NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Diabetes (type 2) - canagliflozin [ID554]

Thank you for agreeing to give us a statement on your organisation's view of the technology and the way it should be used in the NHS.

Healthcare professionals can provide a unique perspective on the technology within the context of current clinical practice which is not typically available from the published literature.

To help you in making your statement, we have provided a template. The questions are there as prompts to guide you. It is not essential that you answer all of them.

Please do not exceed the 8-page limit.

About you

Your name: [redacted]

Name of your organisation.

1. **The University of Oxford.**
2. **The Oxford Centre for Diabetes, Endocrinology and Metabolism.**

Are you (tick all that apply):

- a specialist in the treatment of people with the condition for which NICE is considering this technology? Yes
- a specialist in the clinical evidence base that is to support the technology (e.g. involved in clinical trials for the technology)? Yes
- an employee of a healthcare professional organisation that represents clinicians treating the condition for which NICE is considering the technology? If so, what is your position in the organisation where appropriate (e.g. policy officer, trustee, member etc.)? No
- other? (please specify)

- I am the emeritus founding Chairman of the Oxford Centre for Diabetes, Endocrinology and Metabolism.
- I am the co-chairman of the CANVAS trial, which is the CV outcome study of canagliflozin. As such I receive honoraria from J&J (Janssen) for attendance at steering committee meetings.
- I Chaired the European and American joint guideline group for type 2 diabetes.
- I was a co-investigator of the United Kingdom Prospective Diabetes Study (UKPDS), and am co-author all of the outcome papers, and many of the associated papers of the Group.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the expected place of the technology in current practice?

How is the condition currently treated in the NHS?
The current treatment of type 2 diabetes is complex, based on a wide possibility of choice of second line agents, as set out in the Position Statement of the European Association for the study of diabetes and the American Diabetes Association (EASD and ADA) published in 2012 (1) This outlines that the strict RCT evidence base for the early at-diagnosis treatment of type 2 diabetes is mainly the UKPDS, from which the primary evidence for initial pharmaceutical treatment with metformin is adduced(2).

Is there significant geographical variation in current practice?
The is unanimity in the view that the initial pharmacotherapy for type 2 diabetes should be metformin, but beyond this there are variations dependent on clinical views about the optimum HBa1c level to be aiming for, minimising side effects (nausea, weight increase, hypoglycaemia), and views about costs and potential advantages (weight loss, blood pressure lowering).
Are there differences of opinion between professionals as to what current practice should be? The Position statement of the EASD/ADA makes it clear that there should be a patient-centred view of second-line therapy based on a variety of clinical indicators(1). So current practice is now that there is no single 'right' answer as to what follows metformin therapeutically.

What are the current alternatives (if any) to the technology, and what are their respective advantages and disadvantages?

Class	Prevention of microvascular complications	Prevention of macrovascular complications	Adventages	Disadvantages
Biguanides	• Not proven	• UKPDS, incl. follow up(2-5) • Reduction in mortality	• No weight gain • No provocation of hypoglycemia • Reduction in cardiovascular events	• Gastrointestinal side effects (diarrhea, abdominal cramping) • Lactic acidosis risk (rare) • Vitamin B_{12} deficiency • Contraindications: reduced kidney function; diseases increasing the risk for hypoxia or major ischemia
Sulfonylureas	• UKPDS incl. follow-up • ADVANCE(6)	UKPDS incl. follow-up (2-5)	• Low costs • Experience since 1950s	• Relatively glucose-independent stimulation of insulin secretion: Hypoglycemia, including episodes necessitating hospital admission and causing death • Weight gain • May blunt myocardial ischemic preconditioning • Low "durability"
Meglitinides	Not proven	Not proven	Accentuated effects around meal ingestion	• Hypoglycemia, weight gain, • May blunt myocardial ischemic preconditioning • Dosing frequency
Thiazolidinediones (Glitazones)	Not proven	• PROACTIVE(7) • Metaanalyses	• No provocation of hypoglycemia • β-cell preservation/ durability • HDL-C ↑ TG ↓	• Weight gain • Edema / heart failure • Bone fractures

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Class	Prevention of microvascular complications	Prevention of macrovascular complications	Adventages	Disadvantages
α-glucosidase inhibitors	Not proven	• Stop-NIDDM (prediabetes) (8)	• Non-systemic medication • Post-prandial glucose ↓	• Gastrointestinal side effects (meteorism, flatulence, diarrhea) • Dosing frequency
GLP-1 receptor agonists (incretin mimetics)	Not proven	Not proven (CV outcome studies under way)	• Weight reduction • Potential for improved ß cell mass/function • Cardiovascular protective actions	• Gastrointestinal side effects (nausea, vomiting, diarrhea) • Cases of acute pancreatitis observed • C-cell hyperplasia/ medullary thyroid tumors in animals • Injectable
DPP-4 inhibitors (incretin enhancers)	Not proven	Not proven	• No hypoglycemia • Weight "neutrality"	• Occasional reports of urticaria/angioedema • Cases of pancreatitis observed
Bile acid sequestrants	Not proven	Not proven	• No hypoglycemia • LDL-C ↓	• Constipation • Triglycerides ↓
Dopamine-2 agonists	Not proven	Not proven	No hypoglycemia	• Dizziness/syncope • Nausea • Fatigue • Rhinitis

Are there any subgroups of patients with the condition who have a different prognosis from the typical patient?
Yes. In particular we know of some autosomal dominant variants called Maturity Onset Diabetes of the Young (MODY) (9), and gestational diabetes can be transient during pregnancy, though has a high risk of later relapse to type 2 diabetes(10).

Are there differences in the capacity of different subgroups to benefit from or to be put at risk by the technology?
There is no suggestion that SGT2 inhibitors would be useful or advised either for MODY or for gestational diabetes.

In what setting should/could the technology be used – for example, primary or secondary care, specialist clinics?
Both the dosing regimen and the guidance for the use of SGLT2 inhibitors is straightforward. Patients need to be warned of the increased of vuvovaginitis (in females) and balanitis(in males). They should be warned of the possibility of frequency of micturition and/or nocturia, though in clinical practice these latter possibilities do not seem to be a major problem.

Would there be any requirements for additional professional input (for example, community care, specialist nursing, other healthcare professionals)?
Occasionally, related to vulvovaginits or balanitis (see above).

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

If the technology is already available, is there variation in how it is being used in the NHS? Is it always used within its licensed indications? If not, under what circumstances does this occur?
Yes, dapagliflozin and canagliflozin are both available in Europe. In March 2013, canagliflozin became the first SGLT2 inhibitor to be approved in the United States.

*Please tell us about any relevant **clinical guidelines** and comment on the appropriateness of the methodology used in developing the guideline and the specific evidence that underpinned the various recommendations.*

SGLT-2 inhibitors are too new to be included in guidelines at present. However the ADA/EASD position statement makes it clear that there are no unequivocal evidence-based uniform choices possible for second and third-line therapies(1). This points out that 'For anti-hyperglycaemic management of type 2 diabetes, the comparative evidence basis to date is relatively lean, especially beyond metformin monotherapy'(11)

The advantages and disadvantages of the technology

NICE is particularly interested in your views on how the technology, when it becomes available, will compare with current alternatives used in the UK. Will the technology be easier or more difficult to use, and are there any practical implications (for example, concomitant treatments, other additional clinical requirements, patient acceptability/ease of use or the need for additional tests) surrounding its future use?

If appropriate, please give your view on the nature of any rules, informal or formal, for starting and stopping the use of the technology; this might include any requirements for additional testing to identify appropriate subgroups for treatment or to assess response and the potential for discontinuation.

In general there are no major contra-indications of which I am currently aware. The tablets are easy to take, and, because the SGLT-2 inhibitors do not directly affect the glucose-insulin interactions, Canagliflozin can, potentially, be given with most other oral anti-diabetic agents including insulin. Weight loss occurs secondary to the calorie loss in the urine.

If you are familiar with the evidence base for the technology, please comment on whether the use of the technology under clinical trial conditions reflects that observed in clinical practice. Do the circumstances in which the trials were conducted reflect current UK practice, and if not, how could the results be extrapolated to a UK setting? What, in your view, are the most important outcomes, and were they measured in the trials? If surrogate measures of outcome were used, do they adequately predict long-term outcomes?

These trials are well documented in the submission portfolio. The CANVAS trial(12) was interrogated earlier than the academic community would have wished in order to gain reassurance about cardiovascular safety.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

What is the relative significance of any side effects or adverse reactions? In what ways do these affect the management of the condition and the patient's quality of life? Are there any adverse effects that were not apparent in clinical trials but have come to light subsequently during routine clinical practice?
Our knowledge of side effects is currently predicated entirely on clinical trials.

Equality and Diversity

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that this appraisal:

- *Could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;*
- *Could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology;*
- *Could lead to recommendations that have any adverse impact on people with a particular disability or disabilities*

Please tell us what evidence should be obtained to enable the Committee to identify and consider such impacts

I know of no such exclusions or impacts.

Any additional sources of evidence

Can you provide information about any relevant evidence that might not be found by a technology-focused systematic review of the available trial evidence? This could be information on recent and informal unpublished evidence, or information from registries and other nationally coordinated clinical audits. Any such information must include sufficient detail to allow a judgement to be made as to the quality of the evidence and to allow potential sources of bias to be determined.

I know only of data in the public domain and in relation to my co-chairmanship of the CANVAS trial. In the latter case the Independent Data Monitoring Committee (IDMC) recently reported to the steering committee as follows:
"On the basis of this review, the IDMC recommends: To continue trial unmodified until next scheduled meeting".

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

Implementation issues

The NHS is required by the Department of Health and the Welsh Assembly Government to provide funding and resources for medicines and treatments that have been recommended by NICE technology appraisal guidance. This provision has to be made within 3 months from the date of publication of the guidance.

If the technology is unlikely to be available in sufficient quantity, or the staff and facilities to fulfil the general nature of the guidance cannot be put in place within 3 months, NICE may advise the Department of Health and the Welsh Assembly Government to vary this direction.

Please note that NICE cannot suggest such a variation on the basis of budgetary constraints alone.

How would possible NICE guidance on this technology affect the delivery of care for patients with this condition? Would NHS staff need extra education and training? Would any additional resources be required (for example, facilities or equipment)?

There would be no additional training or staff costs. Canagliflozin is taken like any other oral medication.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

References.

1. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012; 55:1577-96.
2. UKPDS Group, D.R.Matthews. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352:854-65.
3. Holman RR, Paul SK, Bethel MA, Neil HA, Matthews DR. Long-term follow-up after tight control of blood pressure in type 2 diabetes. N Engl J Med. 2008; 359:1565-76.
4. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008; 359:1577-89.
5. UKPDS Group, Matthews. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998; 352:837-53.
6. Patel A, MacMahon S, Chalmers J, Neal B, Woodward M, Billot L, Harrap S, Poulter N, Marre M, Cooper M, Glasziou P, Grobbee DE, Hamet P, Heller S, Liu LS, Mancia G, Mogensen CE, Pan CY, Rodgers A, Williams B. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet. 2007; 370:829-40.
7. Dormandy JA, Charbonnel B, Eckland DJ, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005; 366:1279-89.
8. Chiasson JL, Gomis R, Hanefeld M, Josse RG, Karasik A, Laakso M. The STOP-NIDDM Trial: an international study on the efficacy of an alpha-glucosidase inhibitor to prevent type 2 diabetes in a population with impaired glucose tolerance: rationale, design, and preliminary screening data. Study to Prevent Non-Insulin-Dependent Diabetes Mellitus. Diabetes Care. 1998; 21:1720-5.
9. Winckler W, Weedon MN, Graham RR, McCarroll SA, Purcell S, Almgren P, Tuomi T, Gaudet D, Bostrom KB, Walker M, Hitman G, Hattersley AT, McCarthy MI, Ardlie KG, Hirschhorn JN, Daly MJ, Frayling TM, Groop L, Altshuler D. Evaluation of common variants in the six known maturity-onset diabetes of the young (MODY) genes for association with type 2 diabetes. Diabetes. 2007; 56:685-93.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single Technology Appraisal (STA)

10. Ryan EA, Imes S, Liu D, McManus R, Finegood DT, Polonsky KS, Sturis J. Defects in insulin secretion and action in women with a history of gestational diabetes. Diabetes. 1995; 44:506-12.
11. Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, Marinopoulos SS, Puhan MA, Ranasinghe P, Block L, Nicholson WK, Hutfless S, Bass EB, Bolen S. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Annals of internal medicine. 2011; 154:602-13.
12. Neal B, Perkovic V, de Zeeuw D, Mahaffey KW, Fulcher G, Stein P, Desai M, Shaw W, Jiang J, Vercruysse F, Meininger G, Matthews D. Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)-A randomized placebo-controlled trial. American heart journal. 2013; 166:217-23 e11.