Appendix A: Committee summary report of inconsistent advice on blood pressure targets in NICE's guidelines on chronic kidney disease and type 1 diabetes in adults

Background

An enquirer highlighted that the recent update of the <u>chronic kidney disease</u> (CKD) guideline (NG203) had removed a recommendation which used to provide a blood pressure target for people with diabetes and chronic kidney disease. The CKD guideline now provides no advice on what blood pressure target to use specifically in patients with diabetes and CKD. In contrast, they explained that the <u>type 1 diabetes guideline</u> (NG17) references the NICE CKD guidance but also specifically says that patients with type 1 diabetes and CKD should have a blood pressure target of <130/80 mmHg which is different to what is recommended in the CKD guidance.

The inconsistency was not deemed to affect the <u>type 2 diabetes in adults</u> guideline as the recommendations on diagnosing and managing hypertension were removed from the type 2 diabetes in adults guideline, and instead a link was provided to the <u>NICE guideline on hypertension in adults</u>.

A response was sent to the enquirer explaining the rationale for removing the recommendation during the update of the CKD guideline. However, there remains an inconsistency between the CKD and type 1 diabetes guidelines which was deemed unhelpful to clinical practice and thus needs resolving.

Overview of this document

This document was developed as a summary for the NICE diabetes committee and includes a summary of the recommendations and evidence base from the NICE <u>chronic kidney disease</u> guideline and the <u>type 1 diabetes</u> <u>guideline</u> together with any committee rationale available at the time. The

inconsistency in the recommendation is explained together with a proposed approach for handling it. Annex 1 gives a brief overview of the recommendations and rationale on blood pressure targets from the Hypertension guideline. The advice on blood pressure targets given in the BNF and SIGN guideline is presented in Annex 2.

CKD guideline (NG203)

Recommendations from 2021 update

1.6 Pharmacotherapy

Blood pressure control

See <u>NICE's guideline on hypertension in adults</u> for advice on blood pressure control in people with frailty and multimorbidity.

NICE's guideline on hypertension in adults recommends using clinic blood pressure for monitoring response to lifestyle changes or medical treatment (see recommendation 1.4.15).

1.6.1 In adults with CKD and an ACR under 70 mg/mmol, aim for a clinic systolic blood pressure below 140 mmHg (target range 120 to 139 mmHg) and a clinic diastolic blood pressure below 90 mmHg. **[2021]**

1.6.2 In adults with CKD and an ACR of 70 mg/mmol or more, aim for a clinic systolic blood pressure below 130 mmHg (target range 120 to 129 mmHg) and a clinic diastolic blood pressure below 80 mmHg. **[2021]**

1.6.3 In children and young people with CKD and an ACR of 70 mg/mol or more, aim for a clinic systolic blood pressure below the 50th percentile for height. **[2021]**

Recommendation pre-2021 update (removed)

In people with CKD and diabetes, and also in people with an ACR of 70 mg/mmol or more, aim to keep the systolic blood pressure below

130 mmHg (target range 120–129 mmHg) and the diastolic blood pressure below 80 mmHg^[1]. [2008]

Evidence base

There was no evidence in type 1 diabetes.

The majority of the evidence base was in patients without diabetes, see evidence review for further details.

There was 1 trial (subgroup analysis of the ACCORD trial) which included 1,726 patients with type 2 diabetes and CKD (<u>Papademetriou, 2016</u>). The trial found that intensive BP control (<120 mm/Hg systolic) showed a nonsignificant trend towards a risk reduction in stroke in patients with CKD, compared with standard BP control (systolic <140 mm/Hg). The forest plots for this trial are included in Appendix F of the <u>evidence review</u>, Figures 13-16, along with GRADE tables in Appendix G.

Committee discussion from the guideline

Note this is taken from the <u>committee rationale on the guideline</u> <u>recommendation webpage</u>, unless stated otherwise.

The committee agreed that none of the evidence they had seen warranted changing the recommendations. They also noted that intensive blood pressure targets only result in a marginal reduction in stroke and kidney failure but put a large burden on patients in terms of polypharmacy and associated risks and side effects (such as falls).

The committee agreed that particular care had to be taken with people who were frail or who had multiple morbidities. However, the NICE guideline on hypertension already covers this group, so the committee did not make new recommendations.

^[1] The GDG searched for and appraised evidence on blood pressure control, and did not set out to establish definitive safe ranges of blood pressure in CKD. The evidence presented in the full guideline does not therefore include safety of low blood pressure, but some such evidence does exist. The GDG set out a range of blood pressure targets, given in these recommendations, which in their clinical experience will inform good practice in CKD.

The committee discussed the evidence in people with diabetes [type 2], which showed no meaningful differences between intensive and standard blood pressure therapy for cardiovascular outcomes and decline in eGFR. It noted that there is uncertainty in clinical practice around the particular need for intensive blood pressure therapies to reduce kidney disease progression and cardiovascular outcomes in people with diabetes and that this evidence did not help to resolve that. However, the committee did not think this was an area that needed to be prioritised for a research recommendation (note this paragraph is taken from the <u>evidence review pg. 12</u>).

Type 1 diabetes guideline (NG17)

Recommendations

1.13.8 Recommend blood pressure management at 135/85 mmHg for adults with type 1 diabetes. If they have albuminuria or 2 or more features of metabolic syndrome, recommend blood pressure management at 130/80 mmHg. See also the <u>recommendations on diabetic kidney</u> <u>disease</u> and <u>NICE's guideline on hypertension in adults</u>. [2004, amended 2021]

Please note that the 2021 amendment to the recommendation did not include an evidence update, but merely added a hyperlink to the hypertension guideline.

1.13.13 For guidance on blood pressure management in adults with type 1 diabetes and evidence of renal involvement, see <u>recommendations 1.6.2 to</u> 1.6.4 in NICE's guideline on chronic kidney disease in adults. **[2015]**

Please note that the 2021 update of the CKD guideline (NG203) changed recommendations 1.6.2 to 1.6.4 such that they no longer give specific advice on blood pressure management in adults with type 1 diabetes and CKD. As such this link is no longer appropriate.

Section on diabetic kidney disease:

1.15.14 Maintain the person's blood pressure below 130/80 mmHg by adding other anti-hypertensive drugs if necessary. [2004]

Evidence base

For recommendations in section 1.13

Note the evidence base dates from 2004, see <u>chapter 14.4 from full guideline</u> (pg. 374-77).

Two large multicentre trials included in a systematic review showed an improvement in arterial and microvascular outcome in patients randomised to lower target blood pressures compared with those with less intensive blood pressure-lowering (McAllister, 2002). Evidence supports a treatment goal of a diastolic blood pressure of less than 80 mmHg.

No evidence exists on the appropriate target systolic blood pressure for people with type 1 diabetes. Consensus recommendations from the Canadian Hypertension Recommendations working group is that systolic blood pressure should be less than 130 mmHg (McAllister, 2002).

The SIGN hypertension guideline noted that RCTs use target blood pressures of less than 130/80 mmHg in major outcome trials or 125/75 mmHg when proteinuria of more than 1 g per 24 hours is present (SIGN, 2001).

For recommendations in section 1.15

There does not appear to be any clear evidence specifically for recommendation 1.15.14, see <u>chapter 16.2 from full guideline</u> (pg. 396-99).

Committee discussion from the guideline

Note these recommendations date to 2004 and the committee considerations can be found in the <u>full guideline</u>.

For recommendations in section 1.13

The finding of raised blood pressure in people with diabetes is felt to be of different significance in the presence of nephropathy, if features of the

metabolic syndrome are present, or in the absence of these findings. Other risk factors (age, ethnic group, family history and smoking) will be relevant in the last group, in whom it was felt management should echo that of nondiabetic people of the same age, but regarding the diabetes as a further substantial risk factor (formal risk calculation was considered above under CVD surveillance and is not recommended). The combination of raised blood pressure and nephropathy, or features of the metabolic syndrome is, however, known to be very high risk indeed for premature CVD in early middle age. Accordingly, intervention levels and targets should be lower and more strictly applied than for the person with 'simple' hypertension.

Very many suggestions for intervention levels based on evidence have been put forward by other groups, with (allowing for the gradual evolution of evidence) considerable coherence. The group assessed all the available recommendations in this area and reached a consensus based on small differences between these. The problems of motivating professionals and people with diabetes to manage blood pressure appropriately, despite the clear arterial and macrovascular protection to be gained, were noted to be multifactorial. Accordingly, recommendations emphasising intervention levels, targeting, informed discussions and patient-held record cards were discussed. The problem of potential and minor side effects inhibiting the achievement of major clinical gains was felt to be worth mentioning. It was noted that lifestyle interventions have a role in blood pressure management (considered in more detail in other parts of this guideline). See <u>chapter 14.4 from full guideline</u>.

For recommendations in section 1.15

There does not appear to be any clear rationale for recommendation 1.15.14 See <u>chapter 16.2 from full guideline</u>.

Inconsistency with the type 1 diabetes guideline compared with the CKD guideline

Recommendation 1.13.8 within the type 1 diabetes guideline gives a blood pressure target which could be seen to conflict with the CKD guideline,

although it covers a broader population. It also links to the CKD guideline which now does not contain any recommendations specifically on blood pressure targets for diabetic kidney disease.

Recommendation 1.13.13 within the type 1 diabetes guideline links to the CKD guideline which has since been updated, and therefore the link is incorrect.

Recommendation 1.15.14 from the section on diabetic kidney disease within the type 1 diabetes guideline again mentions a target of 130/80 mmHg.

Approach for handling the inconsistency

One possible approach to amending the <u>type 1 diabetes guideline</u> recommendations was presented to the diabetes committee as follows. 1.13.8 Recommend blood pressure management <u>below135/85</u> 140/90 mmHg (target range 120 to 139 mmHg) for adults with type 1 diabetes. If they have albuminuria or 2 or more features of metabolic syndrome, recommend blood pressure management below 130/80 mmHg (target range 120 to 129 mmHg). See also NICE's guideline on <u>chronic kidney disease</u> and <u>NICE's guideline on</u> <u>hypertension in adults</u>.

Delete recommendation 1.13.13.

1.15.14 Maintain the person's blood pressure (see recommendation 1.13.8 above for blood pressure targets) by adding other anti-hypertensive drugs if necessary.

Four members of the existing NICE diabetes committee responded and no consensus was achieved. In particular, it was noted that recommendation 1.13.8 was not in line with current thinking around ACR.

As such, the following amendment to recommendations is now suggested.

1.13.8 In adults with type 1 diabetes aim for blood pressure targets as follows:

- For adults with a urine albumin:creatinine ratio (ACR) under 70 mg/mmol, aim for a clinic systolic blood pressure under 140 mmHg (target range 120 to 139 mmHg) and a clinic diastolic blood pressure under 90 mmHg.
- For adults with an ACR of 70 mg/mmol or over, aim for a clinic systolic blood pressure under 130 mmHg (target range 120 to 129 mmHg) and a clinic diastolic blood pressure under 80 mmHg.
- In adults aged 80 and over, whatever the ACR, aim for a clinic systolic blood pressure under 150 mmHg (target range 140 to 149 mmHg) and a clinic diastolic blood pressure under 90 mmHg.

Use clinical judgement for adults with frailty, target organ damage or multimorbidity. See NICE's guidelines on <u>chronic kidney</u> <u>disease</u>, <u>hypertension in adults</u>, <u>and multimorbidity</u>.

Note that recommendation 1.13.8 is derived from recommendations 1.6.1 and 1.6.2 within the NICE guideline on CKD, and recommendation 1.4.21 from <u>NICE's guideline on hypertension in adults</u>

Delete recommendation 1.13.13.

1.15.14 Maintain the person's blood pressure (see recommendation 1.13.8 for blood pressure targets) by adding other anti-hypertensive drugs if necessary.

References

CKD guideline

Papademetriou, Vasilios, Zaheer, Misbah, Doumas, Michael et al. (2016) Cardiovascular Outcomes in Action to Control Cardiovascular Risk in Diabetes: Impact of Blood Pressure Level and Presence of Kidney Disease. American journal of nephrology 43(4): 271-80

Type 1 diabetes guideline

McAlister FA, Zarnke KB, Campbell NRC, Feldman RD, Levine M, Mahon J et al. The 2001 Canadian recommendations for the management of hypertension: Part two - Therapy. Canadian Journal of Cardiology. 2002; 18(6):625-641

Scottish Intercollegiate Guidelines Network. Hypertension in older people; Treatment of special groups of older people. SIGN, 2001. Available from: <u>http://www.nhsggc.org.uk/content/mediaassets/pdf/HSD/sign49.pdf</u>

Additional useful resources

Blood pressure reduction in diabetes: lessons from ACCORD, SPRINT and EMPA-REG OUTCOME - PubMed (nih.gov)

Blood pressure control in patients with chronic kidney disease (nih.gov)

Annex 1 – hypertension guideline

Recommendations

1.4.20 Reduce clinic blood pressure to below 140/90 mmHg and maintain that level in adults with hypertension aged under 80. [2019]

1.4.21 Reduce clinic blood pressure to below 150/90 mmHg and maintain that level in adults with hypertension aged 80 and over. Use clinical judgement for people with frailty or multimorbidity (see also <u>NICE's guideline on</u> <u>multimorbidity</u>). [2019]

Rationale

Blood pressure targets

Why the committee made the recommendations

No evidence was identified to determine whether cardiovascular risk or blood pressure targets should be used. The committee agreed that in the absence of evidence the focus should be on blood pressure targets, based on their expertise and experience of current practice.

The evidence for blood pressure targets showed that there were both benefits and harms associated with a lower clinic systolic blood pressure target of 120 mmHg compared with 140 mmHg in people with primary hypertension without type 2 diabetes. Although the evidence suggested some benefit in reducing mortality and cardiovascular events, the lower blood pressure target was associated with a greater risk of harms, such as injury from falls and acute kidney injury. The committee agreed that the long-term implications of these adverse events were unclear and that further research is needed.

This evidence came from the SPRINT trial, which was a large study undertaken in the US. The committee discussed concerns about the population included in the study and the applicability to UK practice of the methods used. The study used automated blood pressure devices with a time delay and an isolated rest period, which is not common practice in the UK. The committee considered that the use of these devices would lead to lower blood pressure readings than in routine UK clinical practice. They also had concerns that some medicines were stopped when blood pressure targets were achieved, which may have had an impact on the results. The committee also discussed concerns about applicability of the population, for example, the participants had high cardiovascular risk levels including many with pre-existing cardiovascular disease or renal impairment and were already receiving treatment before the study started. These concerns made the evidence difficult to interpret and use to inform the recommendations. Further details of the committee's discussion of this study is included in <u>evidence review D: targets</u>.

Evidence from a smaller study also showed some benefit of lowering clinic systolic blood pressure targets to 130 mmHg. However, the committee noted that the study was based on people already receiving treatment and that it lacked information on adverse events.

The committee agreed that there was no evidence to suggest that blood pressure targets should be different in people with type 2 diabetes. Evidence for lower targets in people with type 2 diabetes was also limited, with some evidence to suggest that lower blood pressure targets did not reduce the rate of cardiovascular events. Previous recommendations for people with type 2 diabetes (in <u>NICE's guideline on type 2 diabetes in adults</u>) suggested a blood pressure target below 130/80 mmHg in the presence of target organ damage such as kidney, cerebrovascular or eye disease. The committee noted that the evidence behind this recommendation was based on 2 small studies in people without hypertension. They also had concerns about the relevance of the study design. The committee were also aware of trial data showing less benefit in populations with type 2 diabetes with fewer additional risk factors. The committee therefore agreed that there was insufficient evidence to recommend a different blood pressure target for this subgroup. It was noted that people with later-stage chronic kidney disease are covered by other NICE guidelines.

Overall, the committee agreed that the evidence was unclear and insufficient to determine whether a lower target would be beneficial and whether it would outweigh the associated harms. Therefore, the 2011 clinic blood pressure target of 140/90 mmHg for adults under 80 years was retained and applies to people with or without type 2 diabetes. The corresponding HBPM and ABPM targets were also retained at 135/85 mmHg. The recommendations emphasise the importance of achieving and maintaining a level consistently below the person's blood pressure target, whether this target be based on clinic, HBPM or ABPM.

Based on their experience, the committee members felt that people with postural hypotension are at risk of adverse events if a sitting or lying blood pressure is used for monitoring, because this measurement would overestimate daytime blood pressure and result in overtreatment. For example, a patient with a sitting systolic blood pressure of 140 mmHg might have a much lower blood pressure when standing and be at an increased risk of falls if treated based on their sitting blood pressure. The committee decided to recommend that 3 groups who are at risk of postural hypotension (people over 80 years, with type 2 diabetes and with symptoms of postural hypotension) should have their standing blood pressure measured, and their treatment modified accordingly if they have postural hypotension. The standing blood pressure should be used for future monitoring.

The committee noted that there was a lack of evidence for blood pressure targets in people aged over 80 years. Based on their experience the committee

members agreed to retain the recommendation from the 2011 guideline, which was based on the only large, outcome-based randomised controlled trial in this age group. The committee also agreed that different blood pressure targets might be needed for people who are frail or have other conditions because they may have an increased risk of adverse events and less to gain from the long-term benefits of stricter targets. The committee decided it was not possible to define a blood pressure target for all possible clinical scenarios, and so recommended that clinical judgement should be used to agree an achievable target for each individual after a discussion about the possible risks and benefits. The committee agreed that further research in this area would be helpful and developed a <u>recommendation for research on blood pressure</u> <u>targets for people aged over 80</u> to inform future guidance.

Annex 2 – the BNF and SIGN blood pressure targets

The BNF

The section on hypertension within the BNF has the following:

In **type 1 diabetes**, aim for a clinic blood pressure of 135/85 mmHg or less unless the adult with type 1 diabetes has albuminuria or 2 or more features of metabolic syndrome, in which case it should be 130/80 mmHg or less.

In type 2 diabetic patients with hypertension, NICE recommend a clinic blood pressure below 140/90 mmHg in those aged under 80 years, and below 150/90 mmHg in those aged 80 years and over. SIGN (November 2017) recommend a clinic blood pressure of 130/80 mmHg. SIGN (June 2017) recommend a clinic blood pressure below 135/85 mmHg regardless of age if the patient has established cardiovascular disease.

A target clinic blood pressure below 140/90 mmHg is suggested in patients with renal disease (chronic kidney disease). A blood pressure below 130/80 mmHg is advised in patients with chronic kidney disease and diabetes, or if urine albumin to creatinine ratio (ACR) exceeds 70 mg/mmol). SIGN (2017) recommend a blood pressure below 135/85 mmHg should be considered in patients with established cardiovascular disease and chronic kidney disease.

The SIGN guideline

The <u>SIGN 149 guideline on risk estimation and prevention of cardiovascular</u> <u>disease</u> (2017) has the following relevant recommendations:

Individuals with diabetes should be offered blood pressure-lowering treatment if the baseline clinic systolic pressure is >140 mmHg, to prevent mortality, macrovascular events, and progression of nephropathy and retinopathy.

Individuals with diabetes should be considered for blood pressure-lowering treatment, even if the systolic clinic blood pressure is <140 mmHg, to reduce

the risk of stroke, progression of retinopathy and albuminuria. At this level of blood pressure, treatment should be targeted at patients thought to be at greatest risk of complications.

For individuals with established CVD and diabetes, chronic renal disease or target organ damage a lower blood pressure target of <135/85 mmHg should be considered.

Lowering BP below 130/80 mmHg is not routinely recommended as this brings limited additional benefits and causes significant adverse effects.