**Hypothesis: advancing clinical care in type 2 diabetes through '*Personalized systolic blood pressure target ranges*'?**

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*Intervention thresholds may be too high for some people*

Cardiovascular mortality remains the leading cause of death in type 2 diabetes (T2D). After publication of the results of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure lowering trial,[1] several guideline committees raised target systolic blood pressure (sBP) thresholds for most T2D patients from 130 mmHg to 140 mmHg.[2] This is controversial because some, perhaps many, patients might benefit from lower sBP levels.[1,3]

*Hypothesis*

In T2D, '*personalized sBP target ranges*' will improve CVD outcomes and reduce adverse events compared to using *generalized* sBP intervention *thresholds*.

*'Personalized' rather than 'generalized'*

Some guideline committees have started to consider personalized sBP targets but this approach has a limited evidence base has not been widely promoted: a) the American Diabetes Association recommends a sBP target of <140 mmHg for 'most patients' but recognises a target of <130 mmHg may be appropriate for individuals at high risk of cardiovascular disease if this can be achieved without undue treatment burden;[4] b) the UK's National Institute for Health and Care Excellence recommends a sBP target of <140 mmHg for 'most patients' but <130 mmHg for those with kidney, eye or cerebrovascular damage.[5]

In the same way that glucose targets in T2D are personalized, a 'more stringent' target clinic sBP range (115-130 mmHg) or a 'less stringent' range (120-140 mmHg) could be chosen based on the presence or absence of several factors such as: heart failure; CVD and microvascular complications; CVD risk; patient attitudes to stoke prevention and polypharmacy; postural hypotension; falls risk; cognitive impairment; presence of resources/support systems (figure). Although these factors are based largely on clinical experience, they might be a useful starting point pending data-driven improvements.[4]

*'Ranges' rather than 'thresholds' are designed to encourage physicians to reduce antihypertensive therapy at low sBPs'*

Use of target sBP *ranges* rather than *thresholds* are justified because: a) over-treatment of sBP can lead to myocardial ischemia, syncope and serious injury;[1] b) clinical staff can stop thinking about the risks of over-treatment when simply treating to below a sBP threshold; c) experienced clinicians routinely reduce antihypertensive therapy when sBP levels are 'too low'; d) in clinical practice the risks of adverse events and 'drop outs' could be lower than in

the ACCORD BP trial[1] because the trial did not include a protocol for reducing therapy at low sBP levels; and finally e) few hypertension guidelines recommend reducing therapy at low sBP levels (only in frail elderly patients).[4,6]

*Ranges informed by ACCORD trial data*

The ACCORD trial was the largest to test the hypothesis that intensive sBP lowering reduces cardiovascular risk in T2D.[1] Intensive sBP lowering reduced the risk for stroke and, in what was probably an underpowered trial, there was a suggestion of a reduction in the risk for the primary outcome (HR (95% CI): 0.88 (0.73-1.06)).

If we accept that ACCORD provides the most relevant data, then the method of sBP measurement in this trial should be considered when setting clinical targets. In this trial, sBP values were the average of three automated measurements taken after 5 minutes rest.[1] Target ranges suggested here assume that a single sBP measured in a clinical setting, without 5 minutes rest and with clinic personnel in the room, will be ~10 mmHg higher than in ACCORD.[7]

Therefore, the upper boundary (130 mmHg) of the 'more stringent' sBP range corresponds to the intensive sBP ACCORD target (120 mmHg) and the lower boundary (115 mmHg) is the 'rescue' sBP below which physicians are encouraged to reduce antihypertensive therapy (Figure).

The upper boundary of the 'less stringent' sBP range (140 mmHg), corresponds to the sBP threshold adopted by most clinical guidelines[2] and the lower reading (120 mmHg) is the 'rescue' sBP in these individuals (Figure).

*Exceptional cases: very frail elderly people*

Whilst the suggested personalized target ranges might be appropriate for the majority of individuals, there maybe some very frail elderly individuals who are more appropriately treated to within a higher sBP target range of 130-160 mmHg - as suggested by a recent position statement by the American Diabetes Association[4] and a paper from European Society of Hypertension–European Union Geriatric Medicine Society.[6] As in the preceding text, these recommendations are based on expert opinion; no trail data is available to guide management in these people.

*Blood pressure measurement methods*

We set our target sBP ranges based on single sBP measured without 5 minutes rest because this is how BP is measured in most clinic settings currently. Use of a 5-minutes rest period prior to taking 3 BP measurements could enhance patient care by improving the accuracy, precision and repeatability of BP readings. There could be clinical advantages in aligning routine BP measurements to those used in trials, but this needs further study (see *Future work* below).

*Adverse impact on mortality – a misleading signal from ACCORD?*

The ACCORD trial suggested a potential to increase mortality through intensive sBP lowering (total mortality: HR (95%CI: 1.07 (0.85–1.35); CVD mortality: 1.06 (0.74–1.52)).[1,8] However, these non-significant trends were observed only in the subgroup treated to an aggressive HbA1c target (<6%).[3] Since this HbA1c target is rarely adopted in clinical practice, any potential to increase mortality through intensive sBP lowering could be minimised - especially if low sBP levels prompt a reduction in antihypertensive medication as suggested here. Severe hypoglycaemia in the setting of severe hypotension (reducing

coronary perfusion) could be harmful in T2D especially in the presence of high coronary disease burden, autonomic neuropathy and arterial stiffness. In keeping with this notion, recent *post hoc* data shows that intensive compared to standard sBP lowering in ACCORD participants at high CVD risk in the standard glucose control arm, was associated with lower risks for CVD outcomes: e.g. HR for CVD death, nonfatal MI or nonfatal stroke: 0.69; 95% CI 0.51–0.93.[9]

*Future work*

Future research including clinical trials could usefully: a) test the stated hypothesis (see below); b) define optimal personalized BP ranges for individuals depending on the presence of relevant risk factors (outcomes being CVD risk reduction and treatment-related adverse events);[10] c) if personalized BP ranges are beneficial, incorporate these data in clinical decision support systems aiming to minimise clinical inertia; d) define optimal personalized BP ranges based on automated office BP, home BP and 24-hour ambulatory BP levels; e) standardize and align blood pressure measurement methods in trials and clinical practice.

The stated hypothesis could be tested in a cluster-randomized trial in which patients receive one of three interventions: a) usual care; b) a personalized sBP target level; or c) a personalized sBP target range.

*Conclusions*

We hypothesise that personalized target blood pressure should often be lower than currently achieved and that adoption of BP ranges could reduce CVD risk while minimising adverse events in T2D. This hypothesis could be tested through clinical trials and observational studies.[10]

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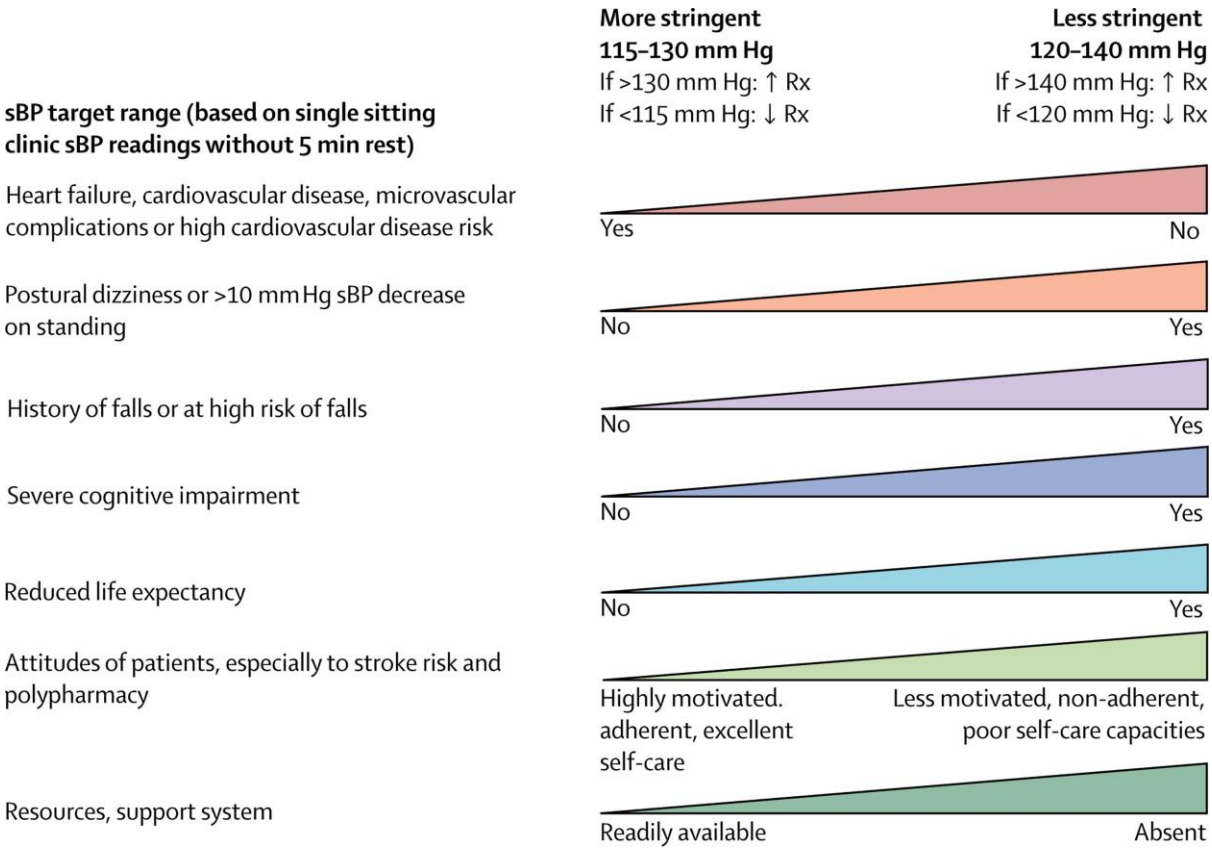
**Figure legend**

Using this approach, physicians can decide on the most appropriate sBP target range depending on the presence or absence of relevant risk factors (figure).




For example, a highly motivated and compliant patient with heart failure and renal impairment who has a positive attitude to polypharmacy and no adverse factors might be better treated to the ‘more stringent’ sBP target range (115-130 mmHg). However, a less motivated patient with heart failure and renal impairment with a history of falls and postural hypotension would be more appropriately managed to the ‘less stringent’ sBP target range (120-140 mmHg).

Asking patients about postural dizziness and measuring sBP lying and standing will help to identify people with postural hypotension. If a patient reports symptoms of postural hypotension or if the sBP levels fall below the lower threshold of the stated ranges then the clinician is encouraged to consider reducing antihypertensive therapy.

The upper boundary for stringent sBP range is based on ACCORD trial data adjusted for sBP measurement methodology. The upper boundary of the ‘less stringent’ sBP range (140 mmHg) corresponds to the sBP threshold adopted by most clinical guidelines.[2] The lower boundaries for the sBP ranges, and the factors influencing decision-making, are based on clinical experience.

The suggested algorithm would be inappropriate a very old and frail individuals (see text).Both upper and lower boundaries for the ranges and the factors influencing the stringency of sBP targets ranges could be modified through the acquisition of trial data.

**Disclosures**

Martin Rutter reports receiving honoraria and consulting fees from Novo Nordisk, Ascensia, Cell Catapult and Roche Diabetes Care. Naveed Sattar has consulted for Boehringer Ingelheim, Novo-Nordisk, Janssen and Eli-Lilly. He has received grant funds from Boehringer Ingelheim and AstraZeneca.

## Authorship

Both authors made substantial contributions to: a) the conception or design of the work; b) drafting the work or revising it critically for important intellectual content; c) final approval of the version to be published and d) agree to be accountable for all aspects of the work.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