TREATMENT OF HYPERTENSION IN NEW FRONTIERS

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MEETING SUMMARY

This symposium provided an excellent forum in which to discuss the global burden of hypertension (HTN), its challenges, and approaches to best management in new frontiers. The symposium speakers also reviewed recent data for clinical practice, especially those relevant for patients at high risk of HTN. The presentations were delivered within a highly interactive setting to facilitate audience questions and discussion.

The symposium was opened by Prof Bryan Williams, who gave a description of the global burden of HTN, emphasising the need for effective, simplified treatment strategies and algorithms to effectively control blood pressure (BP). Prof Gordon Thomas McInnes then gave an overview of the challenges faced when treating HTN in the developing world and the best management practices of HTN adopted across different countries. HTN control in Latin America (LA) and the Caribbean region, and its opportunities and challenges was the subject of the next presentation given by Dr Jesús Isea-Pérez. Lastly, Dr Jorge Sison discussed HTN control in Asia and the Middle East, presenting real-world data in addition to a review of the latest clinical data on optimal management of HTN, and focussing on the use of single-pill combination (SPC) therapies. This engaging and interactive symposium was facilitated by multiple-choice questions posed by speakers, allowing audience participation via an electronic voting system. The meeting closed with a lively panel discussion and concluding remarks from Prof Bryan Williams.

This truly international symposium brought together more than 550 delegates from across Europe and North America, Africa and the Middle East, Asia and Pacific regions, and Central and South America, with attendees representing a wide range of clinical and professional settings.

Welcome and Introduction

Professor Bryan Williams

HTN is a leading risk factor of global mortality and one of the biggest contributors to the global burden of disease (GBD).[1,2] Each year, HTN is estimated to contribute to approximately 7.5 million deaths, representing around 13% of the total annual deaths worldwide.[1]

Despite the availability of effective antihypertensive agents, HTN remains difficult to control in the majority of patients.[3] Awareness of the condition is an important determinant for seeking treatment. In a cross-sectional, multinational study (Prospective Urban Rural Epidemiology [PURE]) involving 153,996 hypertensive patients across countries of all income ranges, almost half of the patients (46.4%) were unaware of their condition and remained untreated. Of those aware of the disease, BP is effectively controlled in only 35% of cases.[3]

Although much progress has been made in the control of BP, the global burden of HTN-related cardiovascular disease (CVD) remains substantial. In 2013, the GBD showed that, while the prevalence of disabilities due to ischaemic heart disease is declining, the number of years of life with disability due to HTN-related conditions has been increasing since 1990.[4] However, thanks to important advances in medical treatments, the number of CVD-free years of life associated with HTN has expanded substantially across age groups.[5] According to recent estimates, for every year gained on treatment, lifetime is extended by at least 1 month overall.[5] The improved survival of many patients with long-term HTN is resulting in a shift of the GBD, with HTN-related conditions, including angina and myocardial infarction, increasingly manifesting at an older age.[5] As the methods of detection and the control of other risk factors such as smoking and high levels of cholesterol improve, it is predicted that high BP will become better detected and managed.

The significance of HTN as a CVD risk factor is now increasingly recognised. Even in patients with controlled HTN (<140/90 mmHg), a 50% risk of a cardiovascular event is seen.[2] HTN currently contributes to 92 million years of disability, making it a leading cause of years lost to disability across the globe, and HTN is predicted to become the leading preventable cause of heart failure associated with ageing. To enable adequate BP control, effective, simplified treatment strategies and treatment algorithms need to be adopted within the current guidelines.[2]

This symposium aimed to explore: (1) the challenges of managing HTN in new frontiers, in particular in Asia, the Middle East, and LA, how these challenges may differ from those in other parts of the world, and the reasons for these differences; (2) current practice for HTN control in non-European and non-North American countries; (3) the key regional HTN guidelines, especially those of relevance to patients at high risk of CVD; (4) the clinical perspectives for real-world management of HTN, particularly in high-risk patients, and recent real-world data for the treatment of HTN in high-risk patients in the aforementioned regions.

Hypertension Management Across Borders

Professor Gordon Thomas Mcinnes

Worldwide, life expectancy has been increasing continuously and substantially over the past 40 years. Despite global and regional health crises, the gap in life expectancy between rich and poor countries has been reduced. A clear example of this can be seen in China, where a 15 year increase in life expectancy between 1970 and 2010 has been reported compared with a 9-year increase in life expectancy in the UK for the same period.[6,7]

HTN is an important public health challenge worldwide.[8] Coronary heart disease (CHD), and CVD in general, are leading causes of death globally, and in developing countries the mortality attributed to CHD is rising.[9] Much of the increase in CVD mortality can be attributed to suboptimal BP, which is considered to be the main 'correctable risk factor' for CVD and mortality.[7]

HTN is currently predicted to affect 639 million adults in developing countries, a prevalence that is expected to rise by 80% by 2025, with 1.56 billion people estimated to be affected globally (Figure 1).[8]

Between 2000 and 2025, the greatest increases in the prevalence of HTN are expected to be seen in the Middle East and North Africa (+107%), Africa (+89%), and South Asia (+81%), followed by LA (+76%), East Asia and Pacific regions (+69%), North America and Western Europe (+29%), and Eastern Europe and Central Asia (+11%). In 2010, the prevalence of HTN reached 33.5% in China, giving an estimated 330 million hypertensive patients in

this country where the rates of awareness (50%), treatment (40%), and control (10%) are low.[10]

Change to a more Western lifestyle, modernisation, and urbanisation are contributors to the shift in the burden of HTN observed across the developing world.[6,11] Regardless of age, HTN is highly associated with the risk of stroke and death due to ischaemic heart disease.[12] Of note is the logarithmic relationship between BP and mortality, which emphasises the importance of rigorous BP control.

However, BP control (<140/90 mmHg) remains low in patients with HTN across regions worldwide.[13-19] The recommendations of the most recent British and European guidelines advocate the use of dual or triple treatments in SPC therapies, with a renin–angiotensin system (RAS) blocker in combination with a calcium channel blocker (CCB) and/or a diuretic.[20,21] Compared with antihypertensive monotherapies, the use of SPC therapies for the treatment of HTN can offer increased efficacy, tolerability, and compliance. In addition, the use of SPC therapies leads to improved reductions in BP due to their multiple mechanisms acting on complementary BP-control pathways and providing neutralisation of counter-regulatory mechanisms.[22,23] The lower-dose components in SPCs and the attenuated compound-specific adverse effects result in improved tolerability.[22,23] Added to this, the use of SPC antihypertensive agents is also associated with improved treatment adherence due to their convenience and reduced pill burden.[22,23]

The variation in the burden of HTN seen across different countries can be attributed to several possible causes, including the healthcare systems, availability of resources, drugs, and technology, as well as the prevalence of high-risk conditions for HTN, such as diabetes mellitus, and drug tolerability (Table 1).[24]

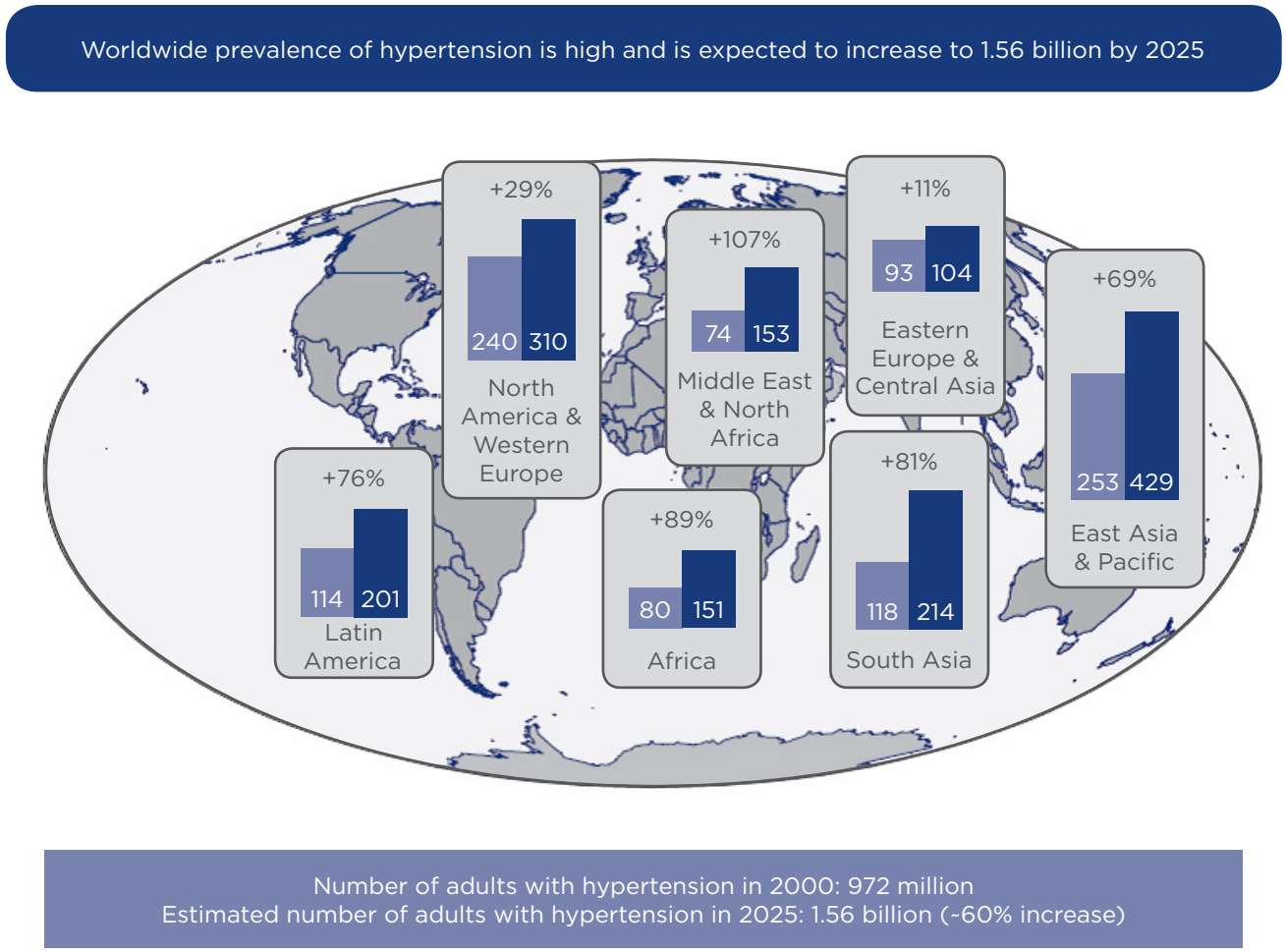

Figure 1: Worldwide prevalence of hypertension.[8]
Number or people aged ≥20 years with hypertension (in millions) for the years 2000 (light blue bar) and 2025 (dark blue bar).

Table 1: Determinants of the burden of hypertension across countries.

Healthcare system
Availability of resources, drugs, and technology
High-risk populations (e.g. patients with diabetes mellitus)
Drug tolerability
• Diuretics: dehydration (when taken during hot weather)
• Diuretics alone or in combination with β-blockers: new onset of diabetes
• Calcium channel blockers in hot weather: ankle oedema
• Angiotensin-converting enzyme inhibitors*: ethnicity-dependent variations in efficacy and adverse events

*Taiwanese hypertension guidelines strongly recommend the use of angiotensin-receptor blockers over angiotensin-converting enzyme inhibitors due to their exceptional tolerability and lowest discontinuation rate among all five classes of antihypertensive drugs tested.[24]

Hypertension Control in Latin America: Opportunities and Challenges

Doctor Jesús Isea-Pérez

The region of LA includes 41 countries that vary in terms of area, population density, and economic size. The region has 588 million inhabitants, representing 8.5% of the world's population, 81% of whom live in urban areas.[25] According to 2010 statistics, LA also has low population growth compared with the rest of the world. This is due in part to low fertility rates (2.3%) and high prevalence of contraceptive use (67%),[25] with life expectancy being 70.3 years in males and 76.6 years in females.[25] Despite important advances in recent decades, extreme variations in access to adequate medical care and education persist across LA and Caribbean (LAC) countries.[25,26] In 2010, 10% of the population in LA were living in conditions of multidimensional poverty,[26] with indigenous people having among the highest rates of morbidity and mortality.

As a consequence of the disparity in access to adequate medical care and socio-economic differences, HTN remains a major concern in LA. Among the non-communicable diseases, CVD takes the highest toll, contributing to 31% of all deaths according to 2010 estimates, and a 60% increase in this rate is predicted over the next 20 years.[25] In 2000, mortality from cerebrovascular disease (CEVD) was 2 to 4-fold higher in LA than in North America. Although both CVD and CEVD have shown a downward trend in LA during the last four decades, wide variations are reported between countries. Poverty and income inequality are driving factors of mortality in the region: 30% of premature deaths from CVD are in the poorest quintile of the population, whereas only 13% are in the wealthiest quintile.[25,27]

Available data on the distribution of cardiovascular risk factors in the LAC region are limited, and the few studies available show significant discrepancies in the prevalence estimates of HTN across the region.[28] According to estimates made in 2010 by the World Health Organization (WHO), the highest prevalence occurs in the Caribbean islands (43–56%) and the lowest occurs in Mexico and Peru (26–41%) for both men and women.[1] In 2013, the Latin American Consortium of Studies in Obesity (LASO) analysed data measuring similar indicators in thousands of individuals across eight countries in the region.[28] The study concluded that major CVD risk factors are highly prevalent in LAC, in particular low high-density lipoprotein (HDL) cholesterol and hypertriglyceridaemia (Table 2).[28] In addition, irrespective of their origin from urban or rural areas, 20–23% of the adult population in LAC have HTN.[29] Marked differences could be seen in the prevalence of HTN between LAC and the USA. While obesity, high total cholesterol, high low-density lipoprotein cholesterol, and hypertriglyceridaemia were more prevalent in the USA, low HDL-cholesterol was more prevalent in LAC.[28]

Table 2: Prevalence of risk factors in Latin America.[28]

Risk factors	Women (%)	Women (95% CI)	Men (%)	Men (95% CI)	All (%)	All (95% CI)
Smoking	19.5	11.2–31.9	32.2*	25.5–39.8	25.8	18.1–35.3
Hypertension	19.4	13.1–27.6	21.1	11.9–34.7	20.2	12.5–31.0
Diabetes mellitus	4.8	3.4–6.8	5.1	3.5–7.5	5.0	3.4–7.9
High total cholesterol	9.6	7.3–12.7	8.2	6.4–10.3	8.9	6.9–11.4
High LDL cholesterol	9.3	6.0–14.2	7.6	5.1–11.0	8.5	5.8–12.2
Low HDL cholesterol	76.9	68.2–83.9	32.8*	18.7–51.0	53.3	47.0–63.4
Hypertriglyceridaemia	23.3	17.6–30.2	29.9*	20.1–41.9	26.5	18.1–35.3

*p<0.05 for prevalence relationships between men and women, adjusted for age and study.
CI: confidence interval; LDL: low-density lipoprotein; HDL: high-density lipoprotein.

The Latin American Consortium of Studies in Obesity (LASO) study is one of several studies that have shown a prevalence of HTN in the LA region within the range registered in developed countries (20–40%).[28,30-32] Hypertensive Latin Americans are, however, 2.7-times more likely to experience myocardial infarction than their normotensive counterparts, a ratio that reaches 3.7-times in Mexico and Venezuela.[28,30-32] In LA, the percentage of strokes attributed to HTN is among the highest in the world (up to 60–80%), with HTN being responsible for a significant number of heart failure cases (22%).[28,30-32] The impact of HTN on chronic renal disease is still unknown. As observed in other parts of the world, HTN is the highest contributor of death in LA, followed by smoking, obesity, hyperglycaemia, and hypercholesterolaemia.[33]

The prevalence of awareness and control of HTN in LAC varies between countries.[34] Surveillance of HTN prevalence studies in LAC published between 2001 and 2010 revealed that the level of awareness ranged from 53% (Peru) to 76% (Mexico) and control rates ranged from 12% (Peru) to 41% (Mexico).[34] In Venezuela, up to 41% of affected individuals do not receive pharmacological treatment. Of those receiving some medication (49%), less than 21% are appropriately controlled.[35] As observed in other LAC countries, angiotensin converting enzyme (ACE) inhibitors and β-blockers are the most frequently used antihypertensive drugs in Venezuela (33% and 25%, respectively), followed by CCBs (15%), diuretics (15%), and angiotensin-receptor blockers (ARBs; 11%).[36]

Several reasons are thought to account for low BP control rates in the LAC region, but a very important one is a lack of adherence to treatment, which can change with patient perception of disease severity (the range of which is reported to be from mild to moderate to severe, depending on the impact of HTN on patient quality of life). An analysis of almost 2,000 hypertensive patients under clinical management revealed that treatment adherence ranged from 50%, when the perception of the severity of HTN was considered mild, to 100% when it was considered severe.[36] This observation highlights the importance of education and awareness of HTN in clinical practice to improve adherence.

The Pan American Health Organization (PAHO) has played a critical role in the prevention and control of HTN in the LAC region.[37] Since 2000, PAHO has worked towards the implementation of standardised surveillance and management systems across the region and emphasised the need for healthcare strategies for effective prevention of HTN to work in close association with those for the prevention of other CVD risk factors.[37] PAHO is using innovative models of care that aim to: (1) involve both patients and communities as essential contributors to defining and monitoring plans of care; (2) use practical

algorithms for diagnosis, treatment, and follow-up; (3) assess CVD risk as a base for planning control of CVD and related risk factors; and (4) simplify treatment and facilitate the availability of medications at low cost.[37]

The following recommendations could be considered in order to improve HTN control in LAC:

- Elaborate and integrate efforts towards the enforcement of a base plan for HTN control
- Establish a wide-coverage campaign for public education
- Establish and reinforce the application of a standard of HTN prevention, diagnosis, and treatment across the region (in the form of standardised guidelines)
- Allow access to drugs free of charge by private insurers and in government-run medical centres
- Establish medical education plans for doctors and patient awareness
- Improve regular surveillance of epidemiological data on HTN, including the development of a single database across the region

Reaching Blood Pressure Control in Asia and the Middle East – Real-World Data

Doctor Jorge Sison

As has been described, the increase in prevalence of HTN has proceeded at an alarming rate, particularly in some countries of the Middle East and South Asia regions where control of BP remains very low.[8,13–19,38,39] This, in addition to the complexity of HTN and its variable pathological background, makes treatment difficult.[40]

To adequately control HTN, the majority of hypertensive patients require the use of two or more antihypertensive agents.[41] Despite this, the use of dual SPC therapies remains low in the Middle East and Asia. An illustration of this can be seen in the Philippines, where, between 2007 and 2013, the use of monotherapy has remained high (75–86%) compared with dual (11–21%) or triple (0.4–21%) SPC.[39]

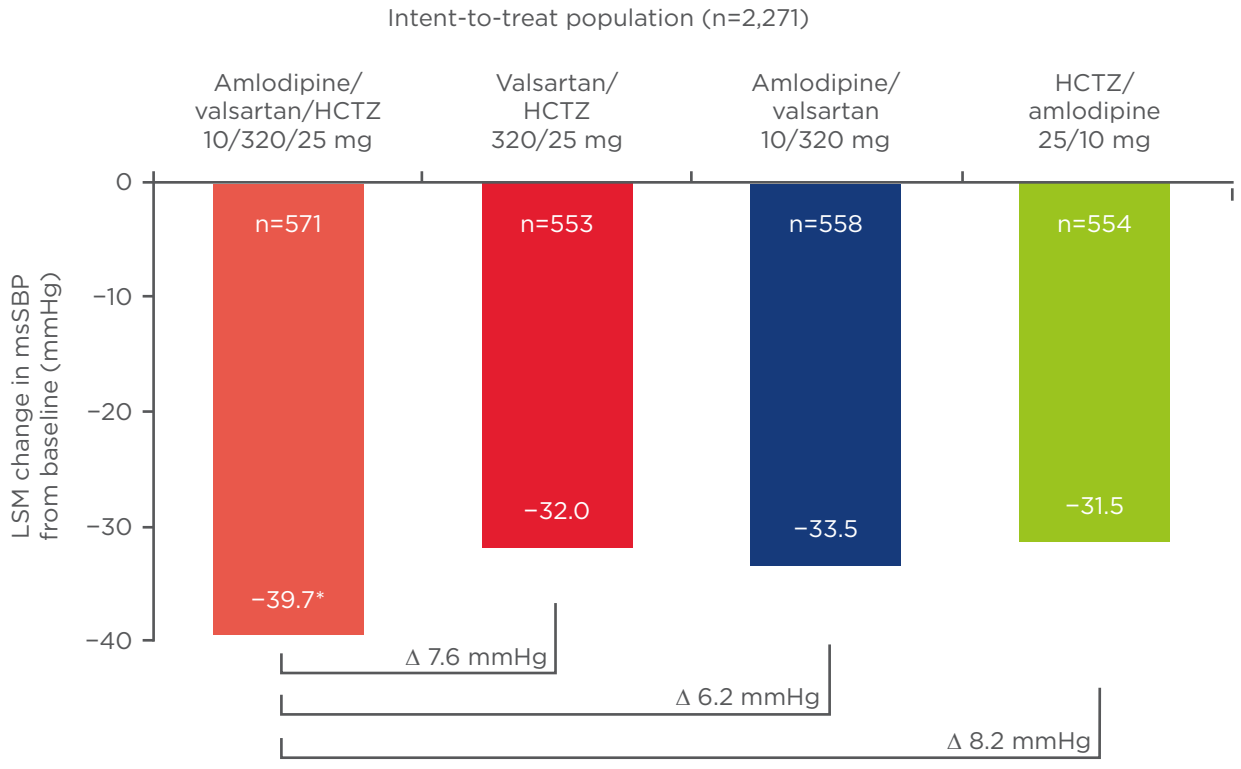

Figure 2: Triple combination therapy with AML/VAL/HCTZ reduces systolic BP significantly more than respective dual therapies.[45]

Randomised, double-blind, multinational, parallel-group, active-controlled study incorporating a single-blind run-in period (maximum 4 weeks) followed by 8-week double-blind treatment period.

*p<0.0001 versus all other combinations.

AML: amlodipine; VAL: valsartan; HCTZ: hydrochlorothiazide; SBP: systolic blood pressure; BP: blood pressure; LSM: least squares mean; msSBP: mean sitting systolic blood pressure.

Clinical studies have demonstrated that a combination of multiple antihypertensive agents is more effective than up-titrating the dose of a single agent, resulting in improvements in antihypertensive efficacy and a reduction in major adverse cardiovascular effects.[42,43] The additional BP reduction as a result of combining drugs of two different classes is estimated to be approximately five-times greater than doubling the dose of one drug.[42,43] US and European guidelines highlight the benefits of combining multiple drugs with a different mechanism of action to improve adherence and BP control. The 2013 European Society of Hypertension (ESH)/ESC guidelines recommend the use of a diuretic (thiazide) plus a CCB or RAS blocker (ACE inhibitors or ARBs), or a CCB plus RAS blocker.[21] When three drugs are required, the preferred combination is a CCB plus RAS blocker and thiazide.[21,44] Dual combination of ACE inhibitors and ARBs is not recommended.[21]

Randomised clinical trials have demonstrated that combination therapies are well tolerated and associated with high antihypertensive effects.[45-47] In patients previously uncontrolled with monotherapy, antihypertensive effects were observed at Week 16 in a dose-dependent manner after a direct switch to amlodipine/valsartan (AML/VAL) in the majority of the patients.[48] Overall, a triple therapy with AML/VAL/hydrochlorothiazide (AML/VAL/HCTZ) results in significantly greater BP reductions than dual therapies (Figure 2),[45] with systolic antihypertensive effects achieved in proportion to HTN severity.

In the real world, the efficacy and tolerability of SPC therapies have also been established by the EXCITE study.[39] The study cohort was a multi-ethnic population of more than 9,700 hypertensive patients treated for 26 weeks in routine clinical practice across the Middle East and Asia. Statistically significant and clinically meaningful BP reductions from baseline across all treatment dosages and severities of HTN were observed after 26 weeks. Oedema and peripheral oedema were the most frequently reported adverse events in the dual and triple groups. The results of the EXCITE study provide evidence that dual SPC therapy with AML/VAL and triple SPC therapy with AML/VAL/HCTZ provide clinically meaningful BP reductions and are well tolerated in a large multi-ethnic hypertensive population.[39]

Further analysis has demonstrated that the effectiveness and tolerability of dual or triple SPC regimens are maintained in patients with the highest risk of CVD events (elderly, obese, and patients with diabetes or isolated systolic HTN).[49]

Summary

The presentations and discussions in this symposium leave no doubt that HTN is a major public health challenge worldwide. The importance of HTN as a risk factor for CVD is increasingly being recognised, and HTN is predicted to become the leading preventable cause of heart failure associated with ageing. Even in patients with controlled HTN (<140/90 mmHg), there is a 50% risk of a cardiovascular event.[2] For changes in the burden of disease resulting from HTN in the developing world to be realised, simplified treatment strategies and the adoption of standardised algorithms to effectively control BP are needed. In addition, accessibility to reliable and affordable drugs, coupled with educational and awareness programmes, can help to deliver care alongside the establishment of common targets and patient monitoring. Multi-drug therapy with SPC can be used effectively and safely to improve treatment adherence in the majority of hypertensive patients, including those at high risk of CVD.

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