

3-year scoping report

Topic: Pharmacological management of glycaemic control in people with type 2 diabetes: literature published since date of SIGN 154 guideline search in 2017

Date of search: September 2021

Searched by: Evan Campbell

Key concepts: Type 2 diabetes, drug*, pharma*

Summary of findings

The purpose of this 3-year scoping is to identify significant new evidence relating to SIGN 154, and whether any sections of the guideline require updating. A rapid search of the literature was conducted; a recent draft update of NICE CG 28 and a relevant page on DynaMed (www.dynamed.com) were identified. Both of these sources are different from SIGN 154 mainly around the consideration of changing the medication of person with type 2 diabetes depending on their cardiovascular risk.

Chair's comments *Include any comments or suggestions on significant new evidence and developments in the field that the Chair has provided*

Comment
The NICE document clearly contains an extensive evidence review that once again will be helpful. I'm not so sure about their conclusions as their network meta-analysis methodology always seems to favour pioglitazone which is rarely used now due to weight gain and fluid retention. In addition, their cost-effectiveness analysis seems to work against the newer drugs: I'm not sure if they have updated their health economic model adequately to capture long term CV outcomes as Appendix L says it "can be found in a separate report" which I haven't managed to locate.

In terms of the clinical trials included it looks like NICE have not included HARMONY (NCT02465515) or AMPLITUDE-O (NCT03496298) as neither is currently available in the UK - but it is possible that they will be as both are CVOTs that showed benefit (with the GLP-1RAs albiglutide and efpeglenatide respectively).

Two other important trials with estimated completion dates in 2024:

- 1) VA-IMPACT: metformin vs placebo CV outcomes trial in prediabetes <https://clinicaltrials.gov/ct2/show/NCT02915198>
- 2) SURPASS-CVOT with the dual GLP-1RA and GIP agonist tirzepatide <https://clinicaltrials.gov/ct2/show/NCT04255433>

Looking back on SIGN 154, the key recommendations were that metformin is first line for individuals with type 2 diabetes - and that for those with established cardiovascular disease, SGLT2 inhibitors with proven cardiovascular benefit (currently empagliflozin and canagliflozin) and GLP-1 receptor agonist therapies with proven cardiovascular benefit (currently liraglutide) should be considered. The metformin recommendation is still supported by current ADA-EASD consensus guidance but European Society for Cardiology guidelines recommend that metformin is not necessarily first-line in high CV risk individuals (who can go straight to SGLT2 inhibitors) – these latter guidelines are supposedly “evidence-based” although it is not clear to me how they derived this. It is easy for us to update the list of agents that have proven cardiovascular benefit in both SIGN lists for those “with established CV disease” based on the CV outcome trials, but some of the recent trials (e.g. REWIND) have been conducted in less high risk populations and there is a feeling in the clinical community that these agents should be increasingly used earlier than supported by SIGN 154, even for those without established CV disease and without necessarily a trial of a DPP-4 inhibitor first.

Relevant evidence and implications for SIGN recommendations

The recommendations for SIGN 154 were mainly based on the Agency for Healthcare Research and Quality (AHRQ) systematic review [Diabetes Medications for Adults with Type 2 Diabetes: An Update](#), published in 2016, and the National Institute for Health and Care Excellence (NICE) guideline CG 28, [Type 2 diabetes in adults: management](#), published in 2015. The AHRQ document was a comprehensive review comparing many different combinations of drugs in different clinical contexts. This review has not been updated since 2016 and was archived by AHRQ in 2019 with the note - *This report is greater than 3 years old. Findings may be used for research purposes, but should not be considered current.*

NICE has updated the pharmacological management section of NICE CG 28 (2015), and published on 15 February 2022. NICE conducted a network meta-analysis comparing the different clinical effects of adding glucose-lowering drugs and measuring glycaemic and cardiovascular outcomes. NICE also conducted a cost-utility analysis for each of the drugs applied in different clinical contexts.

The outcomes of the network meta-analysis are complex and will not be described in detail here. NICE identified and included 16 cardiovascular outcome RCTs (and subsequent linked publications) in their meta-analysis.

- CANVAS, 2018
- CARMELINA, 2019
- CAROLINA, 2019
- DECLARE-TIMI 58, 2019
- ELIXA, 2015
- EMPA-REG OUTCOME, 2015
- EXAMINE, 2013
- EXSCEL, 2017
- LEADER, 2016
- PIONEER, 2019
- PROactive 10, 2008
- REWIND, 2019
- SAVOR-TIMI 53, 2013
- SUSTAIN-6, 2016
- TECOS, 2015
- VERTIS, 2020

It should be noted that all of the drugs included in the network meta-analysis are efficacious in glycaemic control.

The outcome of the cost-utility analysis was that only sodium-glucose co-transporter-2 (SGLT2) inhibitors and injectable semaglutide were cost-effective in any of the following scenarios (although base case incremental cost-effectiveness ratios (ICERs) of SGLT2 inhibitors were always lower than injectable semaglutide):

- replacement of initial therapy
- addition to initial therapy
- replacement of first intensification
- addition to first intensification
- replacement of second intensification

in all of the following groups and subgroups:

- all patients
- high cardiovascular (CV) risk (no prior event)
- high CV risk (prior event)
- all high CV risk
- high body mass index (BMI)

“In the base-case analysis, drugs belonging to the SGLT2 class were associated with the lowest ICERs compared with no cardiovascular outcome trial (CVOT) treatment. Across all subgroups in the base-case dapagliflozin is the SGLT2 inhibitor most commonly associated with an ICER of less than £20,000..”

NICE noted that while injectable glucagon-like peptide 1 (GLP-1) receptor agonists were associated with event hazard ratios of less than one for some CV events, they also had the highest acquisition cost and were also associated with a disutility related to injections. This leads to them being associated with a lower QALY gain and higher costs than the SGLT2 inhibitors when compared with no CVOT treatment. The only GLP-1 receptor agonist to have ICERs in the range of £20,000 to £30,000 was injectable semaglutide.

Having considered the results, the NICE committee agreed they were more certain about the results for SGLT2 inhibitors (considered as a class) than they were for injectable semaglutide. There were two key factors underpinning this decision. First, the results for SGLT2 inhibitors were broadly robust across a range of sensitivity and scenario analyses, and in particular the ICERs were in broadly the same range in the sensitivity analysis making use of CV mortality data from the RCTs. However, for injectable semaglutide, the ICER increased considerably in this sensitivity analysis. Whilst the committee were comfortable this remained a sensitivity analysis, rather than being appropriate as the base-case analysis, they noted that this lower robustness in the results to changed assumptions did reduce their level of certainty in the conclusions of injectable semaglutide, compared with the conclusions for SGLT2 inhibitors. They also noted uncertainty in the clinical evidence for semaglutide as a result of inconsistencies in the trial outcomes for these treatments.

Secondly, they noted the cost-effectiveness results for SGLT2 inhibitors were broadly in the same range as a class, whilst for GLP-1 receptor agonists there was considerable within class variation. Whilst the committee did not think a priori that GLP-1 receptor agonists should necessarily be treated as a class, and were therefore open to the possibility some within the class may be both more effective and more cost-effective, they nevertheless agreed that the inability to use other data from within the class to support the results for injectable semaglutide did reduce their overall level of confidence in those findings, compared again with the findings for SGLT2 inhibitors.

It was the outcome of this cost-utility analysis that drove the recommendations made by NICE.

Both SIGN 154 and NICE CG 28 included prescribing guidance. These are summarised below before being compared.

Dynamed.com also provides guidance on glucose lowering medications in people with type 2 diabetes. This guidance is identical to NICE CG 28 apart from a nuance in prescribing insulin. This will be highlighted later (see section 1.3). For the rest of the discussion it can be assumed that the guidance from NICE CG 28 and dynamed.com agree.

1.1 Prescribing recommendations from SIGN 154

The prescribing algorithm of SIGN 154 can be summarised as follows:

1. Initial treatment of metformin unless patient has osmotic symptoms or intolerant to metformin in which case prescribe a sulphonylurea (reverting to metformin when osmotic symptoms resolve)
2. If after 3–6 months glycaemic targets have not been met add one of the following (taking into account CV risk, lifestyle, and BMI): a sulphonylurea, SGLT2 inhibitor, DPP-4 inhibitor or pioglitazone
3. If after another 3–6 months add another of the oral agents from a different class, or add the injectable agent GLP-1 receptor agonist if the patients BMI <30 kg/m² or basal insulin if the patient's BMI >30 kg/m²
4. If after another 3–6 months the glycaemic target is not being met then refer to specialist help.

1.2 Prescribing recommendations from draft NICE CG 28

The prescribing guidance from the draft NICE CG 28 is more complex and takes into account CV risk. It can be summarised as follows.

When deciding upon first line treatment, first assess HbA1c, CV risk and renal function:

- if low risk of CVD: offer metformin (or metformin modified release (MR) if gastrointestinal (GI) disturbance). If metformin is contraindicated consider DPP-4 inhibitor, pioglitazone, a sulfonylurea or, 'for some people' an SGLT2 inhibitor.
- if high-risk CVD (QRISK2 $\geq 10\%$) offer metformin (or metformin MR if GI disturbance) and consider adding an SGLT2 inhibitor with proven CVD benefit. If metformin is contraindicated consider an SGLT2 inhibitor alone
- if chronic heart failure or established CVD then offer metformin (or metformin MR if GI disturbance) and offer an SGLT2 inhibitor with proven CVD benefit. If metformin is contraindicated offer an SGLT2 inhibitor with proven CVD benefit alone

The NICE guidance then goes on to discuss disease progression:

- if at any point HbA1c is not controlled below individually agreed threshold consider switching or adding the following: a DPP-4 inhibitor, pioglitazone, or a sulfonylurea. SGLT2 inhibitors may also be used in dual or triple therapy
- if at any point the patient has or develops a high risk of CVD then consider switching to or adding an SGLT2 inhibitor
- if at any point the patient has or develops chronic heart failure or established atherosclerotic CVD then offer an SGLT2 inhibitor.

There is also specific guidance on insulin therapy:

- when dual therapy has not continued to manage HbA1c to below the person's individually agreed threshold, also consider insulin-based therapy (with or without other antidiabetic drugs).

Lastly NICE CG 28 discusses GLP-1 receptor agonist treatments:

If triple therapy with metformin and 2 other oral drugs is not effective, not tolerated or contraindicated, consider a triple therapy including a GLP-1 receptor agonist for adults who:

- have a BMI ≥ 35 kg/m² (adjust according from Black, Asian and other minority ethnic groups) and specific psychological or other medical problems associate with obesity

or:

- have a BMI $<35 \text{ kg/m}^2$ and:
 - for whom insulin therapy would have significant occupational implications or
 - weight loss would benefit other significant obesity related comorbidities.

The following note is given in the summary:

At each point follow the prescribing guidance. Switch or add treatments from different drug classes up to triple therapy (dual therapy if metformin is contraindicated). The prescribing guidance referenced is as follows:

Choosing treatments:

Base the choice of the medicine on;

- the person's individual clinical circumstances, for example comorbidities, contraindications, weight, and risks from polypharmacy
- their preferences and needs
- the medicine's effectiveness in terms of metabolic response and cardiovascular protection
- the medicine's safety and tolerability
- monitoring requirements
- the licensed indications or combinations available
- which medicine has the lowest cost in its class.

Reviewing and changing treatments

At each point:

- stop medicines that have not worked or are not tolerated
- optimise the person's current treatment regimen (adverse effects, adherence to medicines, diet and lifestyle advice, dosage and formulations) before thinking about adding or switching medicines
- think about whether switching rather than adding medicines could be effective
- considerations in the list above about choosing treatments

Rescue therapy

For symptomatic hyperglycaemia, consider insulin or sulfonylurea, review when blood glucose control has been achieved.

1.3 Comparison of the two prescribing algorithms

Parts of SIGN 154's prescribing recommendations are not in line with the recommendations in NICE CG 28.

At present SIGN 154 recommends that initial treatment is metformin for 3–6 months and after that point another drug can be added to the treatment if HbA1c targets are not met. NICE CG 28 differs as it includes the consideration of the patient's CV risk, and if they are at high risk when diagnosed with T2DM then the clinician should consider offering SGLT2 inhibitor and if the patient has established CV disease should offer a SGLT2 inhibitor.

The second part of SIGN 154's prescribing algorithm states that if glycaemic targets have not been met in 3–6 months then either a sulphonylurea, SGLT2 inhibitor, DPP-4 inhibitor or pioglitazone could be added to the treatment regimen. If after another 3–6 months there is still no improvement then add another drug from a different class or injectable GLP-1 receptor agonist or basal insulin depending on the patient's BMI. The prescribing algorithm in SIGN 154 does also recommend that CV risk, lifestyle and BMI should be taken into consideration. The prescribing guidance in NICE CG 28 for continued management of a patient with poorly controlled HbA1c is same as SIGN 154 (but does not include timeframes like SIGN 154). However, the NICE guidance differs from SIGN's, as it provides guidance for when a patient's CV risk or status changes. NICE CG 28 suggests considering offering an SGLT2 inhibitor if the patient develops high risk of CVD (QRISK2 $\geq 10\%$) and the offering of SGLT2 inhibitor if the patient develops establish CVD. While SIGN 154 does say that the patient's CV risk should be taken into account, this is only when considering changing the patient's medication due to there being no improvement in glycaemic control and not changing medication in response to a change in CV risk.

There are slight differences between the prescribing algorithm in SIGN 154, dynamed.com and NICE CG 28 for prescribing injectable GLP-1 receptor agonist or basal insulin. According to SIGN 154 and dynamed.com, a GLP-1 receptor agonist can be prescribed as triple therapy while the NICE CG 28 states that a GLP-1 receptor agonist or insulin should only be prescribed after triple therapy. Also the BMI threshold between GLP-1 receptor agonists and insulin is different between the two guidelines. In SIGN 154 it is 30 kg/m² and in NICE CG 28 it is 35 kg/m².

Recommendations for research – note any evidence that addresses evidence gaps highlighted in the original guideline under the Recommendations for research section

Reference <ul style="list-style-type: none"> • Include type of evidence, reference and source of evidence • Where possible, include hyperlinks to the references 	Details <i>Include abstract or summary of evidence</i>	What area for further research does this address? <ul style="list-style-type: none"> • A list of these are given in the Recommendations for research section
Nil identified.		

Potentially important new evidence – note any new important evidence in the field that may be relevant for the update but that hasn't been mentioned in the original guideline

Reference <ul style="list-style-type: none"> • Include type of evidence, reference and source of evidence • Where possible, include hyperlinks to the references 	Details <i>Include abstract or summary of evidence</i>	Why might this be important to include in the guideline?
Nil identified over and above the references provided by John Petrie.		

Consultation feedback

Former members of the SIGN 154 guideline development group were invited to comment on the report and the proposed areas for update.

Reviewer	Comments
Dr David McGrane, Consultant Physician in Diabetes and Endocrinology at the Queen Elizabeth University Hospital, Glasgow	<p>As Prof Petrie said, NICE have conducted a thorough review of the evidence base. I believe the differences between the current NICE and current SIGN guidance, reflect personal experience / opinion of the NICE vs SIGN group.</p> <p>I believe SIGN should conduct an update of the existing guideline and try to provide a better framework around CV disease and preferred classes / agents.</p>

	I also think greater emphasis should be given to lifestyle interventions as part of any new guidance as there is robust trial evidence to support this approach and we cannot continue to only prescribe drugs out of the current type 2 diabetes epidemic.
Dr Chris Schofield, Consultant Physician and Clinical Director NHS Tayside	Quite a lot of new evidence since written. Would be sensible to update.
Allan Cairns, lay representative	As a lay person, from the perspective of my very limited knowledge, the report seems to be very well researched and argued. Having read it I'm would be inclined to believe the guideline does not require much change.
May Millward, lay representative	I've had a look and as I expected have no comments at this stage.

Concluding remarks

The significant change in the evidence available to support recommendations since the publication of SIGN 154 is the publication of several CVOTs and the update of NICE CG 28 which frames effectiveness of glucose-lowering drug treatment for people with Type 2 diabetes more clearly in terms of CV outcomes, rather than glycaemic outcomes. This has led to guidelines from NICE and SIGN differing in subtle ways (eg SGLT2 inhibitors to be offered to people with T2DM who have established CVD (by NICE) and considered for the same group (by SIGN), but as second-line add-on therapy; and in more significant ways (eg availability of GLP-1 agonist or insulin therapy as third-line treatment according to SIGN recommendations, but after triple therapy according to NICE recommendations). The prescribing hierarchy recommended by NICE is predicated on knowledge of the individual's baseline level of CV risk and, given newer evidence about effectiveness in populations at increased (but not maximum) levels of CV risk, there is scope to update the SIGN guideline to consider risk in more detail. It is unclear how scope of this update translates easily into the categories of "some recommendations will change / substantial work and new proposal and withdrawal required".

The request for consideration of lifestyle interventions may be addressed by the separate SIGN guideline in development on prevention and early recognition and treatment of type 2 diabetes.

The recommendation is: some recommendations will change in the light of the new evidence and selected elements of the guideline should be reviewed / substantial work on the guideline is required and a new topic proposal or withdrawal should be sought

Decision

On 19 May 2022 the Work Programme Committee recommended:

This guideline is in need of review and has been accepted onto the SIGN guideline programme.
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Annex 1

Evidence sources

Resource	Results
Dynamed	https://www.dynamed.com/management/glucose-lowering-medications-for-type-2-diabetes
BMJ Best Practice	Based upon NICE CG 28 and SIGN 154
Guidelines and guidance	
Previous HIS projects/advice/guidance relating to this topic	Nil since SIGN 154
NICE	National Institute of Health and Care Excellence. Type 2 diabetes in adults: management. London: NICE 2015. (NG28). [cited 26 Oct 2017]. Available from url: http://www.nice.org.uk/guidance/ng28
AHRQ	Diabetes Medications for Adults with Type 2 Diabetes: An Update (2016)
HTW	Nil
HTA database	Nil
Additional searching (if required)	
Cochrane library	n/a