
IMPROVING DIABETES CARE
IN SCOTLAND 2018
UNDERSTANDING THE PRESENT AND SHAPING THE FUTURE

SIGN 154: Pharmacological management of glycaemic control in people with type 2 diabetes: a national clinical guideline

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2nd February 2018

Disclosures

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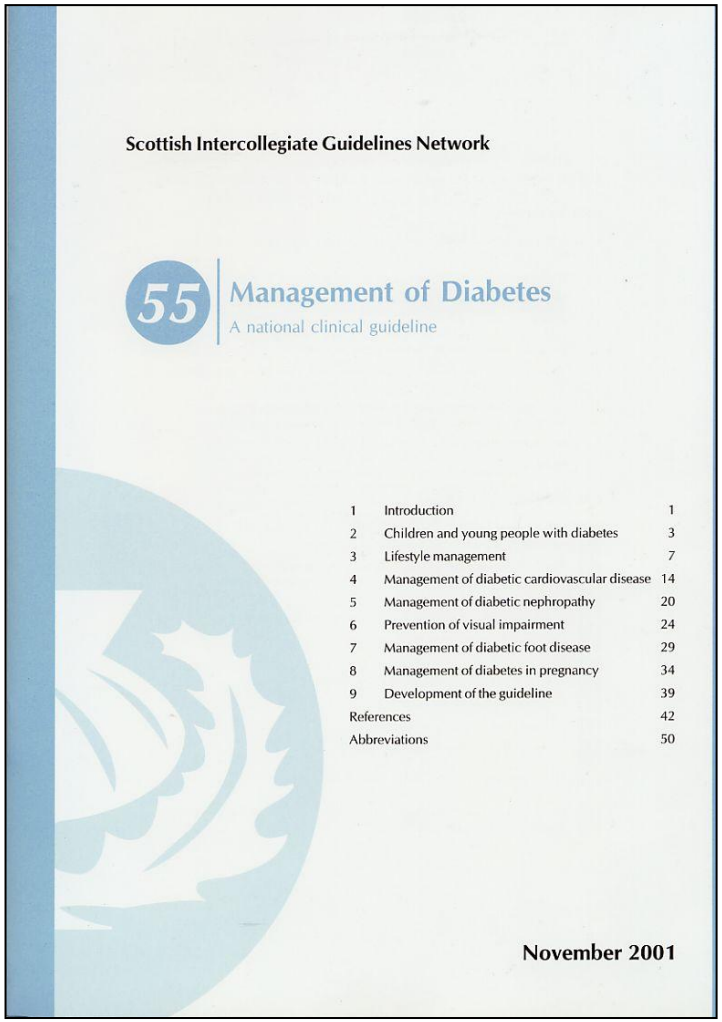
- **Consulting Fees:**
  - Novo Nordisk, Quintiles, ACI Clinical

SIGN Diabetes Guidelines 1996-7

SIGN and diabetes: 2001 to 2010

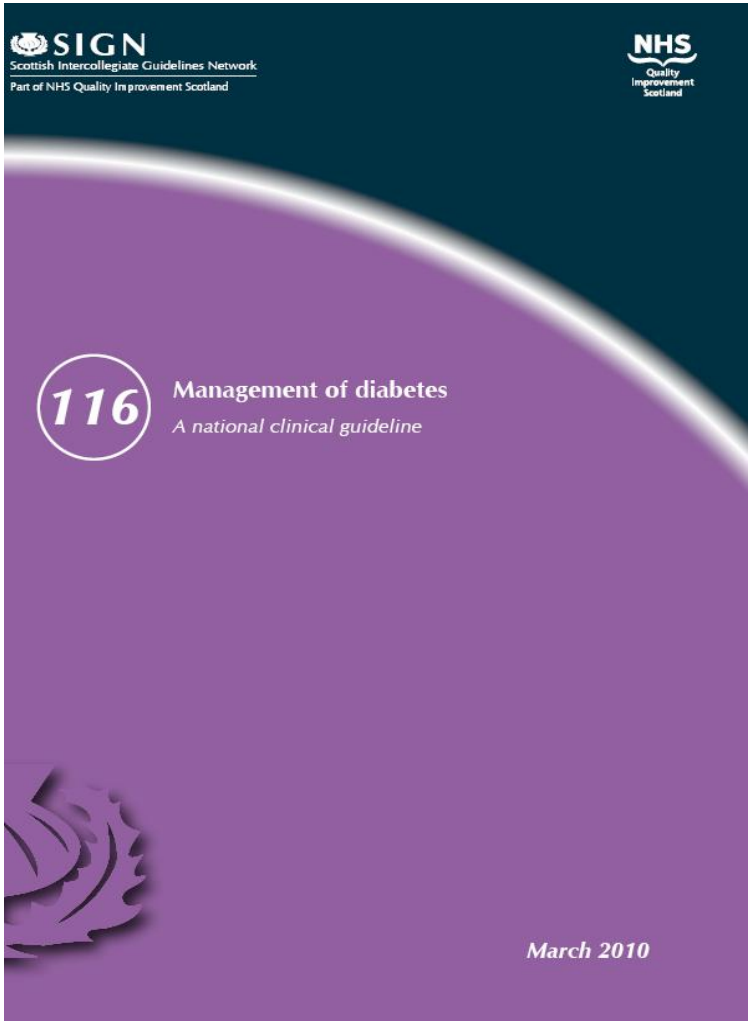


Scottish Intercollegiate Guidelines Network

55 Management of Diabetes

A national clinical guideline

November 2001



SIGN

Scottish Intercollegiate Guidelines Network

Part of NHS Quality Improvement Scotland

NHS Quality Improvement Scotland

116 Management of diabetes

A national clinical guideline

March 2010

Systematic review of T2D guidelines

Annals of Internal Medicine | REVIEW

Evaluation of Guideline Recommendations on Oral Medications for Type 2 Diabetes Mellitus

A Systematic Review

Wendy L. Bennett, MD, MPH; Olaide A. Odelola, MD, MPH; Lisa M. Wilson, ScM; Shari Bolen, MD, MPH; Saranya Selvaraj, BS; Karen A. Robinson, PhD; Eric B. Bass, MD, MPH; and Milo A. Puhan, MD, PhD

Background: Clinical practice guidelines have an important role in guiding choices among the numerous medications available to treat type 2 diabetes mellitus, but little is known about their quality.

Purpose: To assess whether guidelines on oral medications for type 2 diabetes are consistent with a systematic review of the current evidence and whether the consistency of the guidelines depends on the quality of guideline development.

Data Sources: MEDLINE, CINAHL, and guideline-specific databases were searched between July 2007 and August 2011, after the 2007 publication of a peer-reviewed systematic review on oral diabetes medications.

Study Selection: Two reviewers independently screened citations to identify English-language guidelines on oral medications to treat type 2 diabetes that were applied in the United States, United Kingdom, and Canada.

Data Extraction: Reviewers assessed whether the guidelines addressed and agreed with 7 evidence-based conclusions from the 2007 systematic review. Two reviewers independently rated guideline quality by using 2 domains from the Appraisal of Guidelines Research and Evaluation instrument.

Data Synthesis: Of the 1000 screened citations, 11 guidelines met that metformin is favored as the first-line agent. Ten guidelines agreed that thiazolidinediones are associated with higher rates of edema and congestive heart failure compared with other oral medications to treat type 2 diabetes. One guideline addressed no evidence-based conclusions, and 5 guidelines agreed with all 7 conclusions. The summary scores of the rigor of development (median, 28.6% [range, 16.7% to 100.0%]) and editorial independence (median, 75.0% [range, 8.3% to 100.0%]) domains varied greatly across guidelines. Guidelines that received higher quality scores contained more recommendations that were consistent with the evidence-based conclusions.

Limitation: Only English-language guidelines targeting users in the United States, United Kingdom, and Canada that contained recommendations on oral medications were included.

Conclusion: Not all practice guidelines on oral treatment of type 2 diabetes were consistent with available evidence from a systematic review. Guidelines judged to be of higher quality contained more recommendations consistent with evidence-based conclusions. The quality of guideline development processes varied substantially.

Primary Funding Source: Agency for Healthcare Research and Quality.

Ann Intern Med. 2012;156:27-36. www.annals.org

Correspondence

Evaluation of Guidelines on Diabetes Medication

TO THE EDITOR: We were interested to read Bennett and colleagues' systematic review (1) on the evaluation of guideline recommendations on oral medications for type 2 diabetes mellitus. However, we were surprised by the omission of the 2010 update of the Scottish Intercollegiate Guidelines Network (SIGN) guideline on the management of diabetes (2). This guideline covers all aspects of diabetes, with a specific chapter addressing medication for type 2 diabetes, therefore meeting the review's main inclusion criteria.

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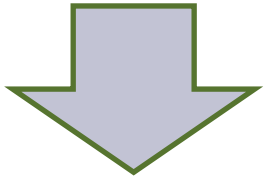

As Dr. Brown and colleagues noted, we missed the SIGN guideline (1) on the management of diabetes. This guideline's summary scores for quality were 97.6% for rigor of development and 100% for editorial independence (0% = lowest; 100% = highest), which were similar to the highest-quality guidelines that we previously reported.

Wendy L. Bennett, MD, MPH
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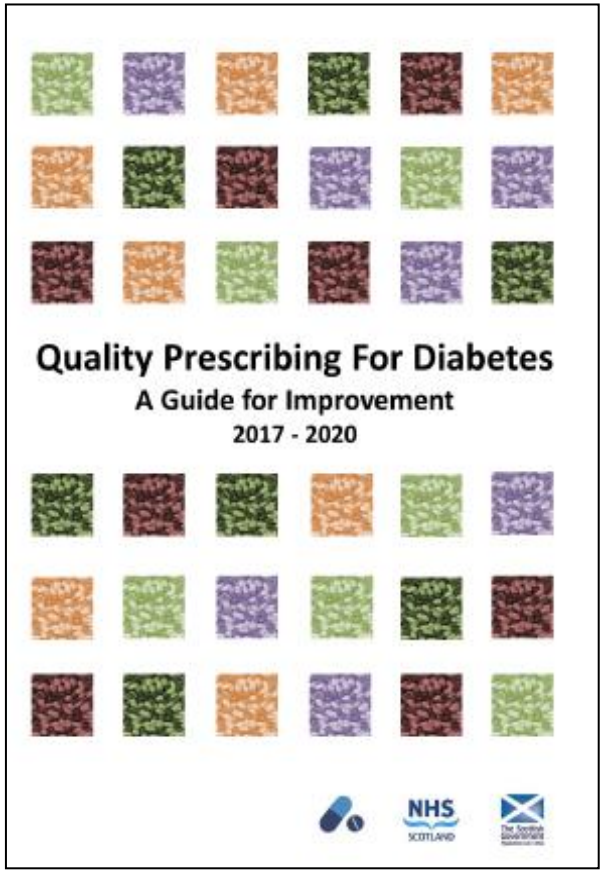
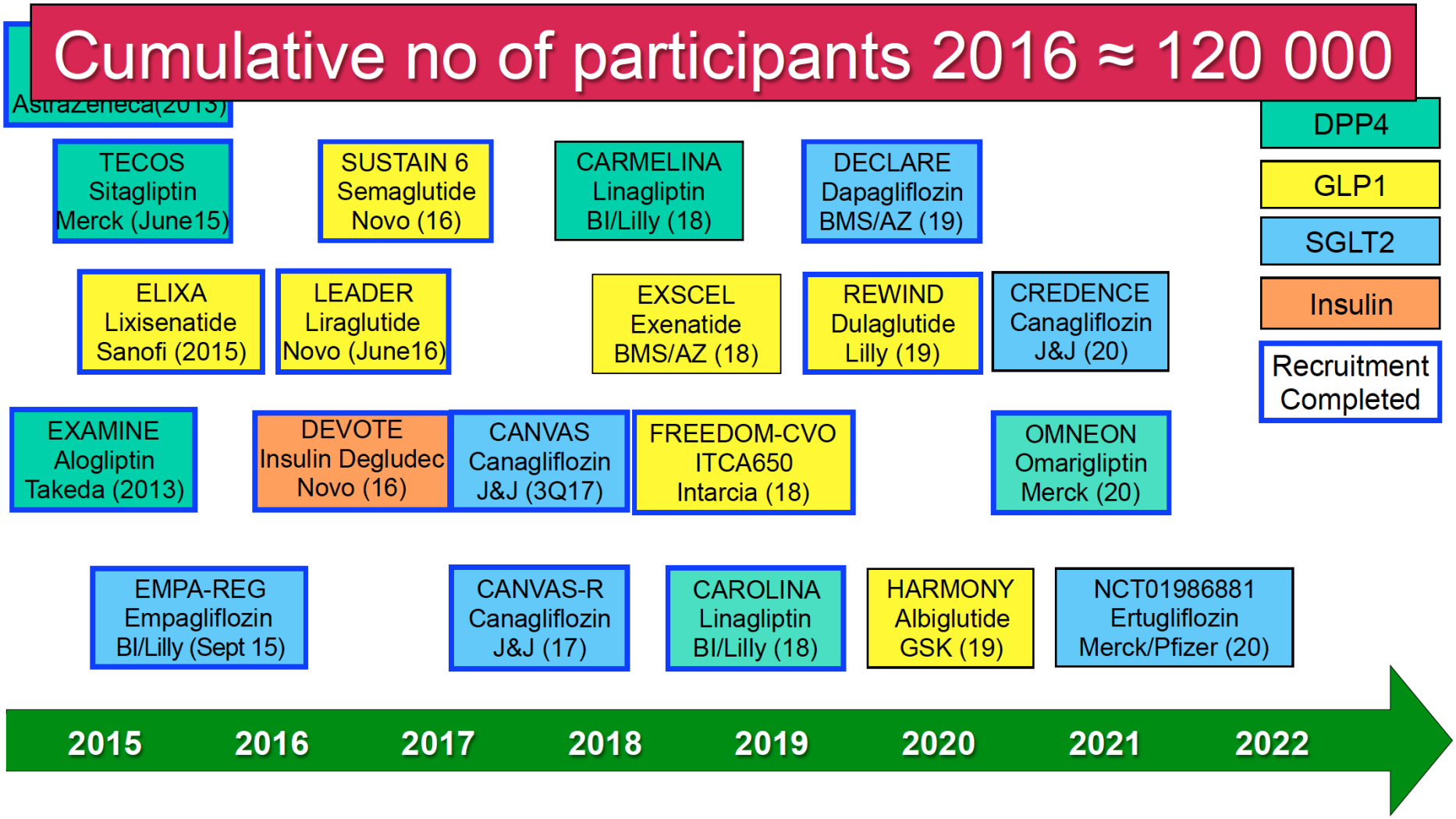
Why an update now?

- Ongoing epidemic of type 2 diabetes
- Significant volume of new evidence
- A new drug class: SGLT2 inhibitors
- Commissioned by Scottish Government to support a revised Scottish Diabetes Prescribing Strategy



Trials of glucose lowering drugs in type 2 diabetes

Compounds tested



Rydén et al. Clin Therap 2016; 38: 1279

SIGN 154 (2017)

- = Chapter 6 of SIGN 116 revised as a new stand alone guideline
- Replaces previous Chapter 6
- Other chapters remain:
  - lifestyle management, psychosocial factors, type 1 diabetes, pregnancy, cardiovascular, kidney, renal, foot

Who?

THE GUIDELINE DEVELOPMENT GROUP

Professor John R Petrie (*Chair*)	*Professor of Diabetic Medicine, Institute of Cardiovascular and Medical Sciences, University of Glasgow*
Mr Allan Cairns	*Lay Representative, Giffnock*
Dr Samantha Carmichael	*Lead Pharmacist Clinical Trials/ Clinical Research and Development, West Glasgow Ambulatory Care Hospital*
Dr Gemma Currie	*Clinical Lecturer, University of Glasgow*
Dr Andrea Llano	*ST5 in Clinical Pharmacology and Therapeutics, Glasgow Royal Infirmary*
Dr David McGrane	*Consultant Physician, Queen Elizabeth University Hospital, Glasgow*
Professor Gerard McKay	*Consultant Physician, Glasgow Royal Infirmary*
Ms May Millward	*Lay Representative, Philpstoun*
Dr Moray Nairn	*Programme Manager, SIGN*
Dr Chris Schofield	*Consultant Physician in Diabetes and Endocrinology, Ninewells Hospital, Dundee*
Dr Carolyn Sleith	*Evidence and Information Scientist, Healthcare Improvement Scotland*

The membership of the guideline development group was confirmed following consultation with the member organisations of SIGN. All members of the guideline development group made declarations of interest. A register of interests is available in the supporting material section for this guideline at **www.sign.ac.uk**

Timetable

- **First meeting:** 27th September 2016
- **First consultation:** June 2017
- **Second consultation (algorithm):** August 2017
- **Publication date:** 29th November 2017

Aims

- Optimal targets for glucose control for the prevention of microvascular and macrovascular complications *(unchanged from SIGN 116)*
- **Risks and benefits of the principal therapeutic classes of glucose-lowering agents and insulins currently available *(updated from SIGN 116)***
- **Updated algorithm to guide choice of first-, second- and third-line glucose-lowering agent, incorporating the summarised evidence and the clinical experience of the guideline development group**

Evidence from . . . (rapid update)

- SIGN 116
- Systematic reviews and meta-analyses from the Agency of Healthcare Research and Quality (2016)
- Evidence summaries from National Institute for Health and Care Excellence (NICE) clinical guideline on type 2 diabetes in adults (2015)
- New SIGN searches for primary literature carried out to update these sources to November 2016
- Cardiovascular outcome trials published during the development period (to September 2017).

Main changes . . .

Metformin and sulphonylureas

- Metformin first line oral treatment:
  - no restriction to those who are overweight
- Sulphonylureas if metformin contraindicated or not tolerated:
  - no restriction to those who are “not overweight”

Metformin and sulphonylureas

ALTERNATIVE APPROACH: if osmotic symptoms or intolerant of metformin

	METFORMIN*	SULPHONYLUREA*
EFFICACY	MODERATE	HIGH
CV BENEFIT	YES	NO
HYPOGLYCAEMIA RISK	LOW	HIGH
WEIGHT	REDUCTION	GAIN
MAIN ADVERSE EVENTS	GASTROINTESTINAL	HYPOGLYCAEMIA
IN CKD STAGE 3A	MAXIMUM 2 g DAILY	CAREFUL MONITORING [1]

- Algorithm emphasises direct pathway to insulin if severe osmotic symptoms with weight loss

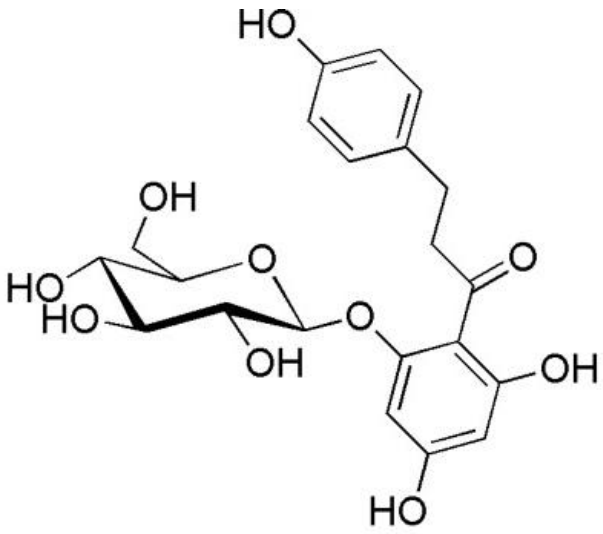
Pioglitazone and DPP-4 inhibitors

- Pioglitazone:
  - risk of fracture not restricted to women
- DPP-4 inhibitors:
  - cardiovascular safety studies summarised but no substantive change in recommendations

Acarbose and meglitinides

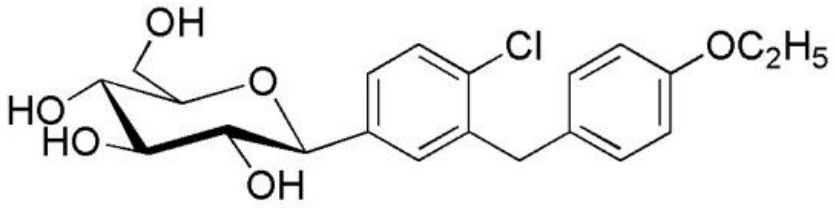
- Removed

Sodium-GLucose co-Transporter-2 inhibitors



Phlorizin

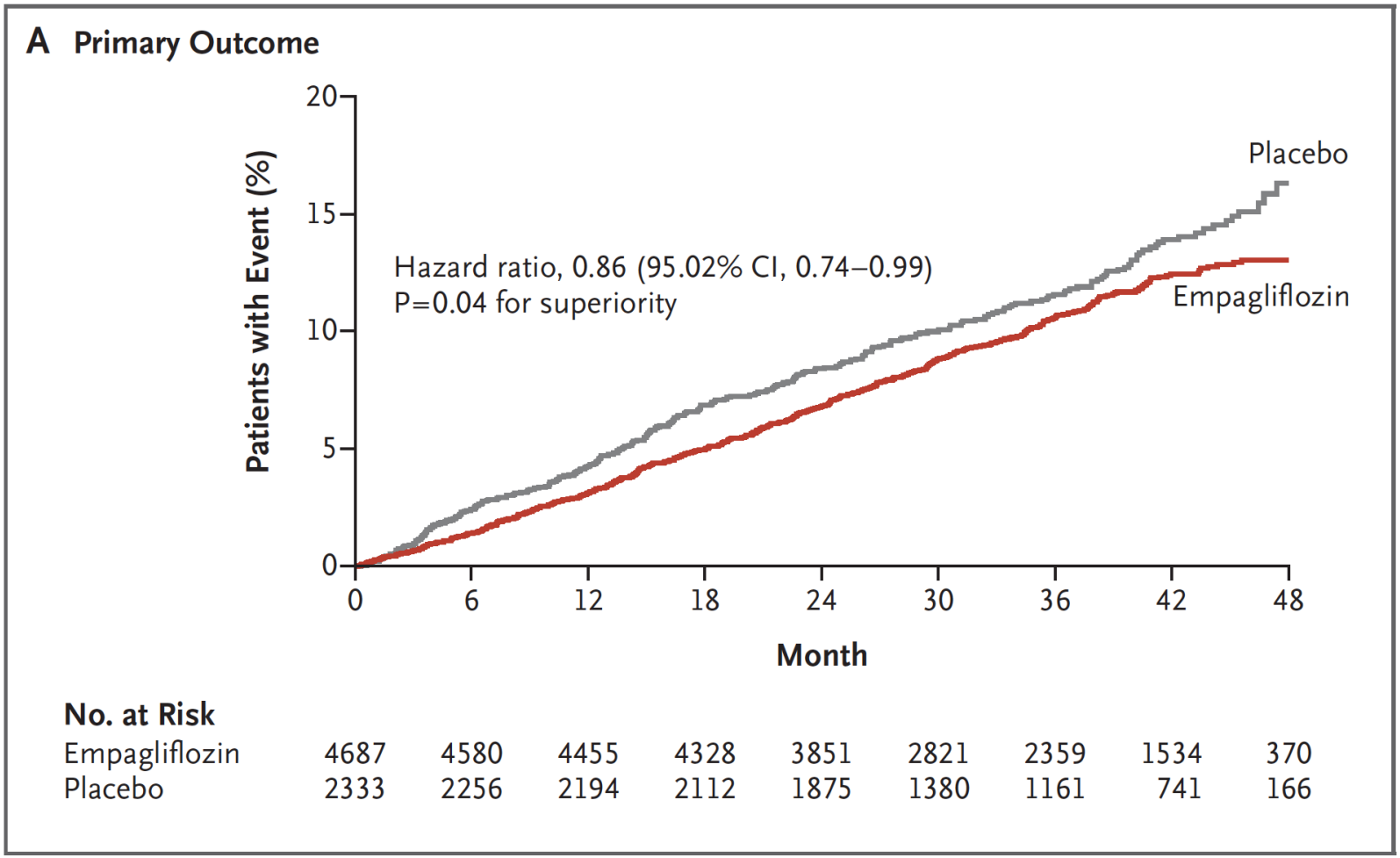
c. 1835



Dapagliflozin

c. 2012

EMPA-REG

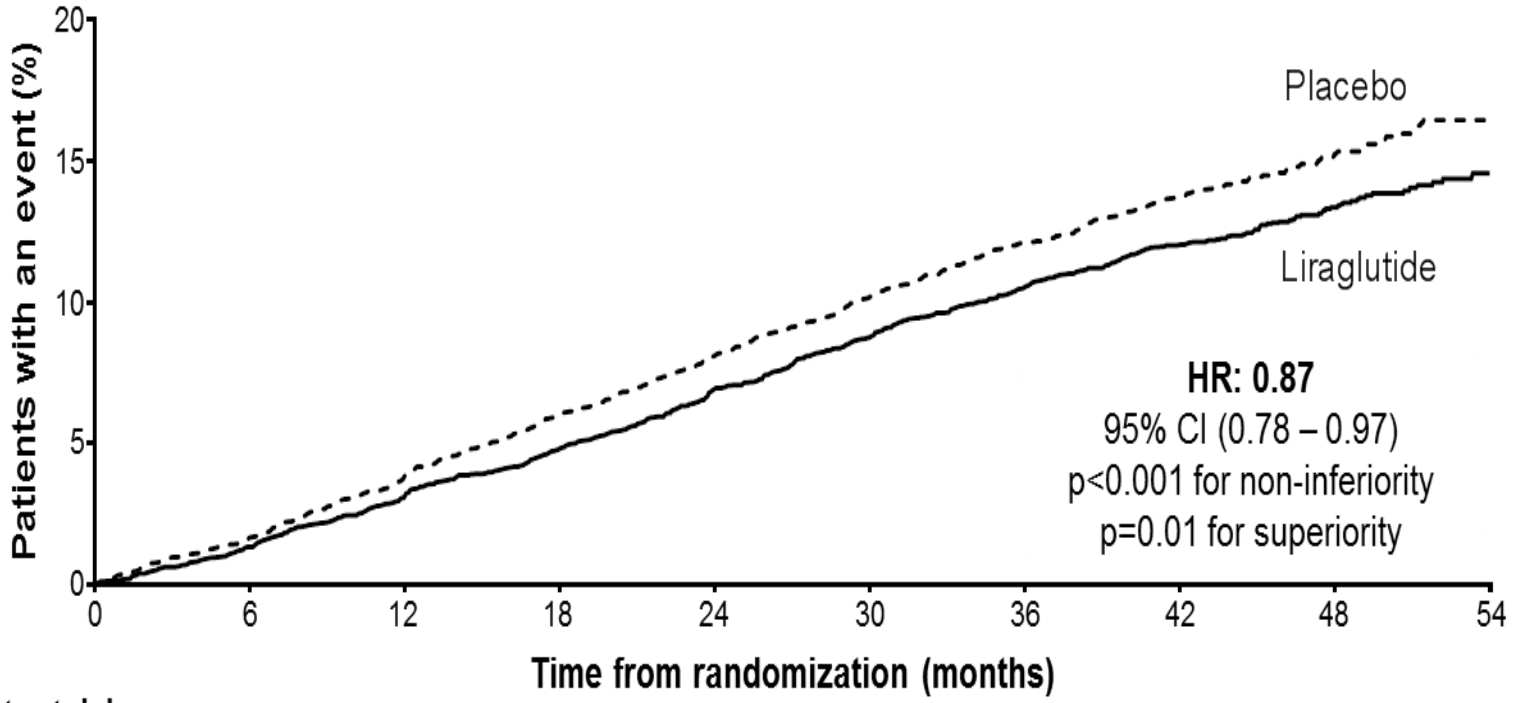

A Primary Outcome
Patients with Event (%)
20
15
10
5
0
Hazard ratio, 0.86 (95.02% CI, 0.74–0.99)
P=0.04 for superiority
Placebo
Empagliflozin
0
6
12
18
24
30
36
42
48
Month
No. at Risk
Empagliflozin 4687 4580 4455 4328 3851 2821 2359 1534 370
Placebo 2333 2256 2194 2112 1875 1380 1161 741 166

SGLT-2 inhibitors: new 2017

- "SGLT-2 inhibitors should be considered as add-on therapy to metformin in people with type 2 diabetes"

- "In individuals with type 2 diabetes and established CVD, SGLT-2 inhibitors with proven CV benefit *(currently empagliflozin and canagliflozin)* should be considered"

LEADER trial



Patients at risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

The primary composite outcome in the time-to-event analysis was the first occurrence of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke. The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; CV: cardiovascular; HR: hazard ratio.

Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

GLP-1 agonists

- “GLP-1 receptor agonist therapy should be considered as an alternative to treatment with insulin in people for whom treatment with combinations of oral agents has been inadequate, and treatment with insulin would otherwise be the next option”

- “In individuals with type 2 diabetes and established CVD, GLP-1 agonists with proven CV benefit *(currently liraglutide)* should be considered”

- Caveat for diabetes duration > 10 years removed

Insulin

- When basal insulin initiated, continue metformin
  - consider stopping or reducing sulphonylurea

Provision of information

- **Basal analogues may be appropriate for:**
  - recurrent episodes of symptomatic or nocturnal hypoglycaemia
  - those who do occupational driving, work with heavy machinery, work at heights, care for young or otherwise vulnerable individuals
  - those who need assistance from a carer or healthcare professional to inject insulin
  - those who would otherwise need twice-daily NPH insulin injections.

1st LINE
In ADDITION to lifestyle measures

SET GLYCAEMIC TARGET: HbA1c <7% (53 mmol/mol) OR INDIVIDUALISED AS AGREED

USUAL APPROACH

	METFORMIN*
EFFICACY	MODERATE
CV BENEFIT	YES
HYPOGLYCAEMIA RISK	LOW
WEIGHT	REDUCTION
MAIN ADVERSE EVENTS	GASTROINTESTINAL
IN CKD STAGE 3A	MAXIMUM 2 g DAILY

ONCE OSMOTIC SYMPTOMS RESOLVED, ADD

ALTERNATIVE APPROACH: if osmotic symptoms or intolerant of metformin

	SULPHONYLUREA*
EFFICACY	HIGH
CV BENEFIT	NO
HYPOGLYCAEMIA RISK	HIGH
WEIGHT	GAIN
MAIN ADVERSE EVENTS	HYPOGLYCAEMIA
IN CKD STAGE 3A	CAREFUL MONITORING [1]

The following are also accepted by the SMC for first-line use where metformin and sulphonylureas are not tolerated:

- *canagliflozin, dapagliflozin or empagliflozin (SGLT2 inhibitors);*
- *linagliptin, sitagliptin or vildagliptin (DPP-4 inhibitors);*
- *pioglitazone (thiazolidinedione)*

IF SEVERE OSMOTIC SYMPTOMS WITH WEIGHT LOSS OR POSSIBILITY OF TYPE 1 DIABETES **(URGENT - PHONE SECONDARY CARE IMMEDIATELY)**

2nd LINE
In ADDITION to lifestyle measures

IF NOT REACHING TARGET AFTER 3–6 MONTHS [2], REVIEW ADHERENCE: THEN GUIDED BY PATIENT PROFILE

ADD ONE OF:

	SULPHONYLUREA* *OR*	SGLT2 INHIBITOR* *OR*	DPP-4 INHIBITOR* *OR*	PIOGLITAZONE*
EFFICACY	HIGH	MODERATE	LOW/MODERATE	MODERATE
CV BENEFIT	NO	YES (SPECIFIC AGENTS) [3]	NO	PROBABLE (BUT FLUID RETENTION)
HYPOGLYCAEMIA RISK	HIGH	LOW	LOW	LOW
WEIGHT	GAIN	LOSS	NEUTRAL	GAIN
MAIN ADVERSE EVENTS	HYPOGLYCAEMIA	GENITAL MYCOTIC	FEW	OEDEMA/FRACTURES [6]
IN CKD STAGE 3A	CAREFUL MONITORING [1]	DO NOT INITIATE [4]	REDUCE DOSE [5]	DOSE UNCHANGED

3rd LINE
In ADDITION to lifestyle measures

IF NOT REACHING TARGET AFTER 3–6 MONTHS, REVIEW ADHERENCE: THEN GUIDED BY PATIENT PROFILE [7]

ADD *EITHER* AN ADDITIONAL ORAL AGENT FROM A DIFFERENT CLASS

	SULPHONYLUREA* *OR*	SGLT2 INHIBITOR* *OR*	DPP-4 INHIBITOR* *OR*	PIOGLITAZONE*
	If BMI >30 kg/m²		**OR AN INJECTABLE AGENT**	*If BMI <30 kg/m²*
	GLP-1 AGONIST*		**BASAL INSULIN***	
EFFICACY	HIGH	• stop DPP-4 inhibitor • consider reducing sulphonylurea • continue metformin • can continue pioglitazone • can continue SGLT2 inhibitor	HIGH	• inject before bed • use NPH (isophane) insulin - or longer-acting analogues according to risk of hypoglycaemia [10] • can continue metformin, pioglitazone, DPP-4 inhibitor or SGLT2 inhibitor • can reduce or stop sulphonylurea
CV BENEFIT	YES (SPECIFIC AGENTS) [3]		NO	
HYPOGLYCAEMIA RISK	LOW		HIGHEST	
WEIGHT	LOSS		GAIN	
MAIN ADVERSE EVENTS	GASTROINTESTINAL		HYPOGLYCAEMIA	
IN CKD STAGE 3A	DOSE UNCHANGED [8]		DOSE UNCHANGED [9]	

IF INSULIN INTENSIFICATION REQUIRED (NEED SPECIALIST INPUT)

4th LINE
In ADDITION to lifestyle measures

IF NOT REACHING TARGET AFTER 3–6 MONTHS, REVIEW ADHERENCE: THEN GUIDED BY PATIENT PROFILE ADD ADDITIONAL AGENT(S) FROM 3rd LINE OPTIONS *(NEED SPECIALIST INPUT)*

ADD PRANDIAL INSULIN OR SWITCH TO TWICE-DAILY MIXED BIPHASIC INSULIN

Algorithm summarises evidence from the guideline in the context of the clinical experience of the Guideline Development Group. It does not apply in severe renal or hepatic insufficiency.

Prescribers should refer to the British National Formulary (www.medicinescomplete.com), the Scottish Medicines Consortium (www.scottishmedicines.org.uk) and Medicines and Healthcare products Regulatory Agency (MHRA) warnings for updated guidance on licensed indications, full contraindications and monitoring requirements.

***Continue medication at each stage if EITHER individualised target achieved OR HbA1c falls more than 0.5% (5.5 mmol/mol) in 3–6 months. Discontinue if evidence that ineffective.**

NOTES: 1. Consider dose reduction, **2**. Do not delay if first line options not tolerated / inappropriate, **3.** See guideline pages 23 & 26-27, **4.** See BNF: specific agents can be continued at reduced dose, **5.** See BNF: no dose reduction required for linagliptin **6**. Pioglitazone is contraindicated in people with (or with a history of) heart failure or bladder cancer, **7.** Do not combine dapagliflozin with pioglitazone, **8.** Caution with exenatide when eGFR<50 ml/min/1.73 m², **9.** Adjust according to response, **10**. Driving, occupational hazards, risk of falls, previous history.

ABBREVIATIONS: CKD 3A = chronic kidney disease stage 3A (estimated glomerular filtration rate 45–59 ml/min/1.73 m²) CV = cardiovascular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