Addressing the Gaps Left by Existing Guidelines

HF UPDATE MAY 13 2022

For Clinicians and Health Professionals who care for HF patients

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Conflict of Interest Disclosures

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- **Consulting fees**: Astra Zeneca, Boehringer Ingelheim, Bayer, Eli Lilly, Janssen

- **Speaker fees**: Astra Zeneca, Boehringer Ingelheim, Bayer (past 2 years)

- **Other**: Cytokinetics (HF PSC), industry partners for CHFA Network

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Society Guidelines

CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction

Primary Panel: Michael McDonald, MD (Co-chair),[a] Sean Virani, MD (Co-chair),[b] Michael Chan, MBBS,[c] Anique Ducharme, MD,[d] Justin A. Ezekowitz, MBBCh,[e] Nadia Giannetti, MD,[f] George A. Heckman, MD,[g] Jonathan G. Howlett, MD,[h] Sheri L. Koshman, Pharm D,[e] Serge Lepage, MD,[i] Lisa Mielniczuk, MD,[j] Gordon W. Moe, MD,[k] Eileen O'Meara, MD,[d] Elizabeth Swiggum, MD,[l] Mustafa Toma, MD,[b] Shelley Zieroth, MD,[m] **Secondary Panel:** Kim Anderson, MD,[n] Sharon A. Bray, EdD,[a] Brian Clarke, MD,[h] Alain Cohen-Solal, MD,[o] Michel D'Astous, MD,[p] Margot Davis, MD,[b] Sabe De, MD,[q] Andrew D.M. Grant, MD,[h] Adam Grzeslo, MD,[r] Jodi Heshka, MD,[s] Sabina Keen, MD,[r] Simon Kouz, MD,[r] Douglas Lee, MD, PhD,[a] Frederick A. Masoudi, MD MSPH,[u] Robert McKelvie, MD,[v] Marie-Claude Parent, MD,[d] Stephanie Poon, MD,[w] Miroslaw Rajda, MD,[n] Abhinav Sharma, MD,[f] Kyla Siatecki, MN, NP,[m] Kate Storm, NP,[n] Bruce Sussex, MBBS,[x] Harriette Van Spall, MD MPH,[r] and Amelia Ming Ching Yip, MD[y]

RECOMMENDATION

1. We recommend that in the absence of contraindications, patients with HFrEF be treated with combination therapy including 1 evidence-based medication from each of the following categories:
   a. ARNI (or ACEI/ARB);
   b. β-blocker;
   c. MRA; and
   d. SGLT2 inhibitor.
   (Strong Recommendation; Moderate-Quality Evidence).

Table 1. Quality of available evidence to support the use of each HFrEF therapy according to clinical setting

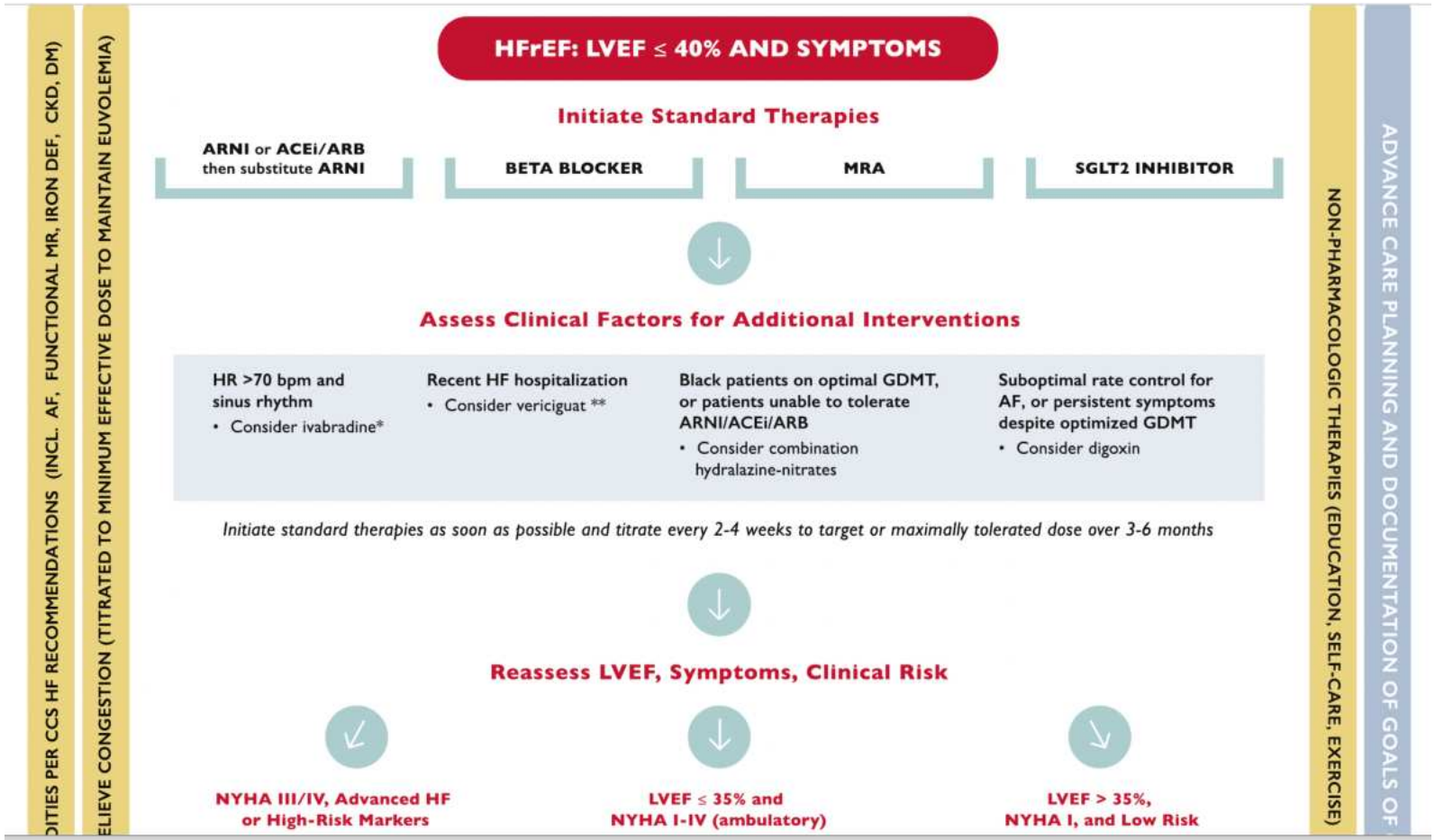
	Quality of evidence supporting recommendation		
HFrEF drug therapy	Chronic ambulatory HF	New-onset HF	HF hospitalization*
Sacubitril-valsartan	High	Low	Moderate
ACEI/ARB	High	High	High†
β-blockers	High	High	High
MRAs	High	High	High†
SGLT2 inhibitors	High	N/A	N/A‡
Ivabradine	High	N/A	N/A
Vericiguat	Moderate	N/A	NA
Digoxin	Moderate	Low	Low
H-ISDN	Moderate	Low	Low

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; HF, heart failure; HFrEF, heart failure with reduced ejection fraction; ISDN, hydralazine and isosorbide dinitrate; MRA, mineralocorticoid receptor antagonist; SGLT2, sodium glucose transport 2; SOLOIST-WHF, Effect of **So**tag**l**iflozin on Clinical Outcomes in Hem**o**dynam**i**cally **St**able Patients With Type 2 Diabetes Post **W**orsening **H**eart **F**ailure.

* Evidence for prescribing HFrEF therapies in the setting of HF hospitalization is derived primarily from studies in which patients had been stabilized after admission.

† Evidence for ACEI/ARB and MRA use in the setting of HF hospitalization is derived primarily from studies of high-risk post myocardial infarction patients.

‡ The recent SOLOIST-WHF trial showed that sotagliflozin (an SGLT1/2 inhibitor) could be safely prescribed before discharge or shortly after discharge in patients with diabetes who were stabilized after hospitalization for heart failure. Ongoing randomized controlled trials will further evaluate the efficacy and safety of initiating SGLT2 inhibitors in a spectrum of HF pa-


DITIES PER CCS HF RECOMMENDATIONS (INCL. AF, FUNCTIONAL MR, IRON DEF, CKD, DM)
ELIEVE CONGESTION (TITRATED TO MINIMUM EFFECTIVE DOSE TO MAINTAIN EUVOLEMIA)
HFrEF: LVEF ≤ 40% AND SYMPTOMS
Initiate Standard Therapies
ARNI or ACEi/ARB then substitute ARNI
BETA BLOCKER
MRA
SGLT2 INHIBITOR
Assess Clinical Factors for Additional Interventions
HR >70 bpm and sinus rhythm
• Consider ivabradine*
Recent HF hospitalization
• Consider vericiguat **
Black patients on optimal GDMT, or patients unable to tolerate ARNI/ACEi/ARB
• Consider combination hydralazine-nitrates
Suboptimal rate control for AF, or persistent symptoms despite optimized GDMT
• Consider digoxin
Initiate standard therapies as soon as possible and titrate every 2-4 weeks to target or maximally tolerated dose over 3-6 months
Reassess LVEF, Symptoms, Clinical Risk
NYHA III/IV, Advanced HF or High-Risk Markers
LVEF ≤ 35% and NYHA I-IV (ambulatory)
LVEF > 35%, NYHA I, and Low Risk
NON-PHARMACOLOGIC THERAPIES (EDUCATION, SELF-CARE, EXERCISE)
ADVANCE CARE PLANNING AND DOCUMENTATION OF GOALS OF

EMPULSE

	Empagliflozin (n = 265) Median (IQR) or n (%)	Placebo (n = 265) Median (IQR) or n (%)
Age (years)	71 (62-78)	70 (59-78)
Sex		
Men	179 (67.5)	172 (64.9)
Women	86 (32.5)	93 (35.1)

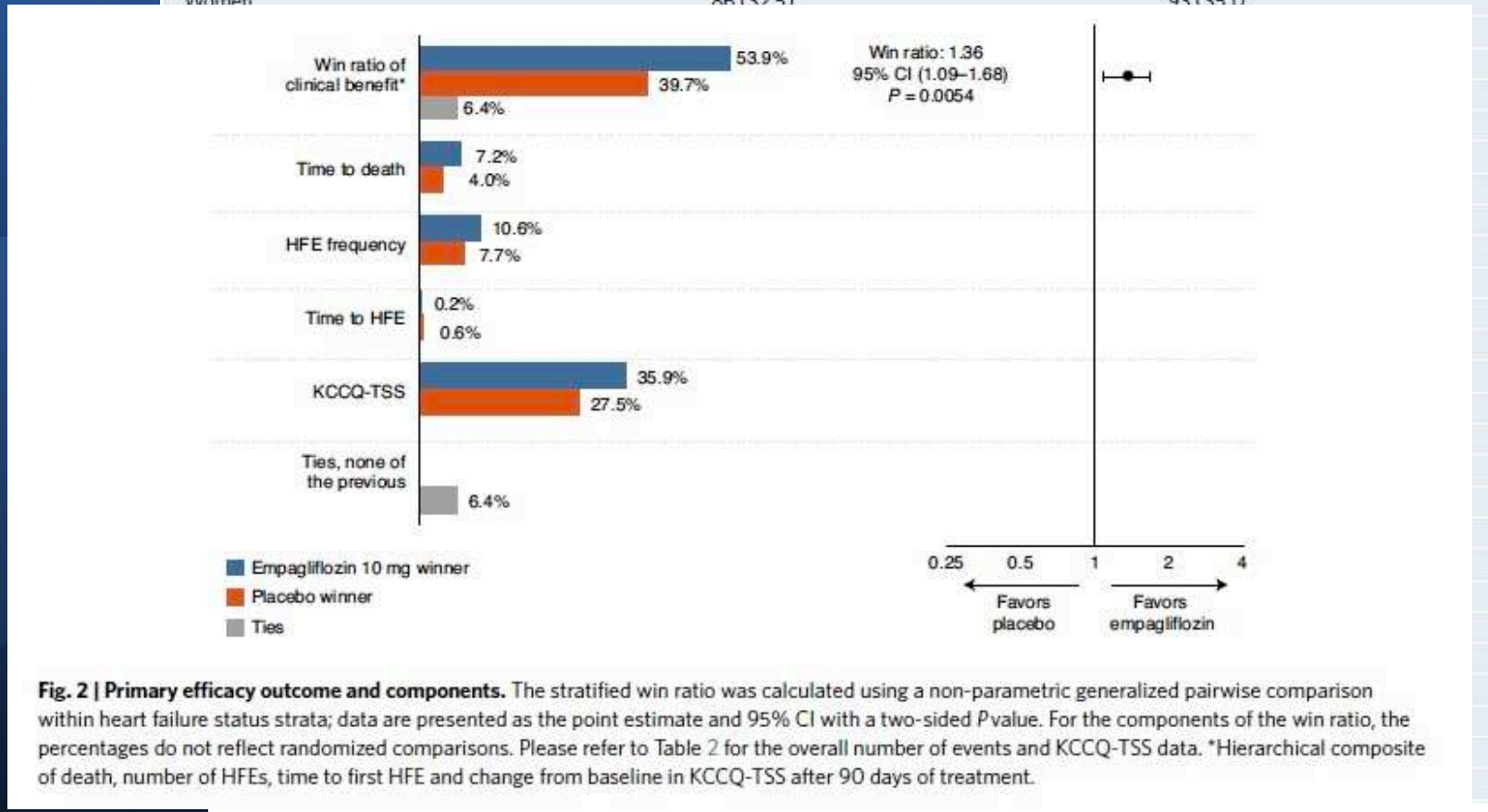
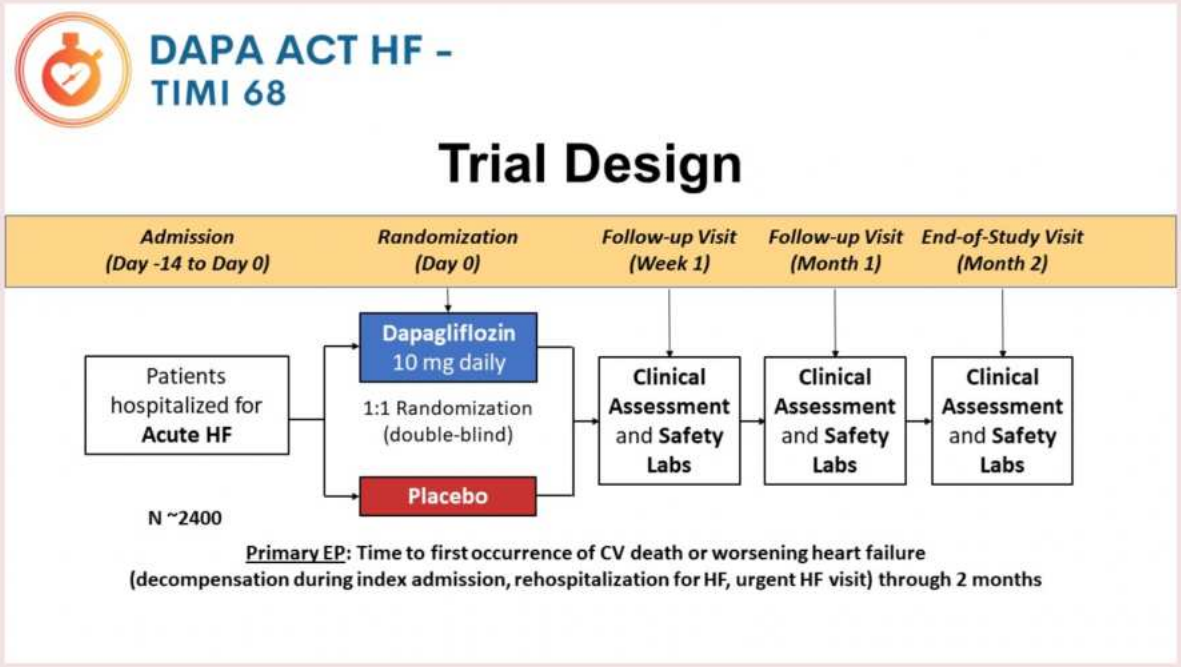


Fig. 2 | Primary efficacy outcome and components. The stratified win ratio was calculated using a non-parametric generalized pairwise comparison within heart failure status strata; data are presented as the point estimate and 95% CI with a two-sided *P* value. For the components of the win ratio, the percentages do not reflect randomized comparisons. Please refer to Table 2 for the overall number of events and KCCQ-TSS data. *Hierarchical composite of death, number of HFEs, time to first HFE and change from baseline in KCCQ-TSS after 90 days of treatment.

DAPA-ACT

DAPA ACT HF-TIMI 68 is an investigator-initiated, randomized, double-blind, placebo-controlled trial in patients with heart failure who have been stabilized during hospitalization for acute heart failure, evaluating the effect of in-hospital initiation of dapagliflozin on the clinical outcomes of cardiovascular death or worsening heart failure.



AHA 2022 HF GUIDELINES

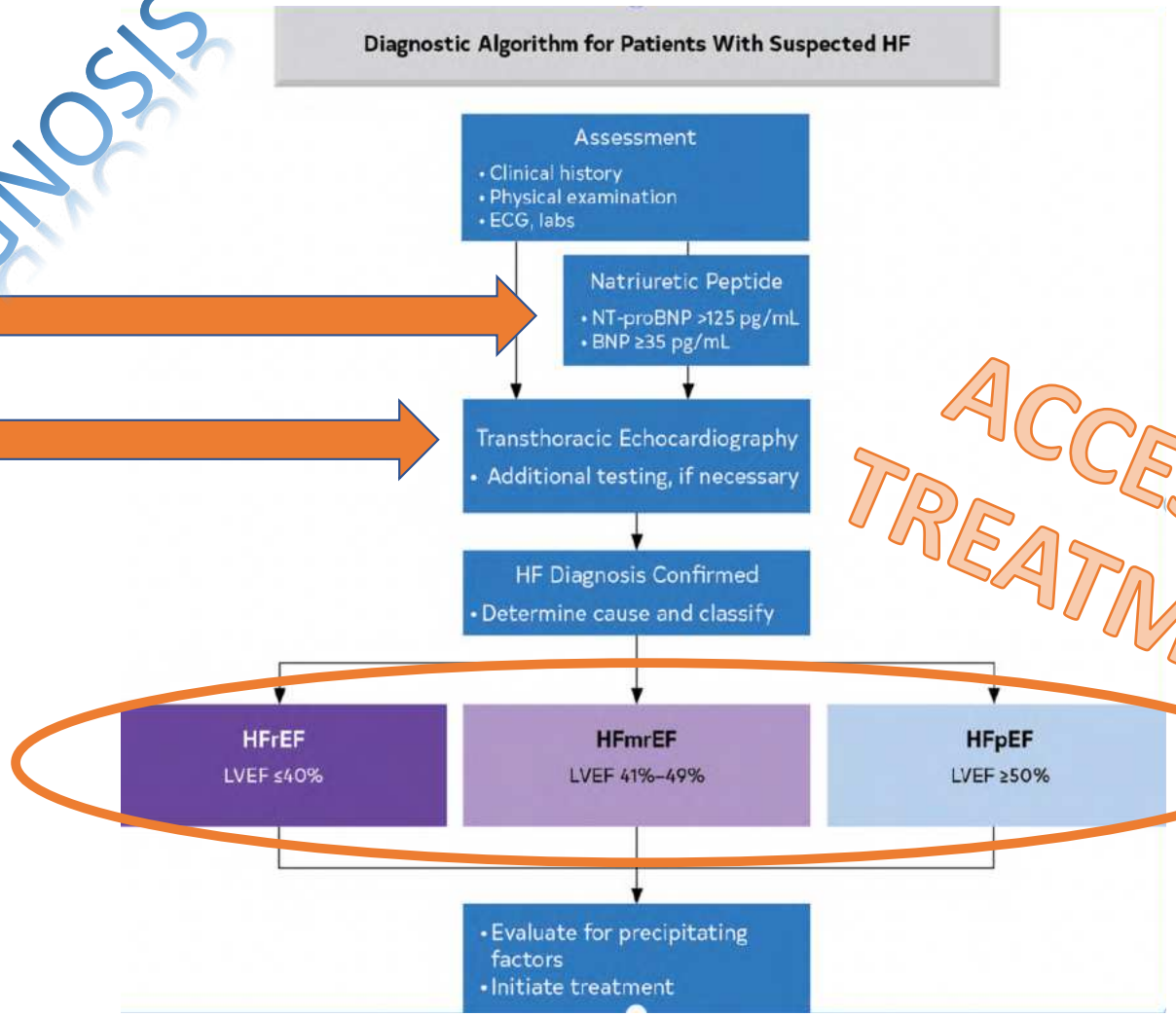
Evidence supporting increased filling pressures is important for the diagnosis of HF if the LVEF is >40%. Evidence for increased filling pressures can be obtained from noninvasive (eg, natriuretic peptide, diastolic function on imaging) or invasive testing (eg, hemodynamic measurement).

Patients with advanced HF who wish to prolong survival should be referred to a team specializing in HF. A HF specialty team reviews HF management, assesses suitability for advanced HF therapies, and uses palliative care including palliative inotropes where consistent with the patient's goals of care.

Primary prevention is important for those at risk for HF (stage A) or pre-HF (stage B). Stages of HF were revised to emphasize the new terminologies of "at risk" for HF for stage A and pre-HF for stage B.

Recommendations are provided for select patients with HF and iron deficiency, anemia, hypertension, sleep disorders, type 2 diabetes, atrial fibrillation, coronary artery disease, and malignancy.

ACCESS TO DIAGNOSIS



ACCESS TO TREATMENTS

Access to each easily?

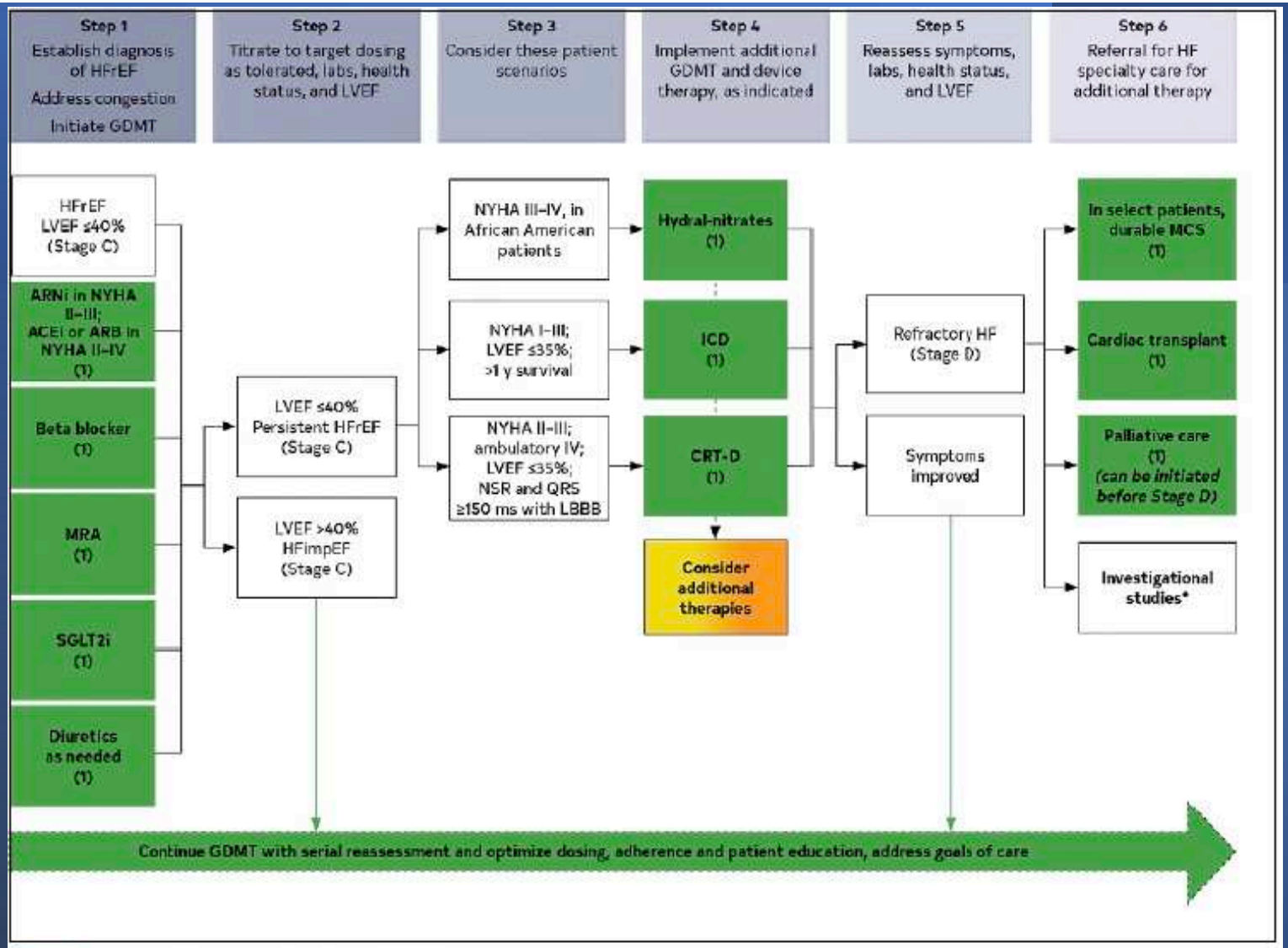


Figure 6. Treatment of HFrEF Stages C and D.

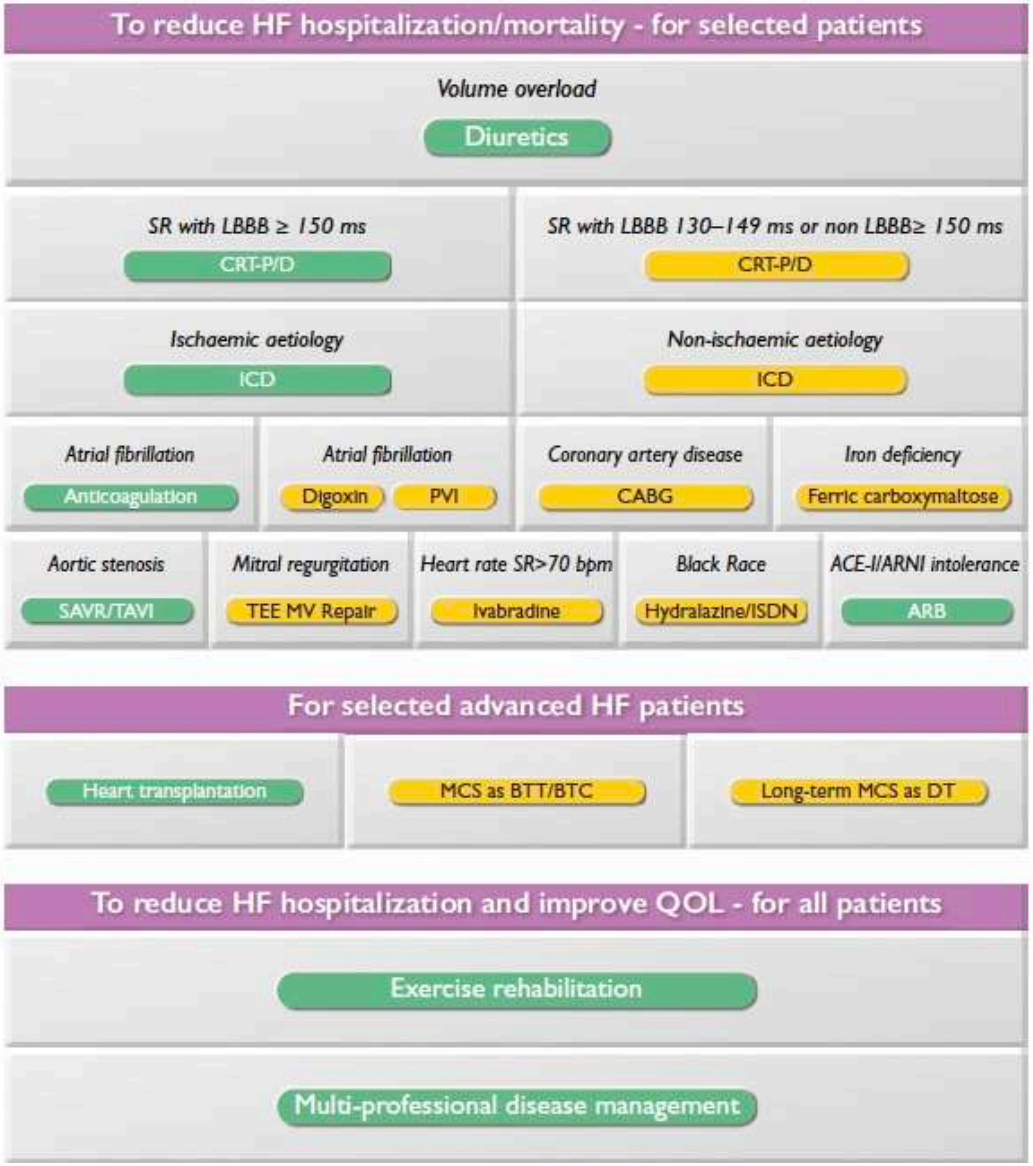
Is our healthcare system able to provide this on a large scale?

In what proportion of patients with HFrEF is this possible? How can we achieve this?

Recommendations for GDMT Dosing: Sequencing and Uptitration
Referenced studies that support the recommendations are summarized in the [redacted].

COR	LOE	Recommendations
1	A	1. In patients with HFrEF, titration of guideline-directed medication dosing to achieve target doses showed to be efficacious in RCTs is recommended, to reduce cardiovascular mortality and HF hospitalizations, unless not well tolerated.[1-10]
2a	C-EO	2. In patients with HFrEF, titration and optimization of guideline-directed medications as frequently as every 1 to 2 weeks depending on the patient's symptoms, vital signs, and laboratory findings can be useful to optimize management.

ESC HF Guidelines 2021



Can we do this? Are we doing this?

Recommendations for the management of anaemia and iron deficiency in patients with heart failure

Recommendations	Class[a]	Level[b]
It is recommended that all patients with HF be periodically screened for anaemia and iron deficiency with a full blood count, serum ferritin concentration, and TSAT.	I	C
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic patients with LVEF <45% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to alleviate HF symptoms, improve exercise capacity and QOL.[720,722,724]	IIa	A
Intravenous iron supplementation with ferric carboxymaltose should be considered in symptomatic HF patients recently hospitalized for HF and with LVEF <50% and iron deficiency, defined as serum ferritin <100 ng/mL or serum ferritin 100–299 ng/mL with TSAT <20%, to reduce the risk of HF hospitalization.[512]	IIa	B

ADVANCED HF – AHA 2022

Table 16. ESC Definition of Advanced HF

All these criteria must be present despite optimal guideline-directed treatment:
1. Severe and persistent symptoms of HF (NYHA class III [advanced] or IV)
2. Severe cardiac dysfunction defined by ≥1 of these:
LVEF ≤30% Isolated RV failure Nonoperable severe valve abnormalities Nonoperable severe congenital heart disease EF ≥40%, elevated natriuretic peptide levels and evidence of significant diastolic dysfunction
3. Hospitalizations or unplanned visits in the past 12 mo for episodes of:
Congestion requiring high-dose intravenous diuretics or diuretic combinations Low output requiring inotropes or vasoactive medications Malignant arrhythmias
4. Severe impairment of exercise capacity with inability to exercise or low 6-minute walk test distance (<300 m) or peak VO_2 (<12–14 mL/kg/min) estimated to be of cardiac origin
Criteria 1 and 4 can be met in patients with cardiac dysfunction (as described in criterion 2) but who also have substantial limitations as a result of other conditions (eg, severe pulmonary disease, noncardiac cirrhosis, renal disease). The therapeutic options for these patients may be more limited.

used to describe this population, including "end-stage," "advanced," and "refractory" HF. In 2018, the European Society of Cardiology updated its definition of advanced HF (Table 16), which now includes 4 distinct criteria.[1] The revised definition focuses on refractory symptoms rather than cardiac function and more clearly acknowledges that advanced HF can occur in patients without severely reduced EF, including those with isolated RV dysfunction, uncorrectable valvular or congenital heart disease, and in patients with preserved and mildly reduced EF.[1,3] The INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support) has developed 7 profiles that further stratify patients with advanced HF (Table 17).[7]

Determining that HF and not a concomitant pulmonary disorder is the basis of dyspnea is important. Severely symptomatic patients presenting with a new diagnosis of HF can often improve substantially if they are initially stabilized. Patients should also be evaluated for nonadherence to medications.[8–11] Finally, a careful review of medical management should be conducted to verify that all therapies likely to improve clinical status have been considered.

EMPA-KIDNEY

Oxford, UK; Ingelheim, Germany and Indianapolis, U.S. 16 March 2022 – The EMPA-KIDNEY trial, evaluating the effect of empagliflozin in adults with chronic kidney disease (CKD), will stop early based on a recommendation from the trial's Independent Data Monitoring Committee. This follows a formal interim assessment that met prespecified criteria for positive efficacy, announced the Medical Research Council (MRC) Population Health Research Unit at the University of Oxford, Boehringer Ingelheim, and Eli Lilly and Company (NYSE: LLY).

As the largest SGLT2 inhibitor trial in CKD to date, EMPA-KIDNEY is evaluating the efficacy and safety of empagliflozin in adults with CKD who are frequently seen in clinical practice but who have been under-represented in previous SGLT2 inhibitor trials, therefore addressing a critical unmet need. The trial includes people:[1,2]

- with mildly to severely reduced eGFR (a measure of kidney function);
- with normal and increased levels of albumin (a type of protein present in the urine);
- with and without diabetes;
- with CKD attributable to a wide range of underlying causes.

EMPA-KIDNEY is a large, double-blind, randomized, placebo-controlled, academic-led trial, including more than 6,600 adults with CKD.[2] The trial is being conducted, analyzed, and reported by the MRC Population Health Research Unit at the University of Oxford. The primary endpoint of the trial is a composite of kidney disease progression* or cardiovascular death. Key secondary outcomes include cardiovascular death or hospitalization for heart failure, all-cause hospitalization, and all-cause mortality.[2]

"Worldwide five to ten million people die each year from chronic kidney disease and many lives are severely disrupted by dialysis treatment," said Associate Professor William Herrington, Clinician Scientist Oxford Population Health, Honorary Consultant Nephrologist, and EMPA-KIDNEY co-Principal Investigator. "We studied a wide range of patients with declining kidney function with the aim of delaying the need for dialysis and avoiding heart disease in as many of them as possible."

e thrilled that the trial has shown that empagliflozin is beneficial among the patients studied in EMPA-KIDNEY," said Professor Richard Haynes, co-Principal Investigator. "We are very grateful to all of the participants who have made this trial

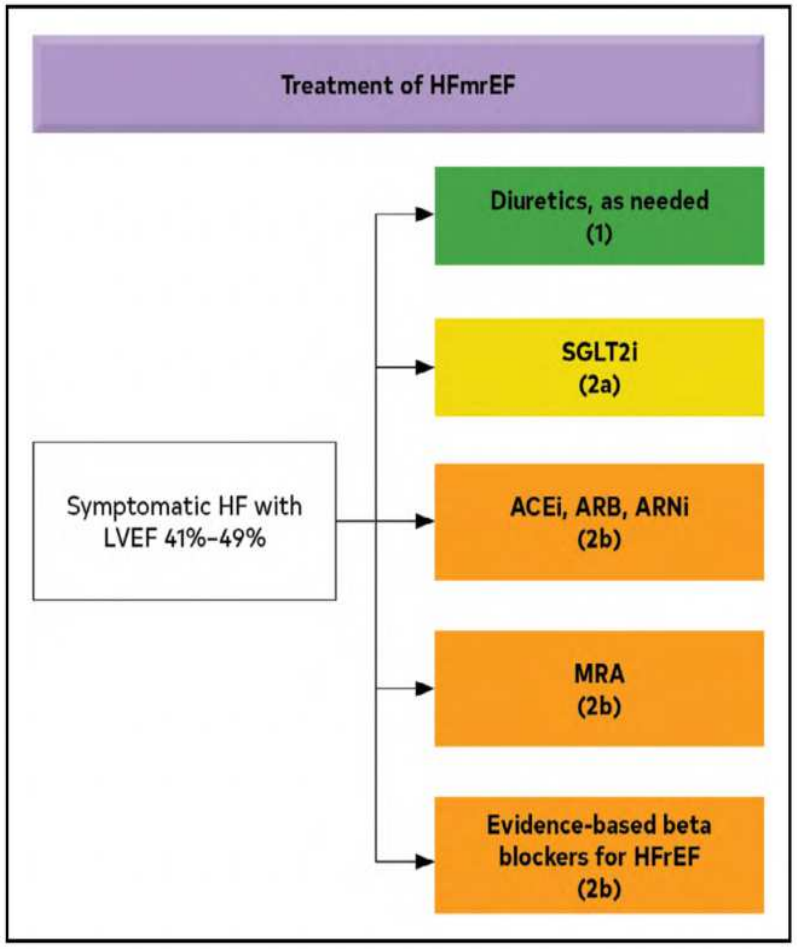


Figure 11. Recommendations for Patients With Mildly

pear to respond to medical therapies similarly to patients with HFrEF. Thus, it may be reasonable to treat these pa-
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with HFmrEF shoul
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Recommendatio

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29% reductio
nificant lower cardiovascular death [HR, 0.91; 95%
CI, 0.76–1.0]), with no benefit on all-cause mortality.

Results from the DELIVER and DAPA-HF Phase III trials demonstrate dapagliflozin's efficacy in heart failure regardless of ejection fraction- Press Release May 5, 2022

- High-level results from the DELIVER Phase III trial showed AstraZeneca's *Farxiga* (dapagliflozin) reached a statistically significant and clinically meaningful reduction in the primary composite endpoint of cardiovascular (CV) death or worsening heart failure (HF). The trial was conducted in patients with HF with mildly reduced or preserved ejection fraction (defined as left ventricular ejection fraction [LVEF] greater than 40%).
- Dr. Scott Solomon, Professor of Medicine at Harvard Medical School and Brigham and Women's Hospital and Principal Investigator of the DELIVER Phase III trial, said: "We are delighted to have met the primary endpoint in this patient population which has few treatment options. DELIVER is the largest and broadest trial to date in heart failure with mildly reduced or preserved ejection fraction. The results of DELIVER extend the benefit of dapagliflozin to the full spectrum of patients with heart failure."
- Mene Pangalos, Executive Vice President, BioPharmaceuticals R&D, AstraZeneca, said: "Today's groundbreaking results coupled with those from the DAPA-HF trial show that *Farxiga* is effective in treating heart failure regardless of ejection fraction. These data build upon our previous studies demonstrating cardiorenal protection across patients with either diabetes, chronic kidney disease or heart failure."
- The safety and tolerability profile of *Farxiga* in the DELIVER Phase III trial were consistent with the well-established safety profile of the medicine.
- The full DELIVER Phase III trial results will be submitted for presentation at a forthcoming medical meeting and regulatory submissions will be made in the coming months.

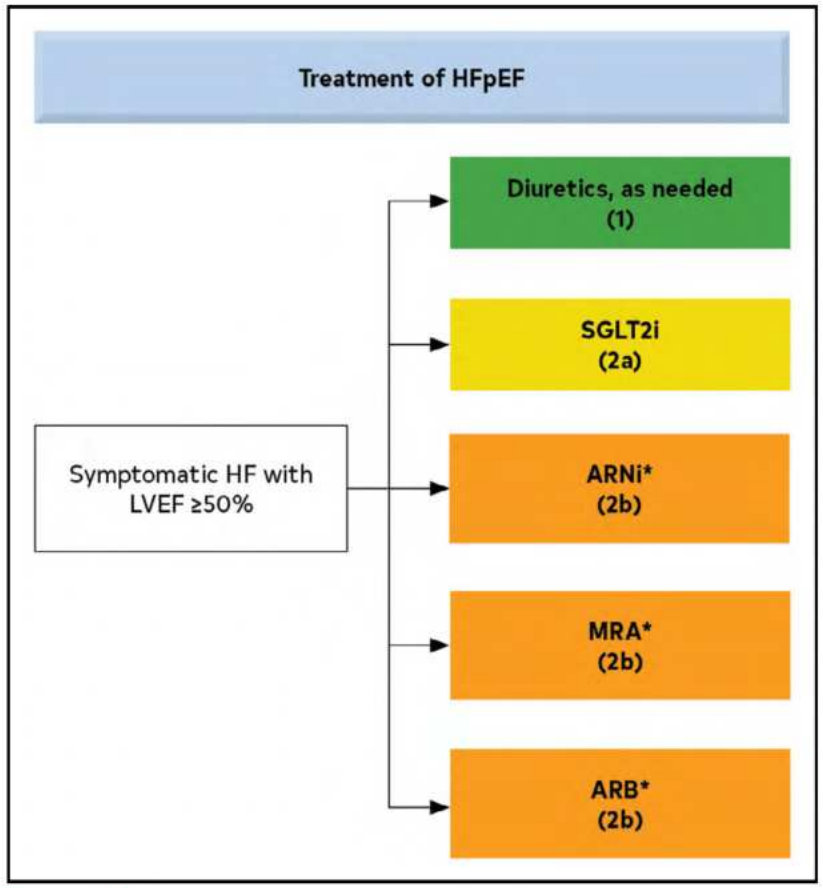


Figure 12. Recommendations for Patients With Preserved LVEF (≥50%).

Recommendation-Specific Supportive Text

1. The role of blood pressure control is well established for the prevention of HF, as well as for reduction of other cardiovascular events and HF mortality in patients without prevalent baseline HF.[1–3,21–24] The SPRINT (Systolic Blood Pressure Intervention) trial and meta-analyses established that more intensive blood pressure control in patients with high cardiovascular risk significantly reduces HF and other cardiovascular outcomes.[2,3,25] In recent clinical practice guidelines for hypertension, blood pressure targets in HFpEF are extrapolated from those for treatment of patients with hypertension in general.[26] However, the optimal blood pressure goal and antihypertensive regimens are not known for patients with HFpEF. RAAS antagonists including ACEi, ARB, MRA, and possibly ARNi, could be first-line agents given experience with their use in HFpEF trials.[8,10,16,20,27,28] Beta blockers may be used to treat hypertension in patients with a history of MI,[27] symptomatic CAD, or AF with rapid ventricular response. These effects need to be balanced with

Patients at the Heart of HF Research

The CHF Alliance is...

- **132** Investigators (42% women)
- **11** Patient/Caregiver Partners
- **14** Indigenous Partners
- **26** Early Career Investigators
- **23** Projects
- **07** Cross Cutting Themes
- **05** Platforms
- **29** Partners from **8** provinces & **1** territory and **28** hospital centers with over **$10.3M** in cash and **$16.4M** in-kind

Marc Bains, co-founder of HeartLife Foundation – a national non-profit organization advocating for heart failure patients and caregivers – is co-leading the new alliance. "The CHF Alliance is patient-driven, encompassing children to seniors, rural to urban communities."

What do Patients with HF Want?

CHFA

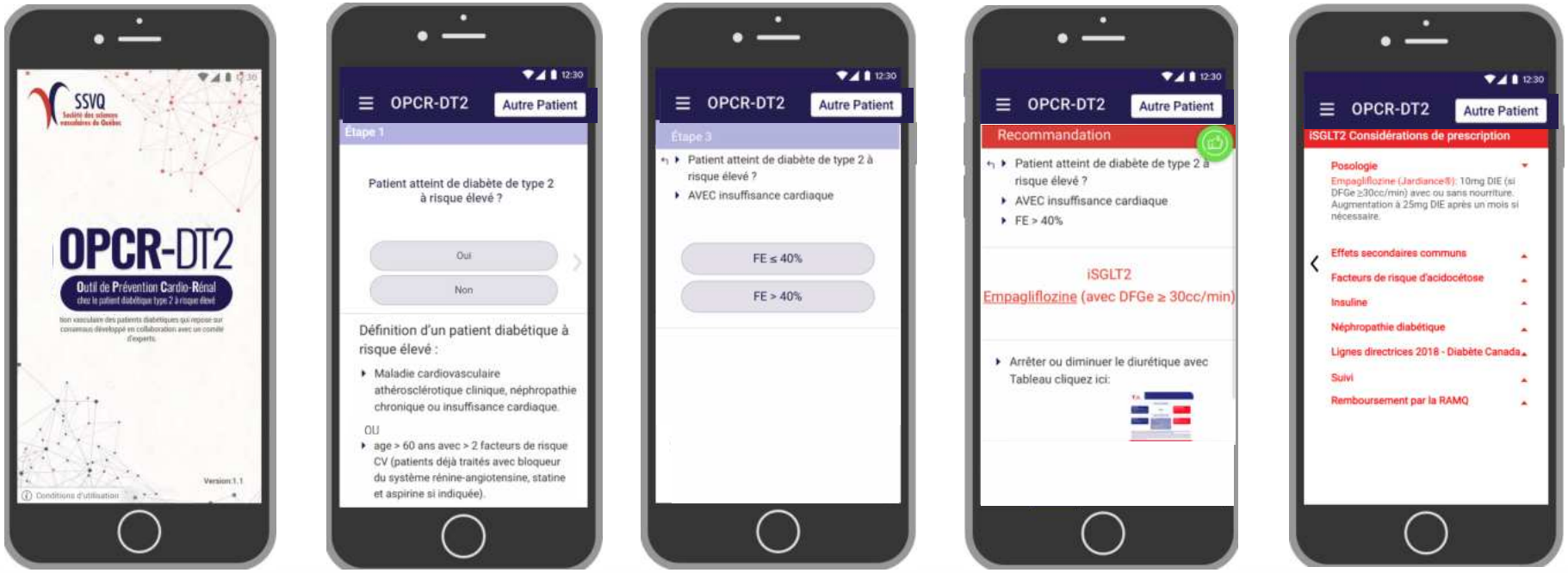
Patient Priorities

- ✓ Receipt of rapid & accurate diagnosis
- ✓ Improving access to & equity of care
- ✓ Self-management & empowerment
- ✓ Improving access to reliable information
- ✓ Lifestyle issues, mental health, sex & exercise
- ✓ Virtual care & innovative interventions

SSVQ Société des sciences vasculaires du Québec
Chef de file en santé vasculaire.

APPLICATION * SITE WEB * BALADOS * VIDÉO EXPLICATIVE * ÉTUDES DE CAS

Nouvelle mise à jour disponible prochainement



Summary
Addressing the gaps left by guidelines

Involve the first line and the patients

Great management algorithms but little guidance on how to realistically achieve the goals within reasonable time given the following constraints

1. Laboratory and imaging diagnostic tools not accessible to all and related to important delays in outpatient settings namely → How can we improve this?
   a. Consider point of care for labs/NPs
   b. Consider locally administered TTE with AI guidance (project)

Reimbursement issues related to missing recommendations or provincial decisions - long delays between publication of studies and publication of guidelines, e.g. HFpEF and SGLT2i or CKD and SGLT2i

Not enough evidence for acute use of SGLT2i ? Ongoing studies (hence difficult to cover the use for non-diabetic or well-controlled diabetic patients in the month following acute HF)

Not enough evidence for IV iron regarding hard outcomes? NEWER FORMULATIONS ARE NOT reimbursed for all patients (rapidly infused formulations) – ongoing studies and need for HFpEF-HFmrEF inclusive studies

Emphasis put on PREVENTION OR AT RISK OF HF mainly done by the AHA guidelines – much more efficient than acting late in the course of the disease

PATIENT PRIORITIES to be addressed and patients to be involved in development and diffusion of guidelines

Update the TOOLS/move closer to the healthcare provider, to the caregivers and to the patients to facilitate and accelerate use (e.g. SSVQ App for patients with diabetes), focusing on acting EARLY and on ACTING FAST for those with overt disease