

National Institute for Health and Care Excellence

Health Technology Evaluation

Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction

Please note: Comments received in the course of consultations carried out by NICE are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

Comment 1: the draft remit and proposed process

Section	Stakeholder	Comments [sic]	Action
Appropriateness	Boehringer-Ingelheim	<p>This topic is appropriate to be appraised by NICE. A timely NICE recommendation for empagliflozin for all patients with chronic symptomatic heart failure (regardless of ejection fraction) is critical in supporting the delivery of national priorities and initiatives for heart failure (HF).</p> <p>Empagliflozin is the only targeted therapy that has demonstrated improvement in outcomes for adult patients with symptomatic chronic heart failure across a broad range of ejection fractions. The European Medicines Agency (EMA) issued a positive opinion for empagliflozin for the “treatment of adults with symptomatic chronic heart failure” on 27th January 2022.¹ Given the earlier than expected EMA Positive Opinion, it’s likely that the MHRA will recommend empagliflozin with the same indication wording by the end of [REDACTED], rather than [REDACTED], as originally expected. NICE have already recommended empagliflozin for the treatment of HF with reduced ejection fraction (HFrEF) (ID3826)² (i.e. ejection fraction [EF] <40%). Thus, to ensure that all patients could benefit from empagliflozin, we recommend that the population for this appraisal is for all patients with HF and a EF >40%.</p>	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.

Section	Stakeholder	Comments [sic]	Action
		<p>An urgent and timely appraisal for empagliflozin is necessary for the following reasons:</p> <ul style="list-style-type: none"> • HF is a highly prevalent cardiovascular disease and a growing public health concern in the UK. <ul style="list-style-type: none"> ○ As noted in the draft scope for this appraisal: <ul style="list-style-type: none"> ▪ Heart failure affects the lives of many people in England. More than 550,000 people in England have heart failure.^{3,4} ▪ The prognosis for HF patients is poor. <ul style="list-style-type: none"> • There were 94,185 hospitalisations in England for heart failure in 2019/20.⁵ • Around 24% of people diagnosed with heart failure die within the first year, with a 5-year mortality rate of 55%.⁶ ○ HF is associated with several co-morbidities that contribute to an even poorer prognosis. <ul style="list-style-type: none"> ▪ Nearly half of all HF patients have moderate to severe kidney dysfunction which increases the risk of hospitalisation or death compared to HF alone.⁷⁻⁹ Furthermore, nearly one-third have comorbid Type II Diabetes (T2DM), also known to increase the risk of hospital admissions and cardiovascular (CV) death.^{7,10} The onset of T2DM increases the risk of HF by two-fold in men and five-fold in women.¹¹ • Improving outcomes for patients with a cardiovascular disease is an important national priority. Several initiatives and quality metrics are already in place in England to support optimisation of care: Policy 	

Section	Stakeholder	Comments [sic]	Action
		<ul style="list-style-type: none"> ○ The NHS Long Term Plan (LTP)¹² <ul style="list-style-type: none"> ▪ Earlier detection in the community through PCNs ▪ A stronger focus on multi-disciplinary care (MDT)-led care ▪ Faster access to specialist care in hospitals Initiatives to implement the NHS LTP ○ Quality Outcomes Framework (QOF)¹³ indicators encourage GP practices to: <ul style="list-style-type: none"> ▪ Confirm diagnoses of HF and establish underlying causes ▪ Increase the proportion of patients who are on the HF register to have a review every 12 months, including functional capacity and a review of medication to ensure medicines optimisation at maximal tolerated dose ○ The 2022/2023 Primary Care Network (PCN) directed enhanced service (DES) contract¹⁴ aims to: <ul style="list-style-type: none"> ▪ Support the earlier identification of HF, through building awareness among PCN staff around the appropriate HF diagnostic pathway, and early identification processes for HF, including the timely use of NT-ProBNP testing ▪ Undertake network development and quality improvement activity to support CVD prevention, including: <ul style="list-style-type: none"> • Reviewing outputs from CVD intelligence tools (including CVDPREVENT, when available) and sharing key learning among PCN staff 	

Section	Stakeholder	Comments [sic]	Action
		<ul style="list-style-type: none"> • Supporting the development of system pathways for people at risk of CVD through liaison with wider system partners • Collaboration with commissioners to improve levels of diagnostic capacity for 'ABC' testing, including the availability of ambulatory blood pressure monitors (ABPMs) and electrocardiogram (ECG) monitors <p>○ The 2021 Get it Right First Time (GIRFT) national review of NHS cardiology services¹⁵ recommended:</p> <ul style="list-style-type: none"> ▪ Establishing clinical cardiology networks to match demand to capacity <ul style="list-style-type: none"> • Each network should ensure that all hospitals provide access to diagnostic techniques ▪ Delivery of a comprehensive multi-disciplinary service. <ul style="list-style-type: none"> • The report recommended that well-co-ordinated multi-disciplinary team (MDT) meetings are vital to delivering optimal treatment strategies ▪ Workforce development <ul style="list-style-type: none"> • The wider heart failure team should be supported to work in extended roles. The report supports the concept of a mobile workforce with the development of 'staff passports' enabling advanced practitioners to work more flexibly across clinical networks <p>• A broad and timely NICE recommendation for empagliflozin supports national priorities and initiatives for improving outcomes for patients by:</p>	

Section	Stakeholder	Comments [sic]	Action
		<ul style="list-style-type: none"> ○ Freeing up the capacity of MDTs specialising in HF management <ul style="list-style-type: none"> ▪ Empagliflozin has shown to reduce the risk of hospital admission and re-admission by 27%.¹⁶ This reduction in the hospitalisation alleviates workforce capacity by reducing the number of patients who require care in hospital and the additional management required post-discharge ▪ This in turn, enables MDTs to reach a larger number of patients suspected of HF and offer them a faster access to a HF diagnosis and treatment. MDTs can also a review every 12 months to more patients who already have HF ○ Empagliflozin does not require any dose adjustment or additional monitoring, and therefore can be initiated upon the advice of a HF specialist without the need for additional outpatient appointments¹⁶ <p>1. Agency, E. M. Jardiance Positive Opinion HFpeF. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/jardiance-0 (2022).</p> <p>2. Excellence, N. I. for H. and C. Empagliflozin for treating chronic heart failure with reduced ejection fraction [ID3826. https://www.nice.org.uk/guidance/indevelopment/gid-ta10719 (2022).</p> <p>3. Digital, N. Quality and Outcomes Framework, Achievement, prevalence and exceptions data 2018-19. https://digital.nhs.uk/data-and-information/publications/statistical/quality-and-outcomes-framework-achievement-prevalence-and-exceptions-data/2018-19-pas (2019).</p> <p>4. SM, D., VL, R. & MM., R. Epidemiology of heart failure with preserved ejection fraction. <i>Nature Reviews Cardiology</i>. <i>Nature Reviews Cardiology</i> 591–602.</p> <p>5. Digital, N. Hospital admitted patient care activity, 2019-20: Primary diagnosis 3 character. https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2019-20. (2020).</p>	

Section	Stakeholder	Comments [sic]	Action
		<p>6. CJ, T., JM, O.-M. & al., R. A. et. Trends in survival after a diagnosis of heart failure in the United Kingdom 2000-2017: population-based cohort study. <i>BMJ</i> 1223 (2019).</p> <p>7. A., L. C. et al. Risk Factors for Heart Failure. <i>Circulation Hear Fail</i> 13, e006472 (2020).</p> <p>8. I, L. et al. Prevalence and prognostic impact of kidney disease on heart failure patients. <i>Open Heart</i> 1, e000234 (2016).</p> <p>9. AA, H. et al. Heart failure in chronic kidney disease: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. <i>Kidney Int.</i> 95, 1304–17 (2019).</p> <p>10. CA, L. et al. Association Between Type 2 Diabetes and All-Cause Hospitalization and Mortality in the UK General Heart Failure Population: Stratification by Diabetic Glycaemic Control and Medication Intensification. <i>JACC Heart Fail.</i> 1, 18–26 (2018).</p> <p>11. HC, K. & ED, A. Heart Failure in Type 2 Diabetes Mellitus. <i>Circ Res</i> 124, 121–141 (2019).</p> <p>12. NHS. The NHS Long Term Plan. https://www.longtermplan.nhs.uk/publication/nhs-long-term-plan/ (2019).</p> <p>13. England, N. QOF indicators for heart failure. <i>Quality and Outcomes Framework guidance for 2021/2022</i> https://www.england.nhs.uk/wp-content/uploads/2021/03/B0456-update-on-quality-outcomes-framework-changes-for-21-22-.pdf.</p> <p>14. NHS. Primary Care Networks – plans for 2021/22 and 2022/23. https://www.england.nhs.uk/publication/primary-care-networks-plans-for-2021-22-and-2022-23/ (2022).</p> <p>15. GIRFT. Cardiology: GIRFT Programme National Specialty Report. https://www.gettingitrightfirsttime.co.uk/girft-reports/ (2021).</p> <p>16. S, A. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. <i>N Engl J Med</i> 385, 1451–1461 (2021).</p>	
	Pumping Marvellous Foundation	It is appropriate	Thank you for your comment. NICE has scheduled this topic into its work programme. No action required.

Section	Stakeholder	Comments [sic]	Action
	UKCPA	<p>Yes Heart Failure with Preserved Ejection Fraction (HFpEF) is a growing problem with an aging population.</p> <p>Currently, apart from diuretics for the management of congestion there are no specific pharmacological interventions recommended by NICE. (amiodarone , calcium channel blockers and anticoagulation are mentioned in the spec but these are not standard of care for all HFrEF patient – their use will depend of co-morbidities)</p>	<p>Thank you for your comment.</p> <p>NICE has scheduled this topic into its work programme.</p> <p>The statement that NICE guideline 106 recommends calcium-channel blockers, amiodarone and anticoagulants to treat all types of heart failure has been removed from the background.</p>
Wording	Boehringer-Ingelheim	BI agree with the wording in this scope, except for the definition of the population. BI recommend that the population is all adult patients with symptomatic chronic heart failure with an EF>40%. Please see the population section for a further explanation.	Thank you for your comment. The population has been updated to 'adults with symptomatic chronic heart failure with a left ventricular ejection fraction of 40% or more'.
	Pumping Marvellous Foundation	Wording reflects the issue	Thank you for your comment. No action required.

Section	Stakeholder	Comments [sic]	Action
	UKCPA	Yes [the wording of the remit reflect the issue(s) of clinical and cost effectiveness about this technology that NICE should consider]	Thank you for your comment. No action required.
Timing Issues	Boehringer-Ingelheim	<p>As discussed above, a timely NICE recommendation for empagliflozin for all patients with chronic symptomatic heart failure (regardless of ejection fraction) is critical in supporting the delivery of national priorities and initiatives to improve service delivery and health outcomes.</p> <p>The EMA issued a positive opinion for empagliflozin for the “treatment of adults with symptomatic chronic heart failure” on 27th January 2022.¹ Given the earlier than expected EMA Positive Opinion, it’s likely that the MHRA will recommend empagliflozin for the same indication by the end of [REDACTED] rather than [REDACTED], as originally expected. BI have already provided this information to NICE.</p> <p>Rapid, robust, and responsive technology evaluation is a key pillar of the NICE Strategy 2021 to 2026.¹⁷ One of the aims of the consultation on NICE Methods and Process was to support delivery of this goal.¹⁸ However, we understand from our communication with NICE that due to capacity & scheduling challenges, the earliest available committee date is March 2023, which is approximately 1 year after Marketing Authorisation. We understand from NICE’s topic prioritisation criteria that the aim is to provide guidance for license extensions within 6 months of Marketing Authorisation. Therefore, a committee meeting in Q4 2022 would align with this metric and ensure that patients receive timely treatment that improves their prognosis and delivers against national priorities and initiatives.</p>	Thank you for your comment. No changes to the scope required.

Section	Stakeholder	Comments [sic]	Action
		<p>BI are open to continued engagement with NICE about scheduling an earlier committee date than March 2023. We understand that capacity challenges are the reason for the later than expected committee date. We understand that a decision about whether an earlier committee meeting than March 2023 could be scheduled would be made in November 2022. However, if a decision is made is made in November 2022, it is unlikely to have a significant impact on the lives of patients with HF. Ideally, a decision about scheduling an earlier committee meeting would be made at the Decision Problem meeting in June/July 2022.</p> <p>To accelerate this appraisal, BI is open to:</p> <ul style="list-style-type: none"> • Submitting the Company Submission within 4 weeks of receiving the Invitation to Participate, instead of the usual 8 weeks, to offer the opportunity for an earlier review by the ERG. • Opt-out of the Technical Engagement step <ul style="list-style-type: none"> ○ NICE and the British Medical Journal Evidence Review Group (BMJ ERG) already provided a through appraisal of empagliflozin in patients with chronic heart failure with an EF <40% (ID3826). This appraisal will re-purpose the economic models used previously and utilise the PULSE CPRD study again to validate the model outcomes. Therefore, to expedite the appraisal of evidence and provide the additional decision certainty that empagliflozin represents value for money; BI will proactively present in Document B the ICER for all cost effectiveness scenarios explored by the BMJ ERG, which are described in the ERG's response to Technical Engagement. 	

Section	Stakeholder	Comments [sic]	Action
		<p>BI are open to engaging with NICE on any additional suggestions to accelerate the appraisal process for multiple indications. Improvement of processes for products with multiple indications was identified as a key priority following the publication of the methods guide. The consultation document “Review of methods, processes and topic selection for health technology evaluation programmes: conclusions and final update, November 2022”¹⁸ identified this as a priority topic for the next manual update. It stated:</p> <ul style="list-style-type: none"> • <i>“NICE has already acknowledged the need to develop new processes to:</i> <ul style="list-style-type: none"> ○ <i>Facilitate rapid entry to managed access</i> ○ <i>Manage technologies with multiple indications</i> <p><i>The challenges we face in these areas were highlighted in previous consultation rounds and received significant support for the potential efficiencies and speed of decision making that such processes could create. This needs further engagement with stakeholders to engineer streamlined and robust processes that account for the appropriate level of risk involved in this alternative approach. As such, more time will be needed to develop this proposal. The outcome will be one of the first modular updates to be published following launch of the new unified manual.”</i>¹⁸</p> <p>1. Agency, E. M. Jardiance Positive Opinion HFpeF. https://www.ema.europa.eu/en/medicines/human/summaries-opinion/jardiance-0 (2022). 17. NICE. The NICE strategy 2021 to 2026. https://www.nice.org.uk/about/who-we-are/corporate-publications/the-nice-strategy-2021-to-2026 (2021). 18. NICE. Review of methods, processes and topic selection for health technology evaluation programmes: conclusions and final update.</p>	

Section	Stakeholder	Comments [sic]	Action
		https://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.nice.org.uk%2FMedia%2FDefault%2FGet-involved%2FMeetings-In-Public%2FPublic-board-meetings%2Fnov-22-pbm-CHTE-methods-process-and-topic-selection.docx&wdOrigin=BROWSELINKhttps://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.nice.org.uk%2FMedia%2FDefault%2FGet-involved%2FMeetings-In-Public%2FPublic-board-meetings%2Fnov-22-pbm-CHTE-methods-process-and-topic-selection.docx&wdOrigin=BROWSELINKhttps://view.officeapps.live.com/op/view.aspx?src=https%3A%2F%2Fwww.nice.org.uk%2FMedia%2FDefault%2FGet-involved%2FMeetings-In-Public%2FPublic-board-meetings%2Fnov-22-pbm-CHTE-methods-process-and-topic-selection.docx&wdOrigin=BROWSELINKin=BROWSELINK (2021).	
	Pumping Marvellous Foundation	Very important considering this is a first in class treatment in HFpEF. Highly innovative.	Thank you for your comment. No action required.
	UKCPA	This is a priority for patients as there are currently no treatments licensed or NICE approved that affect prognosis in HFpEF	Thank you for your comment. No action required.

Comment 2: the draft scope

Section	Consultee/ Commentator	Comments [sic]	Action
Background information	Boehringer-Ingelheim	No comments	No action required.
	Pumping Marvellous Foundation	Accurate	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
	UKCPA	<p>The case numbers are underestimated. UK prevalence is heart failure is around 920,000 with 60,000 new cases annually (NG106)</p> <p>The statement about calcium channel blockers, amiodarone and anticoagulation should be removed as it is incorrect</p>	<p>Thank you for your comment. NICE guideline 106 was published in 2018. The reference for the number of people with heart failure in the UK has been updated to the NHS Digital Quality and Outcomes Framework, 'Achievement, prevalence and exceptions data 2020-21', which is considered to be the most recent data source.</p> <p>The statement that NICE guideline 106 recommends calcium-channel blockers, amiodarone and anticoagulants to treat all types of heart failure has been removed.</p>

Section	Consultee/ Commentator	Comments [sic]	Action
The technology/ intervention	Boehringer- Ingelheim	Yes, BI agree with the description of the intervention.	Thank you for your comment. No action required.
	Pumping Marvellous Foundation	Accurate description	Thank you for your comment. No action required.
	UKCPA	Include details about time that the treatment has been in widespread use and has been used in the management of diabetes for some years. Wealth of clinical experience and safety data	Thank you for your comment. This section is intended to provide a brief description of the technology and is not comprehensive, therefore no changes have been made here.
Population	Boehringer- Ingelheim	<p>Is the population defined appropriately?</p> <p>The European Society of Cardiology (ESC) defines heart failure with preserved ejection fraction as those with an EF >50%.¹⁹ However, the EMPEROR-Preserved population included patients with an EF >40%. EMPEROR-Reduced included only patients with an EF <40%. A scope that includes patients with an EF >50% means that patients with an EF of 40% to 50% would be denied access to treatment.</p> <p>Therefore, for simplicity, BI recommend that the scope of this appraisal is all patients with an EF >40%.</p>	Thank you for your comment. The population has been updated to 'adults with symptomatic chronic heart failure with a left ventricular ejection fraction of 40% or more'.

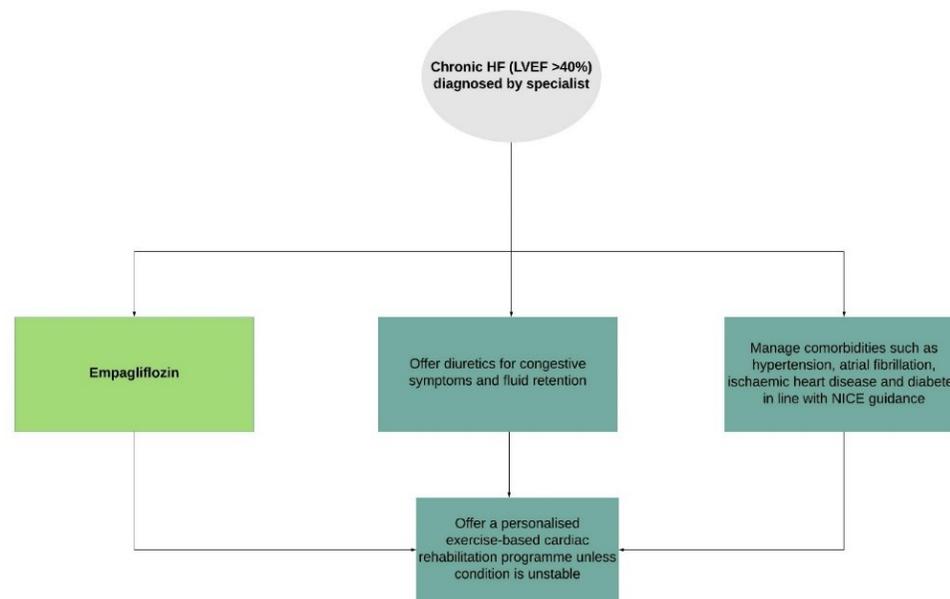
Section	Consultee/ Commentator	Comments [sic]	Action
		<p>Are there any subgroups of people in whom empagliflozin is expected to be more clinically effective and cost effective or other groups that should be examined separately?</p> <p>Empagliflozin will be indicated as an add-on therapy to standard care for all adult patients with chronic symptomatic heart failure. Empagliflozin is the only targeted therapy that has demonstrated benefit across the spectrum of ejection fractions.^{16,20} Therefore, although the economic base case will present an ICER for those patients with an EF >40%, a scenario will be presented to show the cost effectiveness for the whole chronic heart failure population (i.e. EF <40% and >40%). This will be estimated by weighting the ICER for those patients with an EF>40% and <40% by the prevalence of each within the UK population.</p> <p>Demonstrating its total value supports broad use in the NHS. As described in the <i>appropriateness</i> section, broad use of empagliflozin supports delivery of national policies and initiatives to improve outcomes for patients with cardiovascular disease.</p> <p>16. S, A. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. <i>N Engl J Med</i> 385, 1451–1461 (2021).</p> <p>19. A, M., Theresa <i>et al.</i> 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. <i>Eur Heart J</i> 42, ehab368 (2021).</p> <p>20. M., P. <i>et al.</i> Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. <i>New Engl J Med</i> 383, 1413–1424 (2020).</p>	
	Pumping Marvellous Foundation	It is the whole population	Thank you for your comment. The population has been updated to 'adults with symptomatic chronic

Section	Consultee/ Commentator	Comments [sic]	Action
			heart failure with a left ventricular ejection fraction of 40% or more’.
	UKCPA	Need to define group as per trials or ESC definition	Thank you for your comment. The population has been updated to ‘adults with symptomatic chronic heart failure with a left ventricular ejection fraction of 40% or more’.
Comparators	Boehringer-Ingelheim	<p>Have all relevant comparators for empagliflozin been included in the scope?</p> <p>BI suggests that symptomatic management of co-existing conditions is also included as a comparator. This is because the ESC 2021 HF guidelines state “as the vast majority of HFpEF patients have underlying hypertension and/or CAD, many are already treated with ACE-I/ARB, beta-blockers, or MRAs”¹⁹.</p> <p>Where do you consider empagliflozin will fit into the existing NICE pathway, Chronic heart failure? <i>NICE clinical treatment pathway</i></p> <p>At first presentation of symptoms, there is no distinction between those patients with an EF<40% and EF>40%. The diagnosis of HF is multifactorial and encompasses detailed clinical history, physical examinations,</p>	Thank you for your comment. The comparators have been updated to ‘established clinical management without empagliflozin, including but not limited to loop diuretics and symptomatic treatments for co-morbidities’.

		<p>electrocardiograms (ECG), stress tests, chest x-rays, coronary angiograms, cardiac computerised tomography (CT) scans, magnetic resonance imaging (MRI), myocardial biopsies and laboratory tests. Given the uncertainties that are intrinsic to a clear diagnosis of HF on physical examination alone, and the outcome for patients left undiagnosed, the NICE and ESC guidelines recommend testing of serum N-terminal pro-B-type natriuretic peptide (NT pro-BNP) in people with suspected HF as an essential diagnostic tool ^{19,21}. The NT-pro-BNP level; however, cannot differentiate between chronic HF EF $\leq 40\%$ and EF $>40\%$.¹⁹ Transthoracic echocardiography is required for confirmatory diagnosis and to inform classification of HF, which in turn, guides the management of the condition.</p> <p>NICE Chronic Heart Failure guideline (NG106) recommend that all patients diagnosed with chronic symptomatic heart failure receive treatment to manage their signs and symptoms, such as diuretic, calcium channel blockers, amiodarone, and anticoagulants. The guideline also recommends that <i>“people who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics (for example, less than 80 mg furosemide per day). People whose heart failure does not respond to this treatment will need further specialist advice.”</i>²²</p> <p>NG106 also states that for treatment of patients with preserved ejection fraction <i>“co-existing conditions such as hypertension, atrial fibrillation, ischemic heart disease and diabetes are managed in line with other NICE guidelines”</i>.²² The ESC 2021 Guidelines for Heart Failure¹⁹ elaborates on how co-existing conditions are managed in patients with an EF $>50\%$. It states <i>“as the vast majority of HFpEF patients have underlying hypertension and/or CAD, many are already treated with ACE-I/ARB, beta-blockers, or MRAs.</i></p> <p>NG106 does not recommend any targeted therapy for patients with an EF $>40\%$, as none are available until now.²² Therefore, to meet an unmet need, the optimal positioning for empagliflozin in the NICE pathway is after</p>	
--	--	---	--

diagnosis of chronic HF (EF >40%) following treatment with diuretics for symptomatic relief, as described in Figure 1.

Figure 1. Chronic heart failure diagnostic pathway



Source: Adapted from NICE guideline NG106, 2018 ²²

Which treatments would empagliflozin be used in combination with?

Empagliflozin will be indicated as an add-on therapy to standard care for all adult patients with chronic symptomatic heart failure. In EMPEROR-Preserved, several background therapies were permitted.¹⁶ These therapies were consistent with those recommended in NG106 and the ESC 2021 HF Guidelines.^{19,22} These are described in Table 1.

Table 1. Patients taking drugs used in heart failure at baseline - RS¹⁶

HF medication, N (%)		
ACEi/ARBs/ARNI	2,428 (81.0)	2,404 (80.4)
ARNI	65 (2.2)	69 (2.3)
Beta-blocker	2,598 (86.7)	2,569 (85.9)
Diuretics	2,563 (85.5)	2,600 (86.9)
Lipid-lowering drugs	2,103 (70.2)	2,139 (71.5)
Anti-thrombotic drugs	2,631 (87.8)	2,609 (87.2)

RS, randomised set; ACEi, Angiotensin-converting enzyme; ARB, angiotensin II receptor blockers; ARNI, angiotensin receptor-neprilysin inhibitor

16. S, A. Empagliflozin in Heart Failure with a Preserved Ejection Fraction. *N Engl J Med* 385, 1451–1461 (2021).

19. A, M., Theresa *et al.* 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 42, ehab368 (2021).

21. P., P. *et al.* 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 37, 2129–2200 (2016).

22. NICE. Chronic heart failure in adults: diagnosis and management. <https://www.nice.org.uk/guidance/ng106> (2018).

Section	Consultee/ Commentator	Comments [sic]	Action
	Pumping Marvellous Foundation	Agree with comparators	Thank you for your comment. No action required.
	UKCPA	The only comparator is diuretic therapy	Thank you for your comment. The comparators have been updated to 'established clinical management without empagliflozin, including but not limited to loop diuretics and symptomatic treatments for co-morbidities'.
Outcomes	Boehringer-Ingelheim	BI agree that the outcomes included in the draft scope capture the most important health related benefits (and harms) of the technology.	Thank you for your comment. No action required.
	Pumping Marvellous Foundation	Agree – however we should be measuring QOL as a whole, not just the domains that are measured using health questionnaires	Thank you for your comment. No action required.
	UKCPA	Yes [these outcome measures capture the most important health related benefits (and harms) of the technology]	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
Economic analysis	Boehringer-Ingelheim	<p>The economic model presented will follow the NICE reference case. It will mirror the model submitted for the appraisal of empagliflozin in patients with chronic heart failure with reduced ejection fraction (EF <40%) (ID3826)², except that the model will use data from EMPEROR-Preserved.</p> <p>The CPRD study PULSE will be used again to validate model outcomes.</p> <p>2. Excellence, N. I. for H. and C. Empagliflozin for treating chronic heart failure with reduced ejection fraction [ID3826]. https://www.nice.org.uk/guidance/indevelopment/gid-ta10719 (2022).</p>	Thank you for your comment. No action required.
	Pumping Marvellous Foundation	Agreed	Thank you for your comment. No action required.
Equality	Boehringer-Ingelheim	<p>Reducing the gap in equality in access to heart failure care through broad prescribing of SGLT2i's in primary and secondary care</p> <p>BI support NICE's commitment to producing guidance that supports the reduction of health inequalities, consistent with the Social Value Judgments.²³ Principle 9 of NICE's Social Value Judgments states that due regard must be given to reducing inequalities. It states that equality should be considered in relation to the nine protected characteristics in the Equality Act 2010 (age, disability, gender reassignment, race, religion or belief, sex, sexual orientation, marriage and civil partnership, pregnancy and maternity) and socio-demographic factors.²³</p> <p>Broad prescribing of SGLT2i across primary and secondary care can support the reduction in disparity in access to HF care across socio-economic groups within the UK. Waiting for a cardiologist to initiate a SGLT2i would likely widen the gap in health inequalities and lead to a delay as there is limited capacity in secondary care. This is important because lower socio-economic</p>	Thank you for your comment. The committee will consider whether its recommendations could have a different impact on people protected by the equality legislation than on the wider population.

Section	Consultee/ Commentator	Comments [sic]	Action
		<p>status is associated with increased risk of heart failure, hospital admissions, mortality and co-morbidities and a reduced likelihood of seeking medical attention in secondary care.</p> <p>Socio-economic class, sex, age and race are risk factors for the development of heart failure. Conrad et al 2018 ^{24]} reported on a HES-linked CPRD study of 4 million adult patients. A subset of these later developed heart failure (n=45,671). At the same age and sex, patients in the most deprived socio-economic quintile were more likely to experience incident heart failure than more affluent individuals (IRR 1.61, 95% CI 1.58 to 1.64). Further, patients from the most deprived socio-economic quintile were about 3.5 years younger at diagnosis than those from the least deprived group (mean age at diagnosis 74.5 years [SD 13.3] for most deprived vs 77.8 years [SD 12.1]; adjusted difference -3.51 years, 95% CI -3.77 to -3.25). Lawson et al 2020 [3] reported in another HF HES-linked CPRD study that age at HF onset differed significantly by race with younger onset in South Asian group (72 years) and black group (68 years) compared with the older white group (78 years). Following adjustment, age differences compared with the white group were -5.7 years (95% CI, -6.2 to -5.2) for the South Asian group and -9.0 years (95% CI, -9.9 to -8.2) for the black group.</p> <p>There is also a disparity across socio-economic groups in mortality outcomes and the risk of co-morbidities. Lawson et al 2020 ⁷ reported that HF patients from the most deprived group compared to the least deprived group had significantly higher prevalence of most co-morbidities; the biggest difference was for obesity (28% versus 19%), diabetes mellitus (30% versus 23%) and chronic obstructive pulmonary disease (25% versus 14%). This trend was also observed for mortality. Witte et al 2018 reported in a UK prospective cohort study that the risk of death increases for HF patients in lower socio-economic classes. Age-sex adjusted Cox regression analyses indicated</p>	

Section	Consultee/ Commentator	Comments [sic]	Action
		<p>every 10-unit increase in the UK Index of Multiple Deprivation score was associated with 6% higher risk of all-cause mortality (95% CI 2% to 10%, P=0.004), a 9% higher risk of non-cardiovascular mortality (95% CI 3% to 16%, P=0.003) and a non-significant 3% higher risk of cardiovascular mortality (95% CI -2% to 9%, P=0.21).²⁵</p> <p>Socio-economic status has an impact on access to secondary care in the UK, and subsequently access to heart failure treatments. Moscelli et al 2016 reported a statistically significant difference in waiting times across socio-economic groups for patients who attend the same hospital: patients living in more income deprived areas waited longer (35% difference, or 43 days) than patients who lived in less deprived areas. As well as waiting longer, chronic heart disease patients in a lower socio-economic class were admitted to hospital less often than those in a higher class. McCartney et al 2013 reported on a prospective study of 7049 and 8353 women in the west of Scotland followed up for 37 years. The likelihood of a hospital admission for CVD was 21% higher for female patients in socio-economic class IV and V than patients in class I and II. Those patients in class IV and V also stayed 25% longer in hospital (589 vs 736 bed day/1000 person years, respectively).²⁶ However, this trend was not observed in men of different socio-economic classes. Socio-economic factors also impact access to HF treatments. In a Danish Heart Failure registry of 17,122 HF patients, a lower income was associated with 20% lower odds of a prescription of ACEI/ARBs than those with a higher income.²⁷ These studies indicate that if patients in lower socio-economic classes utilize secondary care less often, their opportunity to access HF medications would also be lower if they are solely prescribed in secondary care.</p> <p>Redistribution of resources within NHS hospitals due to COVID-19 and cancellation of non-urgent care may exacerbate pre-existing inequity in</p>	

Section	Consultee/ Commentator	Comments [sic]	Action
		<p>access to secondary care. In a discussion paper, Propper et al 2020²⁸ noted that disruptions to emergency care and cancellation of elective care are most likely to affect the elderly and those from deprived areas. Emergency admissions among those in the more deprived areas in England were considerably higher than those among the less deprived (110 vs 180 admissions per 10% population), although elective procedures were evenly distributed across deprivation deciles.</p> <p>Delayed presentation of CV emergencies in UK hospitals due to COVID-19 emphasizes the need for preventative pharmacological interventions, such as SGLT2is, that can be accessed in primary care. Fersia et al 2020²⁹ reported a 50% drop in the number of patients presenting to cardiology departments in a district hospital in Dumfries and Galloway. Additionally, the number of patients referred from primary care to cardiology outpatient clinics dropped by 80%. All areas of cardiology service provision sustained significant reduction, which included outpatient clinics, investigations and procedures. The authors expect that there will be another surge of patients seeking cardiology care and that services need to plan to treat these patients early and urgently to prevent long term complications.</p> <p>Empagliflozin is the only targeted therapy that has demonstrated improvement in outcomes for adult patients with symptomatic chronic heart failure across a broad range of ejection fractions. To support the broader goal of reducing inequity in access to care for HF patients, in line with NICE's Social Value Judgments, a broad recommendation by NICE for empagliflozin (regardless of ejection fraction) that facilitates prescribing across primary and secondary care is critical.</p> <p>7. A., L. C. <i>et al.</i> Risk Factors for Heart Failure. <i>Circulation Hear Fail</i> 13, e006472 (2020).</p>	

Section	Consultee/ Commentator	Comments [sic]	Action
		<p>23. NICE. Our Principles: Social Value Judgments. https://www.nice.org.uk/about/who-we-are/our-principles (2022).</p> <p>24. Nathalie, C. <i>et al.</i> Temporal trends and patterns in heart failure incidence: a population-based study of 4 million individuals. <i>Lancet Lond Engl</i> 391, 572–580 (2018).</p> <p>25. Witte, K. K. <i>et al.</i> Socioeconomic deprivation and mode-specific outcomes in patients with chronic heart failure. <i>Heart</i> 104, 993–998 (2018).</p> <p>26. G., M., C., H. & G., W. How can socioeconomic inequalities in hospital admissions be explained? A cohort study. <i>BMJ Open</i> 3, e002433 (2013).</p> <p>27. Schjodt, I., Johnsen, S. P., Stromberg, A., Valentin, J. B. & Logstrup, B. B. Inequalities in heart failure care in a tax-financed universal healthcare system: a nationwide population-based cohort study. <i>ESC Heart Fail</i> 7, 3095–3108 (2020).</p> <p>28. Carol, P., George, S. & Ben, Z. The Wider Impacts of the Coronavirus Pandemic on the NHS*. <i>Fisc Stud</i> 41, 345–356 (2020).</p> <p>29. O., F. <i>et al.</i> The impact of the COVID-19 pandemic on cardiology services. <i>Open Hear</i> 7, e001359 (2020).</p>	
	Pumping Marvellous Foundation	Agreed	Thank you for your comment. No action required.
Other considerations	Boehringer-Ingelheim	No further considerations	Thank you for your comment. No action required.
	Pumping Marvellous Foundation	Nil	Thank you for your comment. No action required.
	UKCPA	Need to be clear on the definition of HFpEF other wise will be a risk of inappropriate implementation for patients who are breathless/have fluid retention who may not have HF	Thank you for your comment. The population has been

Section	Consultee/ Commentator	Comments [sic]	Action
			updated to 'adults with symptomatic chronic heart failure with a left ventricular ejection fraction of 40% or more'.
Innovation	Boehringer-Ingelheim	<p>Do you consider empagliflozin to be innovative in its potential to make a significant and substantial impact on health-related benefits and how it might improve the way that current need is met (is this a 'step-change' in the management of the condition)?</p> <p>BI consider empagliflozin to be a step change in the management of HF. Delivering an integrated care service is a core objective of the NHS Long Term Plan and is reflected in a recent white paper to strengthen its implementation ³⁰. Further, NICE recently published a report on implementing NG106. It noted that patients with heart failure often have other co-existing conditions such as diabetes and kidney disease and may end up attending several specialist clinics. ³¹ SGLT2i's offer an opportunity to promote a more holistic approach to treatment of adults with T2DM and HF. Empagliflozin is already indicated for the T2DM and HFrEF, ³² and with data from EMPEROR-Preserved means that it is the only SGLT2i that has demonstrated benefit across a broad spectrum of ejection fractions. This means that all patients, regardless of ejection fraction could benefit from a targeted treatment.</p> <p>Do you consider that there will be any barriers to adoption of this technology into practice? If yes, please describe briefly.</p> <p>In addition to updating NG106, a broad evidence-based recommendation by NICE for prescribing across primary and secondary care will accelerate uptake for SGLT2i's, especially if it is listed as green on local formularies.</p>	Thank you for your comment. The committee will consider the innovation of the technology during the evaluation. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action
		30. NHS. The NHS Long Term Plan. (2019). 31. NICE. NICE impact cardiovascular disease management. Published February 2021. (2021). 32. Compendium, E. M. Jardiance 25mg film-coated tablets Summary of Product Characteristics: Last updated 3rd September 2020. https://www.medicines.org.uk/emc/product/7703/smpc#DOCREVISION (2013).	
	Pumping Marvellous Foundation	This is highly innovative, first in class for the whole treatment population. It is important we consider this when making market access decisions.	Thank you for your comment. No action required.
	UKCPA	Yes	Thank you for your comment. No action required.
Questions for consultation	Boehringer-Ingelheim	All questions for consultation are addressed above.	Thank you for your comment. No action required.
	Pumping Marvellous Foundation	Nil	Thank you for your comment. No action required.
	UKCPA	Does the data indicate any subgroups who are likely to have more benefit from the intervention	Thank you for your comment. No action required.
Any additional comments on the draft scope	Pumping Marvellous Foundation	Nil	Thank you for your comment. No action required.

Section	Consultee/ Commentator	Comments [sic]	Action

The following stakeholders indicated that they had no comments on the draft remit and/or the draft scope

The Somerville Foundation