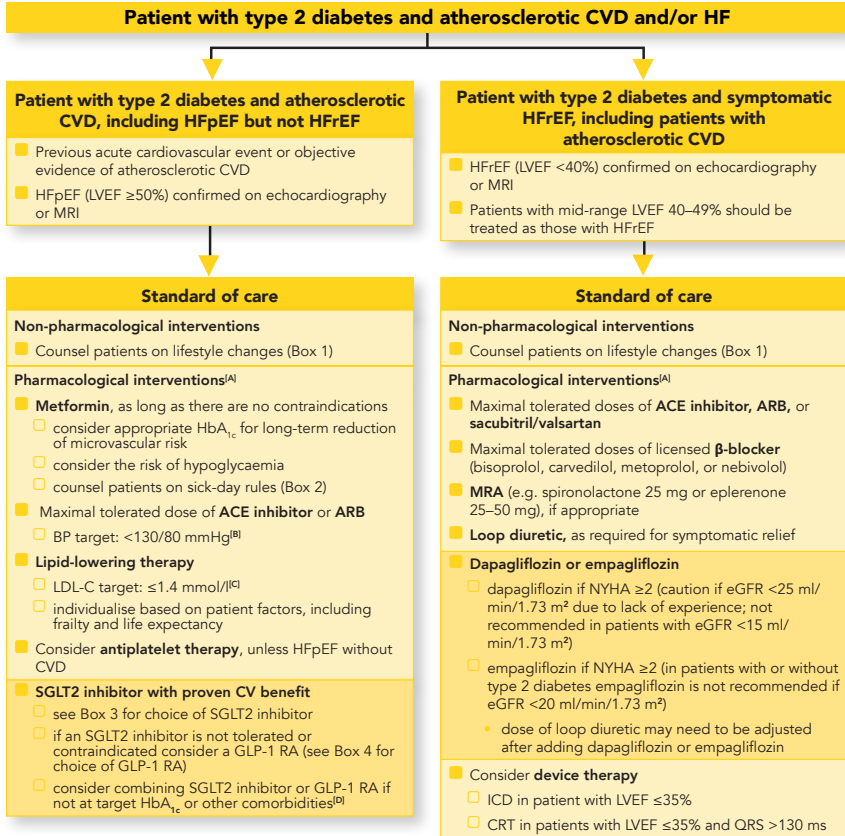


# Best practice treatment and management of patients with type 2 diabetes, cardiovascular disease, and heart failure

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This management algorithm was developed by a multidisciplinary expert panel: Javaid et al with the support of an educational grant from AstraZeneca. See end of algorithm for full disclaimer.



[A] Refer to individual summaries of product characteristics.

[B] Refer to NICE guideline 136.<sup>1</sup>

[C] Refer to NICE clinical guideline 181.<sup>2</sup>

[D] Very little evidence base for incremental CV benefit and cost implications.

ACE=angiotensin-converting enzyme; ARB=angiotensin receptor blocker; BP=blood pressure; CKD=chronic kidney disease; CRT=cardiac resynchronisation therapy; CV=cardiovascular; CVD=cardiovascular disease; DKA=diabetic ketoacidosis; eGFR=estimated glomerular filtration rate; GLP-1 RA=glucagon-like peptide receptor agonist; HbA<sub>1c</sub>=glycated haemoglobin; HF=heart failure; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; ICD=implantable cardioverter defibrillator; LDL-C=low-density lipoprotein cholesterol; LVEF=left ventricular ejection fraction; MRA=mineralocorticoid receptor antagonist; MRI=magnetic resonance imaging; NYHA=New York Heart Association; SGLT2=sodium-glucose co-transporter-2.

## Background

- In recent years, international consensus reports and guidelines have taken into consideration the results of cardiovascular (CV) outcome trials demonstrating CV benefit with sodium-glucose co-transporter-2 (SGLT2) inhibitors and glucagon-like peptide 1 receptor agonists (GLP-1 RAs)<sup>3–18</sup>
- During the development of this algorithm, NICE also updated the treatment algorithm for managing patients in the guideline on management of type 2 diabetes mellitus in adults (NICE guideline 28) to take these CV outcome trials into account<sup>9</sup>
- An expert group has developed a consensus treatment algorithm to help UK primary healthcare professionals manage patients with type 2 diabetes, cardiovascular disease (CVD), and heart failure (HF), incorporating the evidence for CV benefit with SGLT2 inhibitors and GLP-1 RAs
- The algorithm includes two separate pathways for:
  - patients with type 2 diabetes and atherosclerotic CVD or HF with preserved ejection fraction (HFpEF) but not HF with reduced ejection fraction (HFrEF)
  - patients with type 2 diabetes and symptomatic HFrEF, including patients with atherosclerotic CVD
- Atherosclerotic CVD includes patients who have experienced a previous acute cardiovascular event for example, acute coronary syndrome, stroke, or transient ischaemic attack or patients with objective evidence of atherosclerotic CVD (for example, stable angina, previous percutaneous coronary intervention, or peripheral arterial disease)

- HF should be confirmed by echocardiography or magnetic resonance imaging
  - HFpEF is defined as left ventricular ejection fraction (LVEF)  $\geq 50\%$
  - HFrEF is defined as LVEF  $< 40\%$
  - patients with mid-range LVEF 40–49% should be treated as those with HFrEF.

## Patients with type 2 diabetes and atherosclerotic CVD in the absence of HFrEF

- The priority for treatment of patients with type 2 diabetes, atherosclerotic CVD, and HFpEF but not HFrEF is to treat the diabetes and manage cardiovascular risk:
  - standard of care includes non-pharmacological and pharmacological interventions
- Counsel patients on non-pharmacological lifestyle interventions (Box 1)

### Box 1: Lifestyle changes

- Smoking cessation
- Exercise (exercise-based rehabilitation (for patients with HFrEF))
- Salt reduction
- Alcohol reduction
- Weight reduction if overweight or central obesity
- Healthy diet.

HFrEF=heart failure with reduced ejection fraction.

## Pharmacological interventions

- Prescribers should refer to the individual summaries of product characteristics for further information and recommendations regarding the use of pharmacological therapies

**Box 2: Sick-day rules**

- Patients should take medications as normal unless advised otherwise by an HCP<sup>20</sup>
- Consider temporarily stopping the following medications during acute illnesses that can cause dehydration or acute decline in renal function:<sup>21–23</sup>
  - sulfonylureas—increased risk of hypoglycaemia
  - ACE inhibitors—increased risk of developing AKI due to reduced renal efferent vasoconstriction
  - diuretics—increased risk of developing AKI
  - metformin—increased risk of developing lactic acidosis
  - ARBs—increased risk of developing AKI
  - NSAIDs—increased risk of developing AKI due to reduced renal afferent vasodilation
  - SGLT2 inhibitors—increased risk of developing euglycaemic DKA
- Once the person is feeling better and able to eat and drink for 24–48 hours, these medications should be restarted, providing there is no other clinical reason preventing this.<sup>23</sup>

ACE=angiotensin-converting enzyme; AKI=acute kidney injury; ARB=angiotensin receptor blocker; DKA=diabetic ketoacidosis; HCP=healthcare professional; NSAID=non-steroidal anti-inflammatory drug; SGLT2=sodium-glucose co-transporter-2.

- Metformin, as long as there are no contraindications
  - consider appropriate glycated haemoglobin (HbA<sub>1c</sub>) for long-term reduction of microvascular risk
  - take into account the risk of hypoglycaemia
  - counsel patients on sick-day rules (Box 2)
- Maximal tolerated dose of angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB)
  - aim for blood pressure (BP) <130/80 mmHg (refer to NICE guideline 136<sup>1</sup>)
- Lipid-lowering drugs
  - aim for low-density lipoprotein cholesterol (LDL-C) ≤1.4 mmol/l
  - individualise targets for patient factors, including frailty and life expectancy
  - refer to NICE clinical guideline 181<sup>2</sup>
- Consider antiplatelet therapy depending on bleeding risk and severity of atherosclerotic CVD (for example, stenosis >50%), unless the patient is on this pathway because they have HFpEF without atherosclerotic CVD
- SGLT2 inhibitor with proven CV benefit
  - see Box 3 for recommendations for choice of SGLT2 inhibitor
  - if an SGLT2 inhibitor is not tolerated or contraindicated consider a GLP-1 RA (see Box 4 for recommendations for choice of GLP-1 RA)
  - consider combining SGLT2 inhibitor or GLP-1 RA if not at target HbA<sub>1c</sub> or the patient has other comorbidities
    - be aware that there is very little evidence for incremental CV benefit and there are cost implications
  - Box 5 provides considerations when using an SGLT2 inhibitor or GLP-1 RA in patients on existing type 2 diabetes therapy.

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### Patients with type 2 diabetes and symptomatic HF, including atherosclerotic CVD

- The priority for treatment of patients with type 2 diabetes and HFrEF is to manage the HF:
  - standard of care includes non-pharmacological and pharmacological interventions

## Box 3: Recommended SGLT2 inhibitors for patients with type 2 diabetes, atherosclerotic CVD, and HFpEF (but not HFrEF)

- Only three SGLT2 inhibitors within the class have positive CV data (empagliflozin, canagliflozin, and dapagliflozin), there is greater uncertainty around the CV benefits associated with ertugliflozin<sup>19</sup>

### Empagliflozin

- 10 or 25 mg<sup>24</sup>
  - most robust data in this cohort, including CV mortality benefit (EMPA-REG OUTCOME study)<sup>12</sup>
  - for CV risk reduction as add on to standard of care, a dose of 10 mg once daily should be used in patients with eGFR <60 ml/min/1.73 m<sup>2</sup>; in patients with eGFR <30 ml/min/1.73 m<sup>2</sup> empagliflozin is not recommended.<sup>24</sup>

### Canagliflozin

- CV data can be found in the CANVAS and CREDENCE studies<sup>13,14</sup>
- 100 mg canagliflozin if eGFR >30 ml/min/1.73 m<sup>2</sup>; if eGFR <30 ml/min/1.73 m<sup>2</sup> and ACR >300 mg/g continue 100 mg canagliflozin for patients already taking it, but should not be initiated.<sup>25</sup>

### Dapagliflozin

- CV data can be found in the DECLARE-TIMI 58 study<sup>15</sup>
- 10 mg once daily; no dose adjustment is required based on renal function; in patients with eGFR <15 ml/min/1.73 m<sup>2</sup> dapagliflozin is not recommended.<sup>26</sup>

ACR=albumin-to-creatinine ratio; CV=cardiovascular; CVD=cardiovascular disease; eGFR=estimated glomerular filtration rate; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction; SGLT2=sodium-glucose co-transporter-2.

## Box 4: Recommended GLP-1 RAs for patients with type 2 diabetes, atherosclerotic CVD, and HFpEF (but not HFrEF)

### Liraglutide

- Uptitrate to 1.8 mg injectable daily<sup>27</sup>
  - this higher dose has the majority of evidence for cardiovascular benefit (predominantly secondary prevention in LEADER)<sup>16</sup>
  - 1.8 mg dose is 50% more expensive than 1.2 mg dose.<sup>27</sup>

### Semaglutide

- 0.5 mg or 1 mg injectable once weekly<sup>28</sup>
  - proven benefit in a predominantly secondary prevention population (SUSTAIN-6).<sup>17</sup>

### Dulaglutide

- 1.5 mg injectable once weekly<sup>29</sup>
  - proven benefit in a mixed primary and secondary prevention population (REWIND).<sup>18</sup>

CVD=cardiovascular disease; GLP-1=glucagon-like peptide 1; HFpEF=heart failure with preserved ejection fraction; HFrEF=heart failure with reduced ejection fraction.

### Box 5: Considerations when using SGLT2 inhibitors or GLP-1 RAs in patients on pre-existing diabetes therapy

- If on SU and at glycaemic target:
  - eGFR <45 ml/min/1.73 m<sup>2</sup>, continue SU if prescribing an SGLT2 inhibitor; GLP-1 RAs can still lower blood glucose in patients with renal impairment—if adding a GLP-1 RA in patients with CKD stage 3B or higher monitor blood glucose and reduce dose of SU
  - eGFR >45 ml/min/1.73 m<sup>2</sup>, monitor blood glucose and halve dose of SU, and then stop if possible (due to increased risk of hypoglycaemia) when adding an SGLT2 inhibitor or GLP-1 RA
- If on SU and evidence of hypoglycaemia, stop SU
- If on a DPP-4 inhibitor, stop if at glycaemic target after adding in SGLT2 inhibitor or adding GLP-1 RA
- If on pioglitazone, continue unless evidence of HF or other contraindications; consider lowest tolerated dose<sup>30</sup>
- If on insulin, discuss with diabetes specialist team due to significant risk of hypoglycaemia or DKA.

CKD=chronic kidney disease; DKA=diabetic ketoacidosis; eGFR=estimated glomerular filtration rate; GLP-1 RA=glucagon-like peptide 1 receptor agonist; HF=heart failure; SGLT2=sodium-glucose co-transporter-2; SU=sulfonylurea.

- Counsel patients on non-pharmacological lifestyle interventions (Box 1).

### Pharmacological interventions

- Prescribers should refer to the individual summaries of product characteristics for further information and recommendations regarding the use of pharmacological therapies
- Maximal tolerated doses of ACE inhibitor, ARB, or sacubitril/valsartan
- Maximal tolerated doses of licensed  $\beta$ -blocker (bisoprolol, carvedilol, metoprolol, or nebivolol)
- Mineralocorticoid receptor antagonist (MRA) (for example, spironolactone 25 mg or eplerenone 25–50 mg), if appropriate
- Loop diuretic, as required for symptomatic relief
- Dapagliflozin or empagliflozin
  - dapagliflozin if New York Heart Association (NYHA) class remains  $\geq 2$  irrespective of eGFR (caution if eGFR <25 ml/min/1.73 m<sup>2</sup> due to lack of experience in this population, not recommended in patients with eGFR <15 ml/min/1.73 m<sup>2</sup>)<sup>26</sup>
  - empagliflozin if NYHA remains 2 or more (in patients with or without type 2 diabetes empagliflozin is not recommended if eGFR <20 ml/min/1.73 m<sup>2</sup>)
    - dose of loop diuretic may need to be adjusted after adding dapagliflozin or empagliflozin
  - Box 6 provides considerations when using dapagliflozin or empagliflozin in patients on pre-existing diabetes therapy.

### Consider device therapy

- Implantable cardioverter defibrillator (ICD) in patients with LVEF  $\leq 35\%$
- Cardiac resynchronisation therapy (CRT) in patients with LVEF  $\leq 35\%$  and QRS >130 ms.

### Box 6: Considerations when using dapagliflozin or empagliflozin in patients on pre-existing diabetes therapy

- Most patients with HFREF will be elderly and frail, so have a low threshold for de-escalation of glycaemic therapy
- If on SU and at glycaemic target:
  - eGFR <45 ml/min/1.73 m<sup>2</sup>, continue SU
  - eGFR >45 ml/min/1.73 m<sup>2</sup>, monitor blood glucose, halve dose of SU, and then stop if possible (due to increased risk of hypoglycaemia) when adding dapagliflozin
- If on SU and evidence of hypoglycaemia, stop SU
- If on DPP-4 inhibitor, stop DPP-4 inhibitor if at glycaemic target or if specifically on saxagliptin or alogliptin (because of worsening HF signal)<sup>31</sup>
- If on pioglitazone, stop pioglitazone<sup>30</sup>
- If on insulin, discuss with diabetes specialist team due to significant risk of hypoglycaemia or DKA.

DKA=diabetic ketoacidosis; DPP-4=dipeptidyl peptidase-4; eGFR=estimated glomerular function; HF=heart failure; SU=sulfonylurea.

### Useful resources

- British Cardiovascular Society CaReMe resources: [www.britishcardiosocietysociety.org/resources/bcs-videos-and-webcasts/careme](http://www.britishcardiosocietysociety.org/resources/bcs-videos-and-webcasts/careme)
- Down S. *How to advise on sick day rules*: [diabetesonthenet.com/diabetes-primary-care/how-to-advise-on-sick-day-rules/](http://diabetesonthenet.com/diabetes-primary-care/how-to-advise-on-sick-day-rules/)
- IDF. *How to manage diabetes during an illness: "sick day rules"*: [www.idf.org/component/attachments/?task=download&id=2155:IDFE-Sick-day-management](http://www.idf.org/component/attachments/?task=download&id=2155:IDFE-Sick-day-management)
- NICE. *Cardiovascular disease: risk assessment and reduction, including lipid modification*: [www.nice.org.uk/cg181](http://www.nice.org.uk/cg181)
- NICE. *Hypertension in adults: diagnosis and management*: [www.nice.org.uk/ng136](http://www.nice.org.uk/ng136)
- NICE. *Type 2 diabetes in adults: management*: [www.nice.org.uk/ng28](http://www.nice.org.uk/ng28)
- Think Kidneys "sick day" guidance: [www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2018/01/Think-Kidneys-Sick-Day-Guidance-2018.pdf](http://www.thinkkidneys.nhs.uk/aki/wp-content/uploads/sites/2/2018/01/Think-Kidneys-Sick-Day-Guidance-2018.pdf)

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## About this management algorithm

**Disclaimer:** *Guidelines* identified a need for clinical guidance in a specific area and approached AstraZeneca for an educational grant to support the development of a management algorithm. The grant included honoraria for the contributors. This algorithm was developed by *Guidelines*, and the Chair and members of the working group were chosen and convened by *Guidelines*. The content is independent of and not influenced by AstraZeneca, who checked the final document for technical accuracy only. The views and opinions of the contributors are not necessarily those of AstraZeneca, or of *Guidelines*, its publisher, advisers, or advertisers. No part of this publication may be reproduced in any form without the permission of the publisher.

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