NICE National Institute for Health and Care Excellence

2023 exceptional surveillance of chronic heart failure in adults: diagnosis and management (NICE guideline NG106)

Surveillance report
Published: 25 April 2023

www.nice.org.uk

Contents

Surveillance decision

We will update the NICE guideline on chronic heart failure in adults.The update will focus on pharmacological management of chronic heart failure.

Reason for the exceptional review

Members of NICE's cardiovascular disease committee, and other topic experts, highlighted to us that the recommendations on pharmacological treatments of heart failure with reduced ejection fraction (HFrEF) in the NICE guideline are out of date when compared to 2021 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure, and to current UK clinical practice.

Methods

The exceptional surveillance process consisted of:

- Considering the information from topic experts that triggered the exceptional review.
- Considering the development of recommendations through previous guideline updates.
- Examining related NICE guidance.
- Assessing the new information against current recommendations to determine whether or not to update sections of the guideline, or the whole guideline.

For further details about the process and the possible update decisions that are available, see ensuring that published guidelines are current and accurate in developing NICE guidelines: the manual.

Information considered in this exceptional surveillance review

Members of the NICE cardiovascular disease committee and other topic experts highlighted that current practice surrounding pharmacological management of HFrEF is

moving away from the recommendations in the NICE guideline. They highlighted that the introduction of new drug classes since the recommendations on treatment of HFrEF in the NICE guideline were written, in combination with changes in wider clinical practice about the timing of prescribing of first line pharmacological treatments, mean that these recommendations may be considered out of date. It was highlighted that the treatment algorithm associated with the NICE guideline is at particular risk of becoming increasingly out of date, as no reference is made to recently published NICE technology appraisal guidance. In particular the topic experts highlighted the ESC guidelines for the diagnosis and treatment of acute and chronic heart failure published in 2021 as an example of how practice is changing, alongside highlighting key publications about new drug classes.

The pharmacological treatments for HFrEF have typically involved multiple drug types, including 1 of an angiotensin-converting enzyme inhibitor (ACEi), or an angiotensin II receptor blocker (ARB), given with beta-blockers and mineralocorticoid receptor antagonists (MRA). These drug classes are recommended in both the ESC guideline and the NICE guideline as treatments for all people with HFrEF. In addition to these drugs, additional treatments such as ivabradine, sacubitril valsartan (an angiontensin receptor neprilysin inhibitor; ARNI), hydralazine in combination with nitrate, and digoxin are also used when necessary.

In recent years a new drug class, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, have been licenced for the treatment of HFrEF. These pharmacological agents include dapagliflozin and empagliflozin. Topic experts raised the introduction of these drugs as key developments in the field that are changing clinical practice.

The efficacy of dapagliflozin as an additional therapy for people with HFrEF who are taking optimised doses of standard pharmacological treatment based either on an ACE inhibitor or ARB plus beta-blockers and an MRA if tolerated, or on sacubitril valsartan (an ARNI) plus beta-blockers and an MRA if tolerated, was shown in the DAPA-HF trial (McMurray et al. 2019). The DAPA-HF trial was a double-blind randomised clinical trial (n=4,744) comparing dapagliflozin plus standard care, to placebo plus standard care. They used a composite outcome measure consisting of worsening heart failure (hospitalisation or an urgent visit resulting in intravenous therapy for heart failure) or cardiovascular death. Intention-to-treat analyses showed that dapagliflozin plus standard pharmacological treatment reduced the primary endpoint of composite cardiovascular events by 26% compared with placebo plus standard pharmacological treatment (hazard ratio [HR] 0.74, 95% confidence interval [CI] 0.65 to 0.85; p<0.001). NICE's technology appraisal guidance on dapagliflozin for treating chronic heart failure with reduced ejection fraction considered the clinical

evidence for dapagliflozin, for which the DAPA-HF trial was the key trial, they found that its result were broadly generalisable to the NHS and concluded that dapagliflozin should be recommended as an option for treating symptomatic chronic HFrEF in adults, only if it is used as an add-on to optimised standard care as defined above.

The efficacy of empagliflozin as an additional therapy for people with HFrEF who are taking optimised doses of standard pharmacological treatment based on an ACE inhibitor, an ARB, a beta-blocker or an MRA, was shown in the EMPEROR-Reduced trial (Packer et al. 2020). That trial was a double-blind randomised clinical trial (n=3,730) comparing empagliflozin plus standard pharmacological treatment with placebo plus standard pharmacological treatment, as described previously. The study used a composite outcome measure consisting of cardiovascular death or hospitalisation for worsening heart failure. Intention-to-treat analyses showed that empagliflozin plus standard pharmacological treatment reduced cardiovascular death or hospitalisation by 25.0% compared with placebo plus standard pharmacological treatment (HR 0.75; 95% CI 0.65 to 0.86; p<0.0001). NICE's technology appraisal guidance on empagliflozin for treating chronic heart failure with reduced ejection fraction considered the clinical evidence for empagliflozin, and found that the results of the EMPEROR-Reduced trial were broadly generalisable to the NHS and concluded that empagliflozin should be recommended as an option for treating symptomatic chronic HFrEF in adults, only if it is used as an add-on to optimised standard pharmacological treatment as defined above.

These 2 trials were both discussed in the ESC guidelines, and were also raised by topic experts as evidence that have the potential to change clinical practice. There are no direct recommendations considering the use of SGLT2-i's for treatment of chronic HFrEF in the current NICE guideline, though the relevant technology appraisal guidance for dapagliflozin and empagliflozin are highlighted at the start of section 1.4 on treating heart failure with reduced ejection failure.

The ESC guidelines state that 'class I therapeutics', which include ACEi's or ARNI's, beta-blockers, MRA and SGLT-2 inhibitors, should be recommended for all patients with HFrEF to reduce mortality and hospitalisation. These are recommended as equal first line treatment to be started in all patients, and uptitrated to the doses used in the clinical trials, or maximally tolerated doses if this is not possible. This is in contrast to the sequencing of pharmacological treatments for HFrEF currently recommended in the NICE guideline.

Following discussion with representation from NICE's cardiovascular disease committee, it was highlighted that cardiologists managing people with HFrEF are commonly aware of the

new drug classes, and the changing clinical practice of introducing all as a first line therapy alongside ACE inhibitors (or ARNI's), beta-blockers and MRA, but that the treatment of HFrEF was often done by a multidisciplinary team, not all members of which will be experts in chronic heart failure. These team members include cardiologists, cardiac nurses, GP's and pharmacists. It is therefore essential that NICE guideline recommendations, and treatment algorithms, are up to date, so that all patients can receive equitable care.

Topic experts also highlighted research indicating that SGLT2 inhibitors may be an effective treatment for people with chronic heart failure with preserved ejection fraction (HFpEF). The relevant trials include the DELIVER trial for dapagliflozin, and the EMPEROR preserved trial for empagliflozin. Current recommendations for the treatment in the NICE guideline of HFpEF rely on the management of comorbidities such as high blood pressure, atrial fibrillation ischaemic heart disease, and diabetes. The only pharmacological treatment that is currently recommended in the NICE guideline for HFpEF are loop diuretics.

Information considered when developing the guideline

The NICE guideline on chronic heart failure was originally developed in 2003, with guideline updates conducted in 2010 and in 2018. The evidence for individual drug treatments was assessed during these updates as necessary, however there has not been an evidence review assessing the appropriate sequencing of all pharmacological treatments available for chronic heart failure. The recommendations in the NICE guideline on chronic heart failure come from a combination of the evidence reviews done in 2003 and 2010 for the original NICE guideline, and in 2018 for an update to the current guideline, or replicated from relevant NICE technology appraisal guidance on ivabradine and sacubitril valsartan. Although there are no direct recommendations considering the use of SGLT2-i's for treatment of chronic HFrEF in the current NICE guideline, the relevant technology appraisal guidance for dapagliflozin and empagliflozin are highlighted at the start of section 1.4.

Recommendations for the use of ACE inhibitors were developed in 2003, with endorsement and minor amendments made to them in the 2010 guideline update. No evidence review was done in the 2018 update of the NICE guideline.

An evidence review for the use of beta-blockers for the treatment of HFrEF, including the appropriate sequencing of beta-blockers and ACEi's was done in 2010. During development in 2003 explicit mention was made to start ACEi before starting therapy with beta-blockers, however this was replaced by recommendation 1.4.1 stating that clinical judgement should be used when deciding which drug treatment to start first. This was recommended following an evidence review in 2010 which found similar outcome of therapy with ACEi followed by beta-blockers, to those treated with beta-blockers followed by ACEi. The 2010 update also endorsed recommendations made in 2003 with minor amendments. No evidence review was done in the 2018 update of the guideline.

Evidence for the use of ARBs was considered in the 2010 update, assessing whether ARB's exert the same effect as ACEi's. Treatment with an ARB was found to be similarly clinically effective to that with an ACEi, however it was more expensive. Therefore, a recommendation was made to consider switching to an ARB if an ACEi was not tolerated. No evidence review was done in the 2018 update of the guideline.

In the 2018 update, an evidence review was completed for the use of MRA's in addition to existing standard first line treatment in people with HFrEF, which would consist of an ACEi and a beta-blocker. Following assessment of the evidence a recommendation was made to offer an MRA to people with HFrEF who are taking an ACE inhibitor (or ARB) and beta-blocker, but who continue to have symptoms of heart failure.

Other relevant NICE guidance

Some recommendations for the treatment of chronic HFrEF are taken from NICE technology appraisal guidance for drug treatments. These include:

- Ivabradine, covered in recommendations 1.4.19 to 1.4.21, with recommendation text taken from the associated technology appraisal guidance on ivabradine for treating chronic heart failure, published in 2012. Recommendations state that ivabradine should be used in specific clinical situations, and only in addition to standard therapy, which has been given for at least 4 weeks, and includes beta-blockers, ACEi's and an MRA, or when beta-blocker therapy is contraindicated or not tolerated.

- Sacubitril valsartan, covered in recommendations 1.4.22 to 1.4.24, with recommendation text taken from the associated technology appraisal guidance on sacubitril valsartan for treating symptomatic chronic heart failure with reduced ejection fraction, published in 2016, to be used in specific clinical situations, and only when people are taking a stable dose of an ACEi or an ARB.

The NICE guideline currently provides a link to 2 pieces of technology appraisal guidance for SGLT2 inhibitors at the start of the section on treatment of HFrEF, but does not extract the recommendations and present them with the other recommendations on pharmacological treatment. The technology appraisal guidance is:

- Dapagliflozin for treating chronic heart failure with reduced ejection fraction (published 2021)
- Empagliflozin for treating chronic heart failure with reduced ejection fraction (published 2022).

Topic experts also highlighted new evidence for both dapagliflozin and empagliflozin in the treatment of HFpEF. There are 2 pieces of technology appraisal guidance in progress for the use of SGLT2 inhibitors in this population. They are:

- Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction (expected publication 21 June 2023)
- Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction (expected publication 21 June 2023).

Topic experts also highlighted the drug omecamtiv mecarbil for which there is a piece of technology appraisal guidance in development:

- Omecamtiv mecarbil for treating chronic heart failure with reduced ejection fraction (expected publication date TBC).

Equalities

No equalities issues were identified during the surveillance process.

An equalities and health inequalities assessment was completed during this surveillance review. See appendix A for details.

Overall decision

Members of the NICE cardiovascular disease committee and other topic experts raised the fact that the recommendations on the treatment of chronic heart failure do not reflect all treatment options currently available to patients with HFrEF. They also highlighted that the current recommendations on sequential introduction of therapeutic agents is no longer in line with ESC guidelines and that UK clinical practice is changing. The recommendations on treatment of HFrEF were originally developed in 2003, with updates occurring in 2010 and 2018. However the updates did not assess all available treatment options in an evidence review to explore the appropriate sequencing, or the appropriateness of introducing multiple pharmacological agents as equal first line at treatment initiation. After considering the evidence and other intelligence, we will update the recommendations on pharmacological management for people with chronic heart failure.

ISBN: 978-1-4731-5155-0