Hypertension guidelines for type 2 diabetes in South Africa: consensus and controversies

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Introduction

Hypertension is common and integral to the pathophysiology of type 2 diabetes (T2DM). It affects the majority of patients, and is an important modifiable risk factor for both micro- and macrovascular disease.[1]

The recent publication of the South African Hypertension Society guideline (SAHS) 2011[2] and the SEMDSA guideline for the management of type 2 diabetes[3] affords us the opportunity to compare the recommendations for treatment of hypertension in T2DM and consider the consensus and controversies arising from the publications.

Consensus

Both guidelines are unambiguous on emphasising the importance of hypertension as a modifiable risk factor in the patient with T2DM. Blood pressure (BP) reduction is associated with reduction in both micro- and macrovascular complications. Both guidelines emphasise the need for correct BP measurement techniques, the use of combination therapy to achieve the BP goal, use of ACE inhibitors or ARBs for patients with albuminuria, monitoring of renal function and the use of furosemide in preference to thiazides if the estimated glomerular filtration rate (GFR) is reduced. Additionally neither guidelines advocate β-blockers as part of the first-line antihypertensive treatment regimen.

Both guidelines also advocate the use of ambulatory BP monitoring (ABPM) in the assessment of patients, but the SEMDSA guideline restricts this to patients with suspected white-coat or office hypertension. The SAHS guideline advocates the use of ABPM for diagnosis of hypertension, and assessment of white coating, masking, nocturnal BP and response to treatment.

Controversies

The small differences in the SEMDSA and SAHS guidelines reflect the current controversies articulated in the wider domain. The important differences between the guidelines are shown in Table 1.

BP target and the J curve

Several studies have influenced the old adage 'the lower the better in type 2 diabetes'. The 'lower the better' BP targets and the J curve are the most controversial issues currently in hypertension literature. In a critical reappraisal of the European Hypertension Guidelines as far back as 2009, Mancia *et al*. questioned the target BP < 130/80 mmHg in diabetic patients.[4] They concluded that there is a wealth of evidence for treating BP above 140/90 mmHg, but very little to support targets of 130/80 mmHg. However, the target BP has as yet not been adjusted.

This difference in target is highlighted in the SAHS and SEMDSA guidelines. The former suggested < 130/80 mmHg and the latter ≤ 140/80 and ≥ 120/70 mmHg. In the 2006 SAHS guideline, a lower limit of diastolic pressure of 64 mmHg was included, but not in the current guideline.

The guidelines are in agreement with the diastolic pressure target of < 80 mmHg, which was based on the secondary analysis of the HOT study.[5] A systolic target has never been established and was extrapolated from clinical trials. However the ADVANCE study recently showed that benefit was achieved down to a target of 134 mmHg.[6]

In the ACCORD study, patients were randomised to standard versus conventional treatment. The average difference in BP in the first year was 133.5 mmHg in the standard- versus 119.3 mmHg in the intensive-treatment group.[7] From the epidemiological perspective there should have been a marked reduction in cardiovascular (CV) events, but the actual results showed no benefit in the primary endpoint compared to standard treatment, albeit with significantly lower stroke rates.

In a recent publication, the results of diabetic and non-diabetic patients from the ONTARGET study were analysed *post hoc* to determine the effect of BP on outcome.[8] At all levels of BP, cardiovascular events were significantly increased in the diabetics. In agreement with the ACCORD study, the risk of stroke in the diabetic patients continued to decrease to achieved systolic BP values of 115 mmHg, with no evidence of an upward J-curve inflection.

In contrast, for the primary outcome (CV death, myocardial infarction, stroke or hospitalisation for congestive heart failure), the nadir of the J curve lay at about 129.6 mmHg (122.1–137.0 mmHg) systolic BP for diabetic patients and 129.0 mmHg (123.9–134.1 mmHg) for non-diabetic patients. Achieving systolic BP of 130 mmHg instead of 140 mmHg reduced the risk for the primary outcome by 3.4% in diabetic patients and 4% in non-diabetic patients; for CV death, 0 and 1.9%, respectively; for myocardial infarction, –3.7 and 0.1%, respectively; and for stroke, 31.4 and 21.7%, respectively.

For diastolic BP, the primary outcome in both diabetic and non-diabetic patients showed the highest risk occurred in subjects with the lowest or highest in-trial diastolic BP (67.2 and 86.7 mmHg, respectively), whatever the systolic BP values. The increase in risk in the lowest diastolic BP quartile was even greater in diabetics than non-diabetics.

In a Cox hazards risk analysis of the subjects with initial systolic BP < 130 mmHg, after adjusting for the baseline variables, the

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Table 1. Key differences between the SEMDSA and SAHS guidelines.

- BP target and the J curve
- Definition of hypertension in the diabetic patient
- Choice of antihypertensive therapy and combination therapy
- Hypertension algorithm

risk of experiencing events was increased in diabetes (HR: 1.29, 95% CI: 1.05–1.58) and in patients with underlying co-morbidities such as coronary artery disease, peripheral vascular disease and renal dysfunction.

The reader also needs to be cognisant of the important limitations of reported BPs in clinical trials, as outlined by Fischer *et al.* In a systematic review of 1 372 trial reports, there was inconsistency in reporting BP and no study has reported target control in individuals.[9] In addition, the limitations of office BP must be clearly stated. The closer the BP is to target, the greater the uncertainty of the 'actual' mean BP, taking into account the natural variability of BP, white coating and masking. White coating is increasingly exaggerated in older people.

All practitioners, in assessing BP control in diabetics, older individuals and other high-risk patients should make use of ambulatory and home BP monitoring in addition to office measurements to avoid the pitfalls of both over- and under-treatment of high-risk patients. For example, if an office BP is recorded at 170/100 mmHg, and the white-coat or masking effect is 20/10 mmHg, in both instances the patient requires intensification of treatment as the 'actual' mean BP for the white coater would be 150/90 mmHg and for the masker 190/110 mmHg. However if the office BP is recorded at 140/90 mmHg and the white-coat or masking effect is 20/10 mmHg, there is considerable uncertainty. The 'actual' mean BP would be 120/80 mmHg for the white coater and 160/100 mmHg for the masker, resulting in completely different clinical decisions regarding the hypertensive management. It is estimated that up to 30% of hypertensives will display white-coat or masking effects.

However, there is a pattern emerging from these studies where stroke shows no J point at current target BP levels but there is a nadir for coronary artery disease and CV death, particularly at a systolic BP of 130 mmHg and diastolic BP of 67 mmHg. This is especially so in high-risk, elderly subjects, which includes diabetics. In the author's opinion, based on current data, the systolic target should be 130 mmHg (but not below) to balance the competing risks of stroke reduction and increased CV events. In addition, a low diastolic BP < 70 mmHg should be avoided. Greater use of ABPM and home monitoring is advocated to assist in the assessment.

Definition of hypertension

The SEMDSA guidelines use the definition of hypertension if BP remains > 140/80 mmHg instead of the traditional definition > 140/90 mmHg. This is a small detail but there should be consistency of definition.

Choice of antihypertensive therapy and initiation of treatment

There are two areas of disagreement here. With regard to the choice of initial diuretic with normal renal function, the SEMDSA guideline recommends a thiazide while SAHS recommends either a thiazide or indapamide. Low-dose hydrochlorothiazide is a weak antihypertensive in monotherapy and has no outcome data at this dose.[10] Indapamide on the other hand has been clearly shown in the HYVET study to reduce events as first-line therapy.[11] In the author's opinion, if monotherapy with a diuretic is selected then it should be indapamide. However, in combination therapy, these differences are much less important.

The second important point is that the SAHS guideline recommends combination therapy *de novo* if the BP is > 20/10 mmHg above goal. This recommendation is based on two important points. Firstly the average response to any antihypertensive agent is about 10/5 mmHg and 20/10 mmHg for two drugs in combination treatment. Secondly sequential monotherapy has been shown to delay control of BP, but even when combination therapy is instituted, there is 'failure to catch up' with patients given initial combination therapy.[12]

Hypertension treatment algorithm

The hypertension algorithm of the SEMDSA and SAHS guidelines are broadly in agreement, but SEMDSA's is overly complicated. The SEMDSA guideline makes an important distinction regarding calcium channel blockers (CCBs). Non-dihydropyridine (DHP) CCBs are advocated in combination with ACE inhibitors in the presence of albuminuria, whereas for patients without albuminuria, a DHP CCB is advocated. In contrast the SAHS guideline recommends CCBs as part on mono- or combination therapy without reference to the non-DHP or DHP subclass.

The recommendation for using non-DHP CCBs for proteinuria is based on small studies done by Bakris *et al.*[13] In the much larger Benedict study, verapamil was not shown to prevent new-onset microalbuminuria or the progression of microalbuminuria in patients with type 2 diabetes, whereas the ACE inhibitor trandolopril was clearly effective.[14,15] In general, BP control in addition to ACE inhibitors is the most effective strategy to reduce proteinuria and, in the author's opinion, the antihypertensive should be selected on the basis of tolerability and ability to control BP.

Conclusions

Both the SEMDSA and SAHS guidelines provide important guidance for treatment of hypertension in diabetes. In their broad perspective they are very similar and perhaps we should not be distracted by the small differences. After all, if we achieved a target BP of < 140/90 mmHg in the majority our patients with diabetes and hypertension, this would be a giant step forward. Perhaps in the future, the two guidelines could be harmonised to avoid these small differences.

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