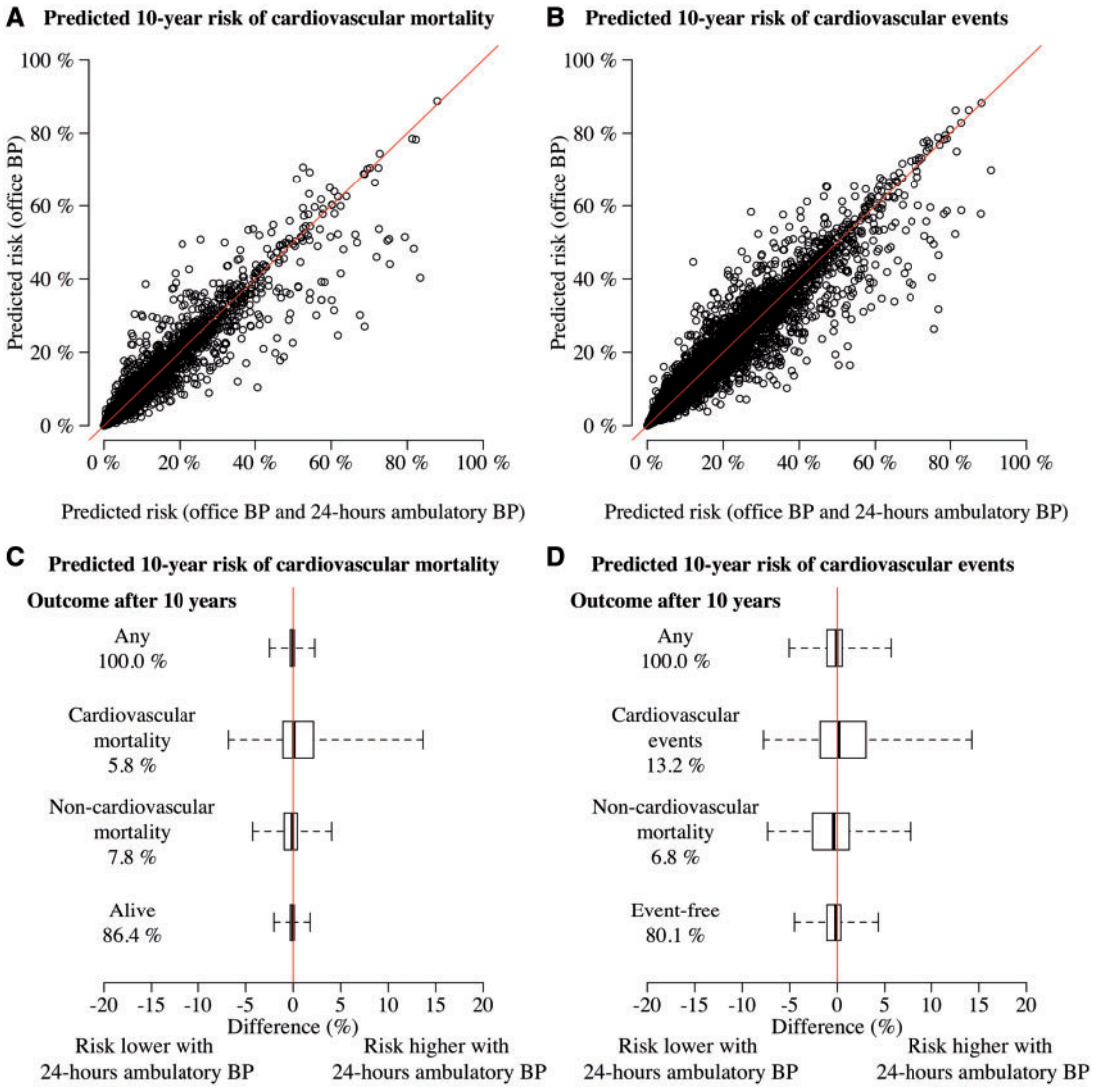

Figure 2 Person-specific 10-year absolute risk predicted using office blood pressure (BP) and 24-h ambulatory BP. Ten-year person-specific absolute risks of cardiovascular mortality (*A* and *C*) and cardiovascular events (*B* and *D*) predicted using office BP and 24-h ambulatory BP. (*A* and *B*) Person-specific predictions based on both office BP and 24-h ambulatory BP vs. only office BP. Boxplots in © and (*D*) show 5, 25, 50, 75, and 95% quantiles of the person-specific differences in predicted absolute risks based on both office BP and 24-h ambulatory BP vs. only office BP conditional on outcome after 10 years (from Mortensen R-N, Gerds T-A, Jeppesen J-L, Torp-Pedersen C. Office blood pressure or ambulatory blood pressure for the prediction of cardiovascular events. See pages 3296–3304).

After 12 weeks, the left ventricular mass index decreased to a greater extent with sacubitril/valsartan compared with olmesartan. These differences remained significant after adjustment for systolic blood pressure. There were no significant differences in local distensibility changes from baseline to 12 or 52 weeks between the two groups; however, there was a larger reduction in central pulse pressure with sacubitril/valsartan than with olmesartan. Thus, it appears that the greater reductions in left ventricular mass might provide valuable advantages of a combined angiotensin receptor and neprilysin antagonism compared with angiotensin receptor blockade alone. These provocative findings are further discussed in an **Editorial** by Luis M. Ruilope from the Hospital 12 de Octubre in Madrid, Spain.[33]

The editors hope that readers of this issue of the *European Heart Journal* will find it of interest.

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