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Unit No. 1

PROTEINURIA AND HYPERTENSION WITH AND WITHOUT TYPE 2 DIABETES MELLITUS: 2023 UPDATE

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ABSTRACT

INTRODUCTION. This 2023 paper is a continuing update of the 2019, 2020, 2021 and 2022 versions. In the 2021 update, two new items of information have been added. First, the 2020 Consensus statement of the Taiwan Hypertension Society and the Taiwan Society of Cardiology on HPDM, which provided recommendations on additional medications to be considered in uncontrolled morning or night blood pressure (BP), are noted. Secondly, the nephroprotective properties of the SGLT-2 inhibitors are highlighted. Similar to the content of the 2019 version, four related areas are reviewed. They are (1) BP definition and classification; (2) hypertension diagnosis; (3) hypertension and proteinuria in non-diabetic patients; and (4) proteinuria and hypertension in the patient with diabetes. METHODOLOGY. PubMed searches were done for papers on the aforementioned four topics published in the last five years (2014 to 2019). These were supplemented by papers from hand searches. Further update of the topic in 2022 by searching for articles using the title of this paper yielded an useful 2021 review paper.[22] RESULTS. For diagnosis of hypertension, the current cut-off of 140/90 mmHg can be reduced to 130/80 to improve cardiovascular outcomes and all-cause mortality. Diagnosis of hypertension should not be based on office BP readings alone. Hypertension in older patients should be treated to prevent worse outcomes and should be individualised. In non-diabetic patients, both low grade and microalbuminuria needs to be treated; adequate BP control is needed to prevent cardiovascular outcomes and all-cause mortality. In the diabetic patient, a BP target of less than 140/90 mmHg applies to most patients, but individualisation of the BP goal is important. CONCLUSION. Much development in the management of proteinuria and hypertension has taken place in the last five years. Attention to multifactorial interventions is highlighted.

Keywords: Hypertension, proteinuria, non-diabetic patients, diabetic patients

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INTRODUCTION

In this update, four related areas are reviewed. They are:

1. BP definition and classification;
2. Hypertension diagnosis;
3. Hypertension and proteinuria in non-diabetic patients; and
4. Proteinuria and hypertension in the patient with diabetes.

LITERATURE REVIEW

PubMed searches were done for papers on the aforementioned four topics published in the last five years (2014 to 2019). These were supplemented by papers from hand searches.

RESULTS

1. BP DEFINITION AND CLASSIFICATION

BP definition

Hypertension is most commonly defined as a systolic blood pressure of ≥140 mm Hg or a diastolic blood pressure of ≥90 mmHg based on three or more occasions.[1,2] The severity of hypertension is classified into *grades* according to the joint statement of the European Society of Cardiology and the European Society of Hypertension (ESC/ESH) or *stages* according to the joint statement of the American Society of Hypertension and the International Society of Hypertension (ASH/ISH).[2]

With the emergence of recent evidence suggesting benefits of lower BP treatment targets, the American Heart Association and the American College of Cardiology (AHA/ACC) have set the definition of hypertension as a BP of 130/80 mmHg for diagnosis.[3] Their severity classification has also been adjusted downwards (Table 1A). Individualisation for treatment remains important as the lower cut-offs may not be tolerated by some patients.

The MOH Clinical Practice Guideline[4] released in 2017 recommends a cut-off of 140/90 mmHg for diagnosis of hypertension (Table 1B). In tandem with the adoption of the lower cut-off of 130/80 mentioned above, there will be a need to make the necessary adjustments that are discussed in this update.

Table 1A. Definition and classification of hypertension[1]

	"Older classification" 2014[A]	"Recent classification" 2017[B]
BP category	BP (mmHg)	BP (mmHg)
Normal BP	<120/80	<120/80
Higher BP	*Pre-hypertension*	*Elevated BP*
	120-139/80-89	<120-129/80
Hypertension	≥140/90	≥130/80
Stage 1	140-159/90-99	130-139/80-89
Stage 2	≥160/100	>140/90

Source: Abdelhafiz et al, 2018[1].

Footnotes: A=Weber et al, 2014,[2] B=Whelton et al, 2017[3]

Table 1B. Definitions and classification of BP levels for adults aged 18 years and older, MOH CPG 2017[4]

Category	Systolic BP	Diastolic BP
Normal BP	< 130 mmHg	< 85 mmHg
High-normal BP	130 to 139 mmHg	85 to 89 mmHg
Grade 1 hypertension	140 to 159 mmHg*	90 to 99 mmHg
Grade 2 hypertension	160 to 179 mmHg*	100 to 109 mmHg
Grade 3 hypertension	≥ 180 mmHg*	≥ 110 mmHg
Isolated systolic hypertension	≥ 140 mmHg*	< 90 mmHg

*Isolated systolic hypertension is graded according to the same level of systolic BP.

Source: MOH CPG: Hypertension 2017 (Tay JC et al, 2018)[4]

2. HYPERTENSION DIAGNOSIS

Office BP measurements

Office BP readings have been accepted for diagnosis and subsequent management for several decades.[5] It is now clear that such readings are prone to inaccuracies as the result of:

- White coat hypertension – which is characterised by high office BP and normal home BP – resulting in overdiagnosis and treatment; and
- Masked hypertension – which is characterised by normal office BP and high home BP – resulting in underdiagnosis and treatment.[1]

There is a need for supplementary measurements with home BP monitoring (HBPM) or ambulatory BP monitoring (ABPM). Both HBPM and ABPM are uniquely capable of identifying patients with white coat hypertension or masked hypertension.

Ambulatory BP monitoring (ABPM) and Home BP monitoring (HBPM)

The usefulness of ABPM for the management of hypertension is currently well established. It is no longer enough to diagnose hypertension based on office BP measurements alone. These readings should be supplemented by ABPM or its alternative HBPM.[5,6]

Ambulatory BP is a stronger predictor of cardiovascular and cerebrovascular events than BP measured in the doctor's office. Table 2 shows the definition of hypertension based on ambulatory blood pressure readings. Normal HBP measurement in the daytime is <135/85mmHg and night-time is 120/70 mmHg.

Table 2. Definitions of hypertension in HPBM and APBM[4]

	Systolic BP	Diastolic BP
HBPM	≥ 135 mmHg	≥ 85 mmHg
ABPM		
Daytime	≥ 135 mmHg	≥ 85 mmHg
24-hour	≥ 130 mmHg	≥ 80 mmHg
Night-time	≥ 120 mmHg	≥ 70 mmHg

Source: MOH CPG: Hypertension (Tay JC et al, 2018)[4]
HBPM = Home BP Monitoring; ABPM = Ambulatory BP Monitoring

HBPM is an acceptable alternative when ABPM cannot be performed.[7] There is good correlation between HBPM and ABPM for accurately diagnosing sustained normotension, white coat hypertension, and masked hypertension in both treated and untreated patients, with sensitivity ranging from 60 to 90 percent. The primary indications for HBPM are confirming elevated office BP in patients with undiagnosed hypertension and monitoring BP trends in patients with known hypertension.[8]

The 2020 Consensus statement of the Taiwan Hypertension Society and the Taiwan Society of Cardiology on HBPM for the management of arterial hypertension has this to say: "HBP-based hypertension management strategies including bedtime dosing (for uncontrolled morning hypertension), shifting to drugs with longer-acting antihypertensive effect (for uncontrolled evening hypertension), and adding another antihypertensive drug (for uncontrolled morning and evening hypertension) should be considered".[9]

The adoption of HBPM has been encouraging. A report published in 2017 by Setia et al[10] described a survey of 60 physicians made up of 30 GPs, 20 cardiologists, and 10 nephrologists. Almost all physicians surveyed (98 percent) stated they recommended HBPM to their patients with hypertension. Overall, 81 percent of hypertensive patients were recommended to measure home BP (85 percent of those treated by cardiologists, 85 percent by nephrologists, and 76 percent by GPs).[10] Barriers to its adoption through understanding and training need to be overcome in the three stakeholders: patients, clinicians, and health system.[8]

Hypertension in older patients

In older patients, besides white coat hypertension – which can be seen in up to 72 percent of clinic BP readings – and masked hypertension, two other types of hypertension are encountered in older patients: namely, isolated systolic hypertension (BP ≥140/90 or <90 mmHg), which accounts for up to 72 percent of clinic BP readings; and postural hypotension (BP drop >20/10 mmHg within three minutes of standing), which is rather common, affecting up to 20 percent of older people.[8]

BP targets in older patients

Older people are heterogeneous in their health status. Hence, one BP target does not fit all. One strategy is to view older people to be made up of three functional categories with different targets ranging from tight BP control in the fit person to a relaxed approach in the frail elderly. Targets need to be individualised and dynamic to follow the changing functional state of the patients as they age.[1] See Figure 1.

Figure 2 shows the special considerations in managing hypertension in older patients, namely: patients with fall risks; with dementia; who are frail; have systolic hypertension; have postural hypotension; have polypharmacy associated with non-adherence; or are dependent and are staying in the long-term care setting.[1]

Figure 1. Suggested BP targets based on patient's functional status

Independent
- Independent community living
- Mild comorbidities

– Target BP <130/80 mmHg

Partially dependent
- Assisted community living
- Moderate comorbidities

– Target BP <140/90 mmHg

Fully dependent
- Care home residency with limited life expectancy
- Severe comorbidities

– Target BP <150/90 mmHg

Source: Abdelhafiz et al, 2018[1] – slightly adapted

Figure 2. Special considerations in the management of hypertension in older patients

Falls
Risk is proportionate to the intensity of therapy
Risk is highest on initiation of medication

Dementia
Does not improve with hypertension treatment
Target SBP should not be <130 mmHg

Frailty
U-shaped relation with cardiac outcome
Target BP should not be <140/90 mmHg

Systolic hypertension
Less responsive to antihypertensives
DBP should not be <70 mmHg

Postural hypotension
Frequent in uncontrolled hypertension
Nocturnal therapy may exacerbate symptoms

Polypharmacy
Associated with non-adherence
Regular medication review

Care home residents
Likely dependent
SBP <130 mmHg
Increases mortality

Source: Abdelhafiz et al, 2018[1] – slightly adapted

Antihypertensive therapy in elderly and frail populations

Untreated, hypertension predicts worse outcomes even in the elderly and frail populations. Treatment of hypertension lowers cardiovascular morbidity and mortality in such populations. Comorbidities and frailty make management of hypertension challenging in these patients, and the approach to pharmacotherapy cannot be simplified into an algorithm like in the general population.[11]

Recent guidelines now support the notion that elderly frail patients should not be precluded from antihypertensive therapy. Rather, physicians should tailor therapy after weighing the benefits of cardiovascular risk reduction against the potential harmful results of such therapy. For therapeutic details on choice of drugs, the reader is referred to the paper by Correa et al.[11]

3. HYPERTENSION AND PROTEINURIA IN NON-DIABETIC PATIENTS

Low-grade albuminuria in non-diabetic and normotensive individuals

A cohort study by Tanaka et al[12] highlighted the important consequences of low-grade albuminuria in a cohort of 3,599 individuals in Japan followed up over 5.9 years. At

entry, the participants were 40 years and older, and were non-diabetic and normotensive, with reserved GFR and no cardiovascular history.

Low-grade albuminuria (LGA) was found to be a predictor of the incidence of cardiovascular disease and all-cause mortality in the participants. A total of 61 individuals had first CVD events, and 85 individuals died.

The hazard ratios (HRs) for CVD incidence and all-cause mortality in the top tercile was 2.79, with 95 percent CI of 1.4.1-5.52; and 1.69, with 95 percent CI of 1.00-2.84, respectively. Population-attributable fractions of the top tercile of LGA for CVA incidence and all-cause death were 37.9 and 20.1 percent respectively.

The conclusion is that in apparently healthy individuals with optimal blood pressure and no diabetes, LGA independently predicts CVD incidence and all-cause death. Low-grade albuminuria should be treated and not be ignored.

Microalbuminuria in primary hypertension

Microalbuminuria conventionally is defined as urinary albumin excretion between 30 and 300 mg/24 hours. Microalbuminuria is associated with left ventricular hypertrophy and carotid atherosclerosis. An emerging issue highlighted by a review of the subject by Viazzi et al[13] is the observed linear relationship between the degree of albuminuria and left ventricular hypertrophy. Would the treatment of blood pressure be able to reduce microalbuminuria and result in better renal outcomes? More studies are needed to answer this.

Meanwhile, urine albumin excretion (UAE) is a low-cost, easy-to-use test and a powerful predictor of cardiovascular diseases. This should be part of the routine evaluation of hypertensive patients.

Changes in albuminuria and cardiovascular risk under antihypertensive treatment

In another review paper, Viazzi et al[14] studied the trials' results and reported pairwise comparisons between antihypertensive treatment for cardiovascular outcome (in 16 randomised controlled trials and 48,580 patients, with a mean follow-up of 45 months, 5,867 cardiovascular events).

The authors discovered that there was a relationship between improvement in urinary albumin excretion (UAE) and blood pressure reduction. Relative risks (RR) pooled was 0.45, with CI 95 percent 0.23-0.85. No improvement in UAE was found between randomised pairs where there was no BP reduction (RR pooled 1.04, with 95 percent CI, 0.86-1.26).

The conclusion was a reduction in UAE under antihypertensive treatment reduced the risk of clinical cardiovascular events.

Proteinuria in CKD patients

A review by Dhaybi and Bakris[5] on the role of mineralocorticoid antagonists (MRAs) in chronic disease patients showed that when used in conjunction with ACEIs or ARBs, proteinuria was reduced. The concern in the past was over worsening kidney function and hyperkalaemia. Recent data from small studies highlight a way that MRAs may be used without fear of hyperkalaemia.

MRAs are highly efficacious for further reducing albuminuria, when added to ACEIs or ARBs. Use of patiromer, a potassium-binding polymer, is well tolerated and enables the use of MRAs in people with advanced CKD. Using patiromer has been shown to further reduce aldosterone and BP when used with MRAs.

A novel nonsteroidal MRA, finerenone, which is associated with less hyperkalaemia, is currently being tested in both renal and cardiovascular outcomes trials to examine effects on outcomes.

4. PROTEINURIA AND HYPERTENSION IN THE PATIENT WITH DIABETES

Prevention of microalbuminuria

A recent systematic review was published in 2016 by Persson et al[16] on the prevention of microalbuminuria. Based on six trials (n=16,921), the authors found that ACE or ARB treatment was effective (RR=0.84) in the prevention of the development of microalbuminuria. Treatment also showed a trend towards a reduction in all cause-mortality (p=0.07).

Blood pressure targets in patients with type 2 diabetes mellitus

A review by Pavlou et al[17] reported that two-thirds of patients with type 2 diabetes mellitus have arterial hypertension. This major risk factor increases the incidence of both microvascular and macrovascular complications in these patients. Furthermore, the co-existence of diabetes and hypertension leads to a fourfold increased risk of cardiovascular disease compared to normotensive non-diabetic controls.

A BP target of less than 140/90 mmHg applies to most patients. However, depending on the patient's age, medical history, and additional cardiovascular risk factors individualising the BP goal is important. For example, NICE (UK 2013) recommends a BP of <140/80, but if there is retinopathy, cerebrovascular disease, or microalbuminuria, the target is <130/80 mmHg.

Review of antihypertensives for treating hypertension in diabetes

A recent review by Sarafidis et al in 2017[18] was done on the effectiveness of currently available antihypertensives used for treating hypertension in diabetes mellitus. The authors reported that several lines of evidence suggest that angiotensin-converting enzyme inhibitors (ACEIs), angiotensin-receptor blockers (ARBs), and calcium-channel-blockers (CCBs) have beneficial or neutral effects on carbohydrate metabolism, whereas old beta-blockers and thiazide diuretics do not. Thiazide diuretics and conventional beta-blockers were shown to reduce insulin sensitivity and to raise the risk of new-onset DM.

Renal outcome trials clearly suggest that in proteinuric diabetic CKD patients, ACEIs and ARBs reduce the rate of disease progression. Thus, an ACEI or an ARB, if tolerated, should be the first choice in diabetic individuals, followed by CCBs, vasodilating beta-blockers, and diuretics, depending on the individual patient characteristics.

Recent studies also suggest that the new antidiabetic class of sodium-glucose co-transporter 2 inhibitors may offer a BP reduction, together with an important decrease in the incidence of cardiovascular and renal events, in patients with type 2 diabetes mellitus. In the Empagliflozin Cardiovascular Outcomes and Mortality in Type 2 diabetes (EMPA-REG OUTCOME) trial[19], the sodium-glucose co-transporter-2 (SGLT2) inhibitor empagliflozin reduced cardiovascular and renal events in type 2 DM, a result that was attributed in part to the small but sustained BP decrease throughout the trial.

In this 2021 update, it is also noted that the accumulated evidence in the past few years clearly suggests that SGLT2-inhibitors have potent nephroprotective properties. In a recent paper published in 2021, Piperidou, Loutradis, and Sarafidis[20] noted that in clinical trials in patients with T2DM, SGLT-2 inhibitors were shown to reduce albuminuria and proteinuria by 30-50 percent and the incidence of composite heard renal outcomes by 40-50 percent.

Management of hypertension in diabetic nephropathy: How low?

A study by Epstein & Sowers in 1992[21] found that hypertension was twice as prevalent in patients with diabetes compared to the general population with the mean blood pressure rising by 5-8 percent a year in those with over-nephropathy. They found that hypertension affected 35 percent of type 1 and 25 percent of type 2 diabetic patients.

A review by Sternlicht and Bakris[22] concluded that, taken together, current data indicate that a blood pressure goal of less than 140/90 mmHg can optimally slow CKD progression in diabetic nephropathy. Blood pressure levels of less than 130/80 mmHg are indicated in those with an estimated GFR of less than 60 and more than 500 mg of urinary protein. However, the evidence is based exclusively on retrospective analysis and is weaker than the 140/90 mmHg goal.

Sternlicht and Bakris also noted that dual RAAS blocking therapy is contraindicated in all populations, since it increases the risk for hyperkalaemia, vulnerability to acute kidney injury, and may increase the risk for all-cause mortality.

In a review paper on trajectories of kidney function in type 2 diabetes, Oshima et al,[22] noted are at least 3 alternative phenotypes in diabetic kidney disease progression besides the prototype diabetes kidney disease leading to kidney failure, cardiovascular disease, and premature death. Several studies have demonstrated the long term benefits multifactorial interventions that address risk factors of diabetic kidney disease progression.

DISCUSSION

With regards to BP definition, the current cut-off of 140/90 mmHg can be reduced to 130/80 to improve cardiovascular and renal outcomes as well as to reduce all-cause mortality.

The diagnosis of hypertension should no longer be based only on office BP readings alone but should be supplemented by HBPM or ABPM.

Hypertension in older patients should be treated to prevent worse outcomes, but individualisation is important. Older patients are heterogeneous in health status and deciding on the degree of control based on function categories is a strategy.

For non-diabetic patients, the presence of albuminuria from low-grade albuminuria to microalbuminuria needs to be treated. Adequate treatment of hypertension is needed to reduce proteinuria, prevent cardiovascular outcomes, and reduce all-cause mortality.

For diabetic patients, it is pertinent to note that hypertension is a major risk factor, and the co-existence of diabetes and hypertension increases the risk for cardiovascular disease fourfold compared to normotensive non-diabetic controls. A target of less than 140/90 mmHg should be applied to most patients.

The importance of multifactorial interventions is the focus of a 2021 review,[22] namely, sodium intake restriction and moderate intensity physical activity, lowering BP with RAAS inhibitors, intensive glucose control on the onset of micro- or macroalbuminuria, lipid management, and the place of renoprotective agents.

CONCLUSION

Much development in the management of proteinuria and hypertension has taken place in the last five years.

- The new cut-off for the diagnosis of hypertension is 130/80 mmHg.
- Office-based BP readings are not enough to diagnose hypertension.
- In both non-diabetic patients and diabetic patients, albuminuria and hypertension should be treated to reduce cardiovascular outcomes and all-cause mortality.
- Multifactorial interventions on the risk factors of diabetes kidney disease progression have long-term benefits.

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LEARNING POINTS

- **For diagnosis of hypertension, the current cut-off of 140/90 mmHg can be reduced to 130/80 mmHg to improve cardiovascular outcomes and all-cause mortality.**
- **Diagnosis of hypertension should not be based on office BP readings alone.**
- **Hypertension in older patients should be treated to prevent worse outcomes and should be individualised.**
- **In non-diabetic patients, both low grade and microalbuminuria needs to be treated. Adequate BP control is needed to prevent cardiovascular outcomes and all-cause mortality.**
- **In the diabetic patient, a BP target of less than 140/90 mmHg applies to most patients, but individualisation of the BP goal is important.**
- **The importance of multifactorial interventions is the focus of a 2021 review,[22] namely, sodium intake restriction and moderate intensity physical activity, lowering BP with RAAS inhibitors, intensive glucose control on the onset of micro- or macroalbuminuria, lipid management, and the place of renoprotective agents.**