Canadian Journal of Cardiology 36 (2020) 159–169

Society Guidelines

CCS/CHFS Heart Failure Guidelines: Clinical Trial Update on Functional Mitral Regurgitation, SGLT2 Inhibitors, ARNI in HFpEF, and Tafamidis in Amyloidosis

Primary Panel and Secondary Panel Writing Members: Eileen O'Meara, MD,[a,*] Michael McDonald, MD,[b,*] Michael Chan, MBBS,[c] Anique Ducharme, MD,[a] Justin A. Ezekowitz, MBBCh,[d] Nadia Giannetti, MD,[e] Adam Grzeslo, MD,[f] George A. Heckman, MD,[g] Jonathan G. Howlett, MD,[h] Sheri L. Koshman, PharmD,[d] Serge Lepage, MD,[i] Lisa M. Mielniczuk, MD,[j] Gordon W. Moe, MD,[k] Elizabeth Swiggum, MD,[l] Mustafa Toma, MD,[m] Sean A. Virani, MD,[m] Shelley Zieroth, MD,[n] Sabe De, MD,[o] Sylvain Matteau, MD,[i,p] Marie-Claude Parent, MD,[a] **External Reviewers and Co-authors:** Anita W. Asgar, MD,[a] Gideon Cohen, MD,[q] Nowell Fine, MD,[r] Margot Davis, MD,[m] Subodh Verma, MD,[s] David Cherney, MD,[t] **Secondary Panel:** Howard Abrams, MD,[u] Abdul Al-Hesayen, MD,[k] Alain Cohen-Solal, MD,[v] Michel D'Astous, MD,[w] Diego H. Delgado, MD,[u] Olivier Desplantie, MD,[x] Estrellita Estrella-Holder, RN,[y] Lee Green, MD,[d] Haissam Haddad, MD,[z] Karen Harkness, RN,[aa] Adrian F. Hernandez, MD,[bb] Simon Kouz, MD,[cc] Marie-Hélène LeBlanc, MD,[dd] Douglas Lee, MD,[u] Frederick A. Masoudi, MD,[ee] Robert S. McKelvie, MD,[ff] Miroslaw Rajda, MD,[gg] Heather J. Ross, MD,[b] and Bruce Sussex, MBBS[hh]

[a] *Institut de Cardiologie de Montréal, Université de Montréal, Montréal, Québec, Canada;* [b] *Peter Munk Cardiac Centre, University Health Network, Toronto, Ontario, Canada;* [c] *University of Alberta, Royal Alexandra Hospital, Edmonton, Alberta, Canada;* [d] *University of Alberta, Edmonton, Alberta, Canada;* [e] *McGill University, Montréal, Québec, Canada;* [f] *Hamilton Health Sciences, McMaster University, Hamilton, Ontario, Canada;* [g] *Schlegel-University of Waterloo Research Institute for Aging, University of Waterloo, Waterloo, Ontario, Canada;* [h] *Cumming School of Medicine, University of Calgary, Libin Cardiovascular Institute, Calgary, Alberta, Canada;* [i] *Université de Sherbrooke, Sherbrooke, Québec, Canada;* [j] *University of Ottawa Heart Institute, Ottawa, Ontario, Canada;* [k] *St Michael's Hospital, Toronto, Ontario, Canada;* [l] *Royal Jubilee Hospital, University of British Columbia, Victoria, British Columbia, Canada;* [m] *University of British Columbia, Vancouver, British Columbia, Canada;* [n] *University of Manitoba, Winnipeg, Manitoba, Canada;* [o] *London Health Sciences, Western University, London, Ontario, Canada;* [p] *Chaleur Regional Hospital, Bathurst, New Brunswick, Canada;* [q] *Sunnybrook Health Sciences Centre, University of Toronto, Toronto, Ontario, Canada;* [r] *University of Calgary, Calgary, Alberta, Canada;* [s] *St Michael's Hospital, University of Toronto, Toronto, Ontario, Canada;* [t] *Division of Nephrology, Department of Medicine, University Health Network, University of Toronto, Toronto, Ontario, Canada;* [u] *University Health Network, Toronto, Ontario, Canada;* [v] *Paris University, UMR-S 942, Hôpital Lariboisière, Paris, France;* [w] *CHU Dumont UHC, Moncton, New Brunswick, Canada;* [x] *Royal Jubilee Hospital, Victoria, British Columbia, Canada;* [y] *St Boniface General Hospital, Winnipeg, Manitoba, Canada;* [z] *University of Saskatchewan, Saskatoon, Saskatchewan, Canada;* [aa] *Hamilton Health Sciences, Hamilton, Ontario, Canada;* [bb] *Duke Clinical Research Institute, Durham, North Carolina, USA;* [cc] *Centre Intégré de Santé et de Services Sociaux de Lanaudière - Centre Hospitalier de Lanaudière, Joliette, Québec, Canada;* [dd] *Institut universitaire de cardiologie et de pneumologie de Québec (IUCPQ), Université Laval, Québec, Québec, Canada;* [ee] *University of Colorado Anschutz Medical Campus, Aurora, Colorado, USA;* [ff] *St Joseph's Health Care, Western University, London, Ontario, Canada;* [gg] *QEII Health Sciences Centre, Halifax, Nova Scotia, Canada;* [hh] *Memorial University, St John's, Newfoundland and Labrador, Canada*

Received for publication November 3, 2019. Accepted November 26, 2019.

*Co-primary authors.

Corresponding author: Dr Eileen O'Meara, Université de Montréal, Institut de Cardiologie de Montréal, 5000 Bélanger, Montreal, Quebec H1T 1C8, Canada. Tel.: +1-514-376-3330 ×3947; fax: +1-514-593-2575.

E-mail: eileenomearamhi@gmail.com

The disclosure information of the authors and reviewers is available from the CCS on their guidelines library at www.ccs.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

https://doi.org/10.1016/j.cjca.2019.11.036

ABSTRACT

In this update, we focus on selected topics of high clinical relevance for health care providers who treat patients with heart failure (HF), on the basis of clinical trials published after 2017. Our objective was to review the evidence, and provide recommendations and practical tips regarding the management of candidates for the following HF therapies: (1) transcatheter mitral valve repair in HF with reduced ejection fraction; (2) a novel treatment for transthyretin amyloidosis or transthyretin cardiac amyloidosis; (3) angiotensin receptor-neprilysin inhibition in patients with HF and preserved ejection fraction (HFpEF); and (4) sodium glucose cotransport inhibitors for the prevention and treatment of HF in patients with and without type 2 diabetes. We emphasize the roles of optimal guideline-directed medical therapy and of multidisciplinary teams when considering transcatheter mitral valve repair, to ensure excellent evaluation and care of those patients. In the presence of suggestive clinical indices, health care providers should consider the possibility of cardiac amyloidosis and proceed with proper investigation. Tafamidis is the first agent shown in a prospective study to alter outcomes in patients with transthyretin cardiac amyloidosis. Patient subgroups with HFpEF might benefit from use of sacubitril/valsartan, however, further data are needed to clarify the effect of this therapy in patients with HFpEF. Sodium glucose cotransport inhibitors reduce the risk of incident HF, HF-related hospitalizations, and cardiovascular death in patients with type 2 diabetes and cardiovascular disease. A large clinical trial recently showed that dapagliflozin provides significant outcome benefits in well treated patients with HF with reduced ejection fraction (left ventricular ejection fraction $\leq$ 40%), with or without type 2 diabetes.

RÉSUMÉ

Dans cette mise à jour, nous nous intéressons à des thématiques précises ayant une pertinence clinique d'importance pour les fournisseurs de soins de santé qui traitent des patients atteints d'insuffisance cardiaque (IC), sur la base d'essais cliniques publiés après 2017. Notre objectif était d'examiner les données probantes et de fournir des recommandations et des conseils pratiques concernant la prise en charge des candidats aux différents traitements d'IC suivants : (1) la réparation de la valve mitrale par cathéter dans le cadre d'une IC avec une fraction d'éjection réduite; (2) un nouveau traitement pour l'amylose de la transthyrétine ou l'amyloïdose cardiaque à la transthyrétine; (3) l'inhibition du récepteur de l'angiotensine et de la névrilysine chez les patients atteints d'IC avec une fraction d'éjection préservée (ICFEP); et (4) les inhibiteurs du cotransporteur sodium-glucose pour la prévention et le traitement de l'IC chez les patients avec et sans diabète de type 2. Nous mettons l'emphase sur le rôle d'une thérapie médicale optimale encadrée par les lignes directrices et sur le rôle des équipes multidisciplinaires lorsqu'une réparation de la valve mitrale par cathéter est envisagée, ceci afin de garantir l'excellence dans l'évaluation et les soins portés à ces patients. En présence de signes cliniques manifestes, les fournisseurs de soins de santé devraient envisager l'éventualité d'une amylose cardiaque et procéder à un examen approprié. Le tafamidis est le premier agent dont une étude prospective a démontré qu'il remanie les effets d'une amylose cardiaque à transthyrétine chez les patients. L'utilisation du sacubitril/valsartan pourrait être bénéfique pour les sous-groupes de patients atteints d'ICFEP; toutefois, des données complémentaires sont nécessaires pour clarifier l'effet de ce traitement chez les patients atteints d'ICFEP. Les inhibiteurs du cotransporteur sodium-glucose réduisent le risque d'incidence de l'IC, les hospitalisations liées à l'IC et les décès d'origine cardiovasculaire chez les patients atteints de diabète de type 2 et de maladie cardiovasculaire. Un vaste essai clinique a récemment montré que la dapagliflozine procure des bénéfices importants sur le plan des répercussions chez les patients correctement traités atteints d'IC avec une fraction d'éjection réduite (fraction d'éjection du ventricule gauche $\leq$ 40 %), avec ou sans diabète de type 2.

The Canadian Cardiovascular Society (CCS) heart failure (HF) guidelines program provides guidance to clinicians, policy makers, and health systems as to the evidence supporting existing and emerging management of patients with HF. The 2019 update on clinical trial data is a brief set of guidelines incorporating new evidence from randomized controlled trials published after the 2017 update on topics of importance for health care providers in HF management. It updates the last version of the CCS HF guidelines on those specific topics.

The constitution and roles of the primary and secondary panels, systematic review strategy, and methods for formulating the recommendations are described at www.ccs.ca. The recommendations were developed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) standards.[1,2] Primary panelists were responsible for writing and reviewing the document, with writing participation of 3 secondary panelists and 6 external content experts.

The objective of this update was to highlight new clinical trial evidence on 4 topics of high importance in terms of changes and evolution in the care of patients with HF: (1) transcatheter mitral valve repair; (2) potential treatments for transthyretin amyloidosis (ATTR) or transthyretin cardiac amyloidosis (CA); (3) the role of angiotensin receptor-neprilysin inhibition in patients with HF and preserved ejection fraction (HFpEF); and (4) prevention of HF outcomes with sodium glucose cotransport (SGLT2) inhibitors. We collaborated with content experts on each topic who provided critical external input and perspective.

1. Percutaneous Mitral Valve Repair for Patients With HF and Reduced Ejection Fraction and Severe Functional Mitral Regurgitation

Functional mitral regurgitation (FMR) secondary to left ventricular (LV) dysfunction and dilatation is an important contributor to the high mortality[3] observed in patients with HF and reduced ejection fraction (HFrEF). Observational studies and 1 previous randomized trial[4] showed the potential benefits of surgical correction or percutaneous mitral valve repair (PMVR) for improving symptoms and promoting reverse remodelling. However, this has not been routinely recommended to date.[4-7] Such data have raised awareness regarding the importance of FMR on progression of HF and

the potential for treatment of FMR to improve outcomes. Although a number of technologies are in clinical development, edge-to-edge leaflet repair with the MitraClip system (Abbott Structural Heart) is currently the only Health Canada-approved device for PMVR.

In a previous retrospective observational study mitral interventions (either transcatheter or surgical) were compared with conservative management.[8] Conservative management in patients with FMR was associated with a higher mortality compared with PMVR (hazard ratio [HR], 1.79; 95% confidence interval [CI], 1.34-2.39), with no significant mortality difference identified between the PMVR and surgical arms (HR, 0.86; 95% CI, 0.54-1.38). Of note, the death rate was numerically higher for patients treated with PMVR vs surgery (33% vs 23%), in keeping with the higher mean **Euro**pean **S**ystem for **C**ardiac **O**perative **R**isk **E**valuation (EuroSCORE) II observed in this group of patients (8.9 vs 4.7; $P < 0.001$). Because of the nonrandomized observational study design, these findings are not conclusive with respect to the role of PMVR in patients with HF and severe FMR.

In 2018, 2 randomized controlled trials were published that compared the efficacy of PMVR using the MitraClip device (Abbott Structural Heart) in addition to guideline-directed medical therapy (GDMT) with GDMT alone in patients with FMR for whom mitral valve surgery was not deemed appropriate.[7,8] These trials differed with respect to patient characteristics and outcome definitions. The Percutaneous Repair with the **Mitra**Clip device for Severe **F**unctional/Secondary Mitral **R**egurgitation (MITRA-FR) 9 trial enrolled 304 patients with at least moderate-severe FMR (mean effective regurgitant orifice area of 31 mm^2) and severe LV dilatation (indexed left ventricular end-diastolic volume of 135 ± 37 mL/m^2). PMVR did not provide a benefit in survival over GDMT alone (24.3% vs 22.4%; HR, 1.11; 95% CI, 0.69-1.77) or in the rate of unplanned hospitalization for HF (HHF; 48.7% vs 47.4%; HR, 1.13; 95% CI, 0.81-1.56) during the 1-year follow-up period.

In contrast, the **C**ardiovascular **O**utcomes **A**ssessment of the MitraClip **P**ercutaneous **T**herapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT)[10] trial enrolled 614 patients after optimization of GDMT (only one-third of the screened patients were eventually randomized; Table 1) with longer (2-year) follow-up. Trial participants had higher brain natriuretic peptide (BNP) concentrations (mean, 1043 vs 800 ng/L), smaller indexed LV end-diastolic volume (101 ± 34 mL/m^2), and more severe FMR (mean effective regurgitant orifice area, effective regurgitant orifice area of 40.5 mm^2 compared with the MITRA-FR population).[11,12] Patients who received PMVR had lower all-cause mortality at 2 years compared with GDMT alone (29.1% vs 46.1%; HR, 0.62; 95% CI, 0.46-0.82; $P < 0.001$). PMVR also reduced the risk of HF hospitalizations (35.8% vs 67.9% per patient-year; HR, 0.53; 95% CI, 0.4-0.7; $P < 0.001$) and resulted in significant improvements in Kansas City Cardiomyopathy Questionnaire (KCCQ) quality of life scores and 6-minute walk distances.

Taken together, these 2 trials suggest that PMVR has the potential to reduce mortality and HF hospitalization for selected patients with symptomatic moderate to severe or severe (3+ to 4+) FMR despite optimal GDMT. For patients with moderate FMR or severely dilated left ventricles, the benefits, if any, remain unproven.[9] Some have suggested that the lack of demonstrable benefit with PMVR in the MITRA-FR trial might have been attributable to the extent of LV dilatation and negative remodelling in the context of less severe FMR and the absence of forced medical GDMT optimization. Conversely, in the COAPT trial,[10] intervention occurred earlier in the course of the disease process, with optimized GDMT having already been in place (Table 1).

A third randomized controlled trial of GDMT vs PMVR therapy, a European study, A **R**andomize**d** **S**tudy of t**h**e Mitr**a**Cli**p** D**e**vice in **H**eart **F**ailure Patients With Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF 2, NCT02444338) is currently enrolling patients with results expected by the end of 2021. Finally, a trial designed to evaluate the potential benefits of early transcatheter intervention in HFrEF patients with less severely dilated left ventricles and moderate FMR, the **Ev**aluation of **O**utcomes of Transcatheter Mitral Valve Repair for the Treatment of **L**ow Ejection Fraction and Moderate Functional Mitral **V**alv**e** Regurgitation in **H**eart **F**ailure (EVOLVE-HF; NCT03705312) trial, is currently under way. These trials might further refine our understanding of optimal patient selection and timing for intervention.

Neither the COAPT nor the MITRA-FR trials included a surgical arm. Whether surgery or PMVR results in similar clinical benefit in patients with FMR is being addressed in the **M**ulticenter, Randomized, Controlled Study to Assess Mitral V**a**lve Recons**t**ruc**t**ion for Advan**c**e**d** Insufficiency of Functional o**r** Isc**h**emic **Orig**i**n** (MATTERHORN) randomized trial (NCT02371512) including 210 participants, with the study completed in December 2019.

RECOMMENDATION

1. We recommend that maximally tolerated GDMT, including cardiac resynchronization therapy and revascularization where appropriate, be implemented before consideration of PMVR for patients with HFrEF and severe FMR (Strong Recommendation, High-Quality Evidence).
2. We suggest that patients with symptomatic HF (HFrEF) despite maximal GDMT and severe mitral regurgitation be evaluated for PMVR (Weak Recommendation, Moderate-Quality Evidence).
3. We recommend that a multidisciplinary dedicated heart team (including interventionalists, cardiac surgeons, imaging specialists, and HF specialists) perform the evaluation and care of potential candidates for PMVR (Strong Recommendation, Low-Quality Evidence).

Values and preferences. These recommendations emphasize optimization of all other established therapies for HFrEF and FMR before consideration of PMVR. They also highlight the role of optimizing GDMT (because this has been clearly associated with improved outcomes)[13] vs reduction in FMR severity per se. The use of multidisciplinary teams reflects the approach taken in the clinical trials to ensure excellent evaluation, care, and follow-up associated with PMVR.

Practical tip. Caution should be used when treating FMR in patients with HFrEF because the encouraging results from the COAPT trial[10] must be considered in the context of new medical treatments that were not frequently incorporated into clinical practice when the trial was performed (sacubitril-valsartan, ivabradine),[14] as well as treatments currently under study in patients with HFrEF.

Practical tip. The identification of candidates with HFrEF and FMR most likely to benefit from the PMVR procedure might be informed by the characteristics of patients enrolled in the COAPT and MITRA-FR studies (Table 1). Patients with severe LV dilatation (typically LV end diastolic dimension $>$ 70 mm) and less than severe mitral regurgitation might be poor candidates for MitraClip (Abbott Structural Heart).

Practical tip. Patients with FMR should first receive maximally tolerated GDMT, including pharmacological and nonpharmacological HF therapies (eg, cardiac resynchronization therapy where applicable) for a reasonable minimum period of time (eg, 3 months), before PMVR is considered.

Practical tip. Patients considered for PMVR should be referred to centres with:

- Experience in the evaluation of patients with advanced HF;
- High volumes of patients with valve disease managed medically and surgically;
- High likelihood of achieving the volume of PMVR (eg, 2-4 per month) required for developing and maintaining competence in well selected patients.[15,16]

2. Treatment of CA: Focus on Transthyretin CA

A comprehensive CCS/Canadian Heart Failure Society (CHFS) joint position statement on the evaluation and management of CA is forthcoming and will include GRADE standard recommendations on the diagnostic workup and therapeutic approaches for management of this disease. For the purposes of this update, practical tips are provided in the context of recent clinical trial evidence for the management of a subtype of amyloidosis known as ATTR.

Amyloidosis is a group of heterogeneous disorders in which a specific precursor protein pathologically misfolds, aggregates, and forms amyloid fibrils that deposit extracellularly within various organs including the heart, resulting in organ failure.[16] CA is a form of infiltrative cardiomyopathy that develops when amyloid deposits infiltrate myocardial tissue. This infiltrative process results in progressive ventricular stiffness, wall thickening, and diastolic filling abnormalities, which typically manifest as HFpEF and restrictive physiology.[17] When the disease is severe and advanced, systolic dysfunction might also be seen.[18]

The most common subtypes of CA are ATTR and the immunoglobulin light chain amyloidosis (known as AL amyloidosis). ATTR is further categorized into a hereditary form, due to one of numerous disease-causing genetic mutations and the "wild type" ATTR, in which a mutation is not present.[19,20] Rarely, other types of amyloid proteins can affect the heart, including amyloid A, apolipoprotein A1, heavy chain, and atrial natriuretic peptide. Because recent clinical trial evidence applies only to the pharmacologic treatment of ATTR-CA, it is of the utmost importance to accurately identify the amyloid subtype to initiate specific treatment and avoid inappropriate application of therapy.[21]

Recognizing the possibility of CA

It must be emphasized that the clinical phenotypes of all forms of CA are similar, which makes distinction between subtypes difficult using clinical assessment alone. When CA

Table 1. Comparison of trial patients and outcomes in the MITRA-FR and COAPT studies

Variable	MITRA-FR	COAPT
Trial and patient characteristics		
Comparison	MitraClip vs GDMT	MitraClip vs GDMT
Heart team evaluation and GDMT	Heart team evaluation, GDMT not described over time	Heart team evaluation, GDMT described over time
Study period	2013-2017	2012-2017
Follow-up period, year(s)	1 (2)*	2
Patients enrolled/patients considered for trial, n (%)	307/452 (67.9)	665/1576 (42.2)
Mean LVEDVI (SD), mL/m^2	135 (35)	101 (34)
Mean baseline EROA (SD), mm^2	31 (10)	41 (15)
Mean LVEF (SD), n %	33 (7)	31 (9)
Outcomes		
Procedural complications†	21/144 (14.6)	25/293 (8.5)
MR grade $\geq$ 2 at discharge	30/123 (24.4%)	46/260 (17.7)
MR grade $\geq$ 2 at 1 year	48/97 (49.5)	65/210 (31.0)
All-cause mortality/HF hospitalization at 1 year, n (%)		
MitraClip arm	83/151 (54.6)	102/302 (33.9)
GDMT arm	78/152 (51.3)	145/312 (46.5)
P	0.53	$<$ 0.001

MitraClip is from Abbott Structural Heart.

COAPT, **C**ardiovascular **O**utcomes **A**ssessment of the MitraClip **P**ercutaneous **T**herapy for Heart Failure Patients With Functional Mitral Regurgitation; EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; HF, heart failure; LVEDVI, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; MITRA-FR, Percutaneous Repair with the MitraClip device for Severe Functional/Secondary Mitral Regurgitation; MR, mitral regurgitation.

*At this time, the 2-year follow-up data have been presented but are not published.

†MitraClip group only.

Modified from Tang, et al.[57] with permission from the American Medical Association.

is suspected, AL amyloidosis should be ruled out using serum free light chains (kappa and lambda), and serum and urine protein electrophoresis with immunofixation. The presence of light chains alone is not specific for AL-CA because > 20% of patients with ATTR have an unrelated monoclonal gammopathy of unknown significance.[22] In this scenario, tissue biopsy (bone marrow or endomyocardial) with immunohistochemistry or mass spectrometry is necessary to determine the subtype of CA. Further, when AL amyloidosis has been ruled out, technetium-labelled scintigraphy such as pyrophosphate scan can be used to help confirm a diagnosis of ATTR-CA.[23-25] This imaging modality is > 99% sensitive and 86% specific for ATTR CA, with false positive tests occurring almost exclusively in the setting of AL-CA. In one study, the presence of a positive scan in the absence of a monoclonal gammopathy had 100% specificity and positive predictive value for ATTR-CA.[26]

Practical tip. In the setting of undifferentiated CA, the presence of light chains does not confirm the diagnosis of AL-CA because monoclonal gammopathy of unknown significance and ATTR-CA can coexist. In such settings, tissue biopsy is frequently necessary to exclude AL-CA.

Practical tip. Technetium-labelled scintigraphy should be performed, where available, to diagnose ATTR-CA when plasma cell dyscrasias have been ruled out.

Until recently, treatment of ATTR-CA was mostly supportive in nature with a median survival of 3.5 years[27] after diagnosis. Different therapeutic modalities have been investigated in recent years using transthyretin stabilizers (eg, diflunisal and tafamidis), suppressors of ATTR synthesis (gene silencers), and amyloid fibrils degraders (doxycycline with tauroursodeoxycholic acid or ursodeoxycholic acid and epigallocatechin 3-gallate found in green tea extracts).[28-33] Historically,[31] most studies that have investigated these drugs have been small and observational in nature and used surrogate end points. The recently published Transthyretin Amyloidosis Cardiomyopathy Trial (ATTR-ACT) randomized 441 patients with wild type or mutant (hereditary) ATTR-CA to either tafamidis, a transthyretin tetramer stabilizer, or placebo, and were followed for 30 months.[34] At the end of the study, patients who received tafamidis had significantly lower all-cause mortality (HR, 0.70; 95% CI, 0.51-0.96) and reduced cardiovascular hospitalizations (HR, 0.68; 95% CI, 0.56 to 0.81). Tafamidis also significantly reduced the rate of decline in functional capacity and quality of life ($P < 0.001$ for both outcomes).[34]

As of the time of writing, tafamidis is not approved by Health Canada for the treatment of ATTR-CA (it was recently approved by the US Food and Drug Administration). However, it is the first agent that has been shown in a prospective study to alter patient outcomes by improving survival and reducing cardiovascular hospitalizations. The CCS/CHFS joint position statement will address formal recommendations on the use of tafamidis and other therapeutic options for ATTR-CA on the basis of the totality of published evidence. Pending the availability of ATTR-CA-specific treatments in Canada, and the forthcoming comprehensive amyloid recommendations, it is reasonable to consider the following practical tips.

Practical tip. Patient selection for tafamidis should reflect the inclusion criteria for the major randomized controlled clinical trial that showed clinical benefits of tafamidis over placebo with respect to mortality and cardiovascular hospitalization, including established ATTR-CA and objective evidence of HF (with elevated natriuretic peptides where available).

Practical tip. Patients with New York Heart Association (NYHA) class IV symptoms or severe functional disability, measured using a 6-minute walk test < 100 m, were excluded from ATTR-ACT and should not routinely be considered for treatment with tafamidis.

Practical tip. Subgroup analysis from the ATTR-ACT trial suggested that the reduction in cardiovascular hospitalizations seen with tafamidis might be limited to patients with less severe symptoms (NYHA class I or II).

Practical tip. Because of the complexity in diagnosing CA and the potential for offering advanced or experimental treatment options, consideration should be given to referring patients with CA to experienced centres.

Practical tip. Other agents are currently under investigation, which might modify current treatment recommendations.

3. New Evidence for Angiotensin Receptor Neprilysin Inhibitors in Patients With HFpEF

HFpEF is rising in prevalence and is associated with significant morbidity and mortality.[35,36] Although evidence-based and mortality-reducing therapies exist for HFrEF, no therapies have shown a mortality benefit in those with an ejection fraction (EF) > 40%. In PARAMOUNT (**P**rospective Comparison of **ARNI** with **A**RB on **M**anagement **o**f Heart Fail**u**re With Preserved Ejectio**n** Frac**t**ion) (NCT02371512), a phase II trial with patients with HFpEF, sacubitril/valsartan reduced N-terminal pro−B-type natriuretic peptide levels and left atrial enlargement and also improved NYHA class compared with valsartan.[37] **P**rospective Comparison of **ARNI** with **A**RB **G**lobal **O**utcomes in Heart Failure With Preserved Ejectio**n** Fraction (PARAGON-HF) was a randomized double blind active comparator trial that tested the hypothesis that sacubitril/valsartan compared with valsartan would reduce the composite primary end point of total (first and recurrent) HF hospitalizations and cardiovascular death.[38] After a run-in phase, patients were randomized to sacubitril/valsartan 97/103 mg twice daily vs valsartan 160 mg twice daily. Secondary end points included improvement in NYHA functional class at 8 months, changes in KCCQ clinical summary score at 8 months, time to first occurrence of worsening renal function, and time to all-cause mortality.

Eligible patients were 50 years of age or older with symptomatic HF (NYHA II-IV) and an EF ≥ 45%. Inclusion criteria also specified treatment with diuretics for at least 30 days before enrollment as well as structural heart disease identified as left atrial enlargement or LV hypertrophy using echocardiography. Natriuretic peptide thresholds were stratified for the presence or absence of atrial fibrillation.[39] In an attempt to capture the total burden of disease, the primary analysis incorporated total HF hospitalizations and cardiovascular death. In total 4822 patients were randomized, and treatment discontinuation for any reason other than death occurred in 25% of the sacubitril/valsartan arm vs 27% in the valsartan arm. The mean age in this trial was 73 years and

52% were female. Most patients had NYHA class II symptoms. Before randomization, 87% of patients in both arms were treated with either an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB). All baseline characteristics were balanced with the exception of mineralocorticoid receptor antagonists use, which was more common in the valsartan arm (27.1% vs 24.6%). In the PARAGON-HF trial, 1009 events were observed, equivalent to 14.6 per 100 patient-years in the valsartan arm in contrast to 894 events with a rate of 12.8 per 100 patient-years in the sacubitril/valsartan arm. This equated to a 13% relative risk reduction in the sacubitril/valsartan arm that did not meet clinical significance (95% CI, 0.75-1.01; $P = 0.06$). The reduction in the primary end point was driven predominantly by a reduction in HF hospitalizations, which were reduced by 15% and also narrowly missed statistical significance ($P = 0.06$). The KCCQ score was improved greater than 5 points more often in the sacubitril/valsartan group (odds ratio, 1.30; 95% CI, 1.04-1.61; $P = 0.02$). Worsening renal function defined by a composite renal end point was significantly less frequent in the sacubitril/valsartan arm. A similar safety profile was seen in PARAGON-HF as was seen in previous studies of sacubitril/valsartan in patients with HFrEF.[40] In a multivariable model of prespecified subgroups that incorporated all interaction terms, only sex and LV EF (LVEF) appeared to modify the treatment effect. Women achieved a significant 27% overall reduction in the primary end point, and patients at or below the trial median LVEF of 57% achieved a 22% reduction in primary end point. The *P* values for both were significant in multivariable interaction testing.

In summary, in a comparison of sacubitril/valsartan with valsartan in HFpEF patients, PARAGON-HF showed a modest but nonsignificant 13% reduction in the primary outcome, which was driven by a reduction in first and recurrent HF hospitalizations. In secondary end point analysis, improvement in quality of life and renal function suggested potential benefits with sacubitril/valsartan compared with valsartan. The data further suggest heterogeneity in the treatment response with greater benefit in women and in individuals with a lower LVEF.

Although these results are intriguing, they should be considered hypothesis-generating; important patient subgroups with HFpEF might benefit from sacubitril/valsartan treatment, but further data are needed to clarify the effect of this therapy in patients with HFpEF. Key outstanding issues to be addressed include:

- More granular understanding of the biological and pathophysiological differences in HFpEF according to sex.
- Further analysis of the interaction between sex and LVEF.
- LVEF thresholds at which clinically important benefits of angiotensin receptor-neprilysin inhibition are seen.
- Possible heterogeneity of treatment effect according to etiology and/or phenotype.

The statistically negative results of the PARAGON-HF primary end point analysis preclude any recommendation for the general use of sacubitril/valsartan in patients with HFpEF. The PARAGON-HF trial has provided a number of interesting insights; further analysis and investigation might inform future specific recommendations on the management of HFpEF.

4. New Evidence for SGLT2 Inhibitors and HF

SGLT2 inhibitors lead to a reduction in plasma glucose by inhibiting renal tubular glucose reabsorption, with resultant glucosuria. These glycemia-related changes are also associated with natriuresis, an osmotic diuresis, modest weight loss, an increase in hematocrit, and a reduction in blood pressure. All of these effects represent potentially favourable changes that might lead to a reduction in incident HF in patients with type 2 diabetes, as initially shown in the landmark **Empa**gliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients - **R**emoving **E**xcess **G**lucose (EMPA-REG OUTCOME) trial.[41] In 2017, the CCS HF guidelines[15] recommended the use of SGLT2 inhibitors for prevention of HF events in patients with type 2 diabetes and known history of cardiovascular disease. In view of the rapidly evolving research on this topic, we have updated our recommendations.

The SGLT2 inhibitor empagliflozin was the first glucose-lowering drug to show an improvement in cardiovascular outcomes in a large randomized controlled clinical trial.[42] The EMPA-REG OUTCOME trial randomized 7020 patients with type 2 diabetes and established cardiovascular disease (with estimated glomerular filtration rate [eGFR] $>$ 30 mL/min/1.73 m^2) to receive either empagliflozin 10 mg or 25 mg or placebo. The study showed a statistically significant reduction in the composite outcome of cardiovascular death or HHF (HR, 0.83; 95% CI, 0.73-0.95; $P = 0.005$) in the empagliflozin group vs placebo. A prespecified outcome, adjudicated HHF, was also significantly reduced with empagliflozin, with an HR of 0.73 (95% CI, 0.61-0.88).[42] The benefit of empagliflozin was observed in patients with and without an investigator-reported history of HF, and unrelated to baseline level of renal function (eGFR) or conventional risk factors, such as A1c, blood pressure, or lipids.[41]

The **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy—**R**enal (CANVAS-R) Program was the second major study of an SGLT2 inhibitor to show cardiovascular benefit in patients with type 2 diabetes.[43] In total, 10,142 patients with type 2 diabetes (eGFR $>$ 30 mL/min/1.72 m^2) with established cardiovascular disease or aged $>$ 50 years with $\geq$ 2 risk factors for cardiovascular disease were randomized to receive canagliflozin (either 100 or 300 mg/d), or placebo.[44] The **Can**agliflozin Cardio**v**ascular **A**ssessment **S**tudy (CANVAS) Program also showed a 33% reduction in HF hospitalization with canagliflozin therapy (HR, 0.67; 95% CI, 0.52-0.87). A subsequent analysis[45] showed that this benefit occurred in patients with and without a preexisting atherosclerotic cardiovascular disease.

In the **D**apagliflozin **E**ffect on **C**ardiovascu**lar** **E**vents (DECLARE)-**T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) 58 study,[46] dapagliflozin vs placebo was evaluated in 17,160 patients, 10,186 of whom did not have documented existing atherosclerotic cardiovascular disease.[47] Furthermore, unlike

the previous studies, patients with a creatinine clearance of 60 mL or more per minute were enrolled. The primary safety outcome was a composite of major adverse cardiovascular events (MACE), defined as cardiovascular death, myocardial infarction, or ischemic stroke. The primary efficacy outcomes were MACE and a composite of cardiovascular death or HHF. The rates of MACE were not statistically different (HR, 0.93; 95% CI, 0.84-1.03; $P = 0.17$), however, the composite of cardiovascular death or HHF was reduced (HR, 0.83; 95% CI, 0.73-0.95; $P = 0.005$). The latter finding was driven primarily by a reduction in HHF (HR, 0.73; 95% CI, 0.61-0.88) and similar relative benefits were observed in patients with or without preexisting atherosclerotic cardiovascular disease or HF.

In a secondary analysis of the DECLARE study, 671 patients were noted to have an LVEF < 45% (documented in patients with available echocardiograms) whereas 1316 had a history of HF without a reduced EF (808 with a documented EF ≥ 45% and 508 without a documented EF).[48] In this analysis, subjects with LVEF < 45% treated with dapagliflozin derived a larger decrement of cardiovascular death or HF hospitalization (HR, 0.62; 95% CI, 0.45-0.86) compared with those without known lower LVEF (HR, 0.88; 95% CI, 0.76-1.02; P interaction = 0.046), the difference driven by a reduction in cardiovascular mortality (HR, 0.55; 95% CI, 0.34-0.90). In addition, only those with lower EF treated with dapagliflozin experienced a reduction in all-cause mortality (HR, 0.59; 95% CI, 0.40-0.88; $P = 0.01$). Because these analyses were not prespecified, the findings are hypothesis-generating and require confirmation in prospective studies of well characterized patients with established HF.

Preexisting renal disease is a known risk factor for cardiovascular death and HF hospitalization. Recently the results of **C**anagliflozin and **R**enal **E**vents in **D**iabetes With **E**stablished **N**ephropathy **C**linical **E**valuation (CREDENCE),[49] the first renal-dedicated SGLT2 inhibitor trial has been reported. In this trial, 4401 patients with type 2 diabetes and chronic albuminuric renal disease (eGFR 30-90 mL/min/1.73 m^2) were randomized to receive placebo or canagliflozin 100 mg/d. Importantly, all patients were required to be receiving background stable doses of ACE inhibitor or ARB for at least a 4-week period. The trial was stopped early for efficacy at a median follow-up of 2.6 years and showed a 30% lower rate in the primary outcome of renal progression or cardiovascular death (HR, 0.70; 95% CI, 0.59-0.82; $P = 0.00001$). In addition, lower rates of HHF (HR, 0.61; 95% CI, 0.47-0.80; $P < 0.001$) were observed. There was no significant between group difference in the risk of cardiovascular death (HR, 0.78; 95% CI, 0.61-1.00; $P = 0.05$) or in the risk of death from any cause (HR, 0.83; 95% CI, 0.68-1.02). These findings confirm the renal benefits observed in subanalyses from the earlier prevention trials and extend the HF benefits of SGLT2 inhibitors to patients with albuminuric chronic kidney disease.

The TIMI Study Group recently published a systematic review and meta-analysis of 3 large trials of SGLT2 inhibitors: EMPA-REG OUTCOME, the CANVAS Program and DECLARE-TIMI 58.[50] The meta-analysis included 34,322 patients, of whom, 60.2% had established cardiovascular disease. Overall, patients treated with SGLT2 inhibitors experienced a lower rate of nonfatal myocardial infarction, stroke, or cardiovascular death (HR, 0.89; 95% CI, 0.83-0.96; $P = 0.0014$), however, this benefit was limited to patients with established cardiovascular disease. The composite rate of cardiovascular death or HHF was reduced by 23% (HR, 0.77; 95% CI, 0.71-0.84; $P < 0.001$) and the rate of HHF alone was reduced by 31% (HR, 0.69; 95% CI, 0.61-0.7, $P < 0.001$) in patients who received SGLT2 inhibitors.[50] The benefits of SGLT2 inhibitors on preventing hospitalizations for HF were observed to a greater degree in those with mild to moderate renal dysfunction and with a history of HF, although only 10%-15% of patients with diabetes included in this meta-analysis had a history of HF.

Taken together, the available data clearly show the efficacy of SGLT2 inhibition to reduce incident HF in a broad group of patients with type 2 diabetes.

Established HF due to reduced LVEF

The landmark study to evaluate the effect of **Dapa**gliflozin on Incidence of Worsening **H**eart **F**ailure or Cardiovascular Death in Patients with CHF (DAPA-HF) has recently been pubslished.[51] In this large, international, multicentre, double-blind, parallel, randomized, placebo-controlled trial 4744 patients were enrolled with stable class II-IV HFrEF and receiving optimal medical therapy and serum N-terminal pro-B-type natriuretic peptide > 600 pg/mL (> 400 if hospitalized within the past year, > 900 if atrial fibrillation or flutter present) and eGFR > 30 mL/min/1.73 m^2 to either placebo or dapagliflozin 10 mg daily. Baseline characteristics and medical therapy of study participants in this study were well balanced between the two groups and were similar to those of other recently reported large randomized trials of HFrEF. Importantly, patients with (45%) and without (44%) diabetes were included in this event-driven study. Over a median 18-month follow-up, treatment with dapagliflozin reduced the primary end point, the composite of time to first worsening of HF (hospitalization or urgent visit requiring intravenous therapy for HF) or death due to cardiovascular causes (386 vs 502; HR, 0.74; 95% CI, 0.65-0.85; $P < 0.001$). This was driven by hospitalization (237 vs 326; HR, 0.70; 95% CI, 0.59-0.83) and cardiovascular death (227 vs 283; HR, 0.82; 95% CI, 0.69-0.98). There were also fewer total deaths observed in the dapagliflozin group (276 vs 329; HR, 0.83; 95% CI, 0.71-0.97). In subgroup analysis, only increasing NYHA class was associated with attenuated efficacy of dapagliflozin, although this finding might have been because of chance because no such interaction of outcomes was observed in the prespecified groups with increased baseline natriuretic peptides, those with lower EF, or those with previous hospitalization.

Notably, the DAPA-HF study participants were well treated, with > 90% ACE/ARB and β-blocker use and > 70% mineralocorticoid use at baseline. No treatment interaction with baseline medical therapy was seen, including with angiotensin receptor-neprilysin inhibitors (ARNI), whereas the primary end point showed statistical consistency with the overall trial (HR, 0.75; 95% CI, 0.50-1.10), which reinforces the efficacy of SGLT2 inhibitors in the setting of contemporary optimal medical therapy. Treatment with ARNI was used in approximately 11% of patients at baseline

considering the timing of recruitment for this trial in relation to the publication of the **P**rospective Comparison of **ARN**i With **A**CEi to **D**etermine **I**mpact on **G**lobal **M**ortality and Morbidity in **H**eart **F**ailure (PARADIGM-HF) trial.

The DAPA HF study included most participants (approximately 58%) who did not have concomitant diabetes. Subgroup analysis revealed a nearly identical reduction in the primary end point among nondiabetic patients (HR of 0.73 [95% CI, 0.60-0.88] in those without diabetes vs an HR of 0.75 [95% CI, 0.60-0.90] in those with diabetes). As such, SGLT2 inhibition with dapagliflozin has been shown for the first time to reduce morbidity and mortality in nondiabetic patients with HFrEF. Analyses of adverse events of interest in all patients, including volume depletion, adverse renal events, hypoglycemia, amputation, and ketoacidosis showed no increase in the dapagliflozin arm, reinforcing the favourable safety profile of this treatment in patients with HFrEF. Table 2 summarizes the results of large published clinical trials regarding the impact of SGLT2 inhibitors on heart failure and other cardiovascular outcomes.

Future directions

Although potential theories have been advanced to explain the benefits observed with SGLT2 inhibitors in preventing HF events, including reduction of preload via osmotic diuresis, lowering of afterload, alteration of myocardial energy substrate toward a more efficient glucose oxidation, modulation of renal sympathetic afferent tone, or direct reduction in myocardial mass, precise mechanisms associated with the clinical effect remain unknown. Further work in this area, including mechanistic studies in patients with established and treated HF, are needed and will be forthcoming. In addition, effective dosage of SGLT2 inhibitors is not yet known.[52-55]

There are several other outstanding issues regarding the effect of SGLT2 inhibitors and prevention of HF events. First, additional data are required to clarify the relative effect of SGLT2 inhibitors according to LVEF and according to disease severity. Ongoing HF outcome studies should address existing evidence gaps across a range of EF values and clinical status. Accordingly, the **Emp**agliflozin Outcom**e** T**r**ial in Patients With Chr**o**nic Hea**r**t Failure With **Reduced** Ejection Fraction (EMPEROR-Reduced), the **Emp**agliflozin **O**utcome Trial in Patients With Chronic Heart Failure With Preserved Ejection Fraction (EMPEROR PRESERVED), the **D**apagliflozin **E**valuation to Improve the **Live**s of P**r**eserved Ejection Fraction Heart Failure (DELIVER) trials, and the Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure (SOLOIST-WHF) trial will further clarify the role of these agents in a broad spectrum of HF patients. For now, uncertainty remains regarding potential benefits of SGLT2 inhibitors for the following patient subgroups:

- Preserved or midrange LVEF;
- Acute HF;
- Isolated right HF or pulmonary hypertension;
- Advanced HF;
- Patients taking target doses of concomitant HF therapies including mineralocorticoid receptor antagonists, sacubitril-valsartan, ivabradine;
- Stage 4 and 5 kidney disease.

RECOMMENDATION

5. **Updated.** We recommend SGLT2 inhibitors, such as empagliflozin, canagliflozin or dapagliflozin, be used for treatment of patients with type 2 diabetes and atherosclerotic cardiovascular disease to reduce the risk of HF hospitalization and death (Strong Recommendation, High-Quality Evidence).
6. **New.** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with type 2 diabetes aged $>$ 50 years with additional risk factors for atherosclerotic cardiovascular disease to reduce the risk of HHF (Strong Recommendation, High-Quality Evidence).
7. **New.** We recommend SGLT2 inhibitors, such as canagliflozin, be used in patients aged $>$ 30 years with type 2 diabetes, and macroalbumineric renal disease, to reduce the risk of HF hospitalization and progression of renal disease (Strong Recommendation, High-Quality Evidence).
8. **New.** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF ($\leq$ 40%) and concomitant type 2 diabetes, to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (Strong Recommendation, High-Quality Evidence).
9. **New.** We recommend SGLT2 inhibitors, such as dapagliflozin be used in patients with mild to moderate HF due to reduced LVEF ($\leq$ 40%) and without concomitant diabetes, to improve symptoms and quality of life and to reduce the risk of hospitalization and cardiovascular mortality (Conditional Recommendation, High-Quality Evidence).

Values and preferences. These recommendations place weight on the results of multiple large, randomized, placebo-controlled trials, which have tested 3 different SGLT2 inhibitors. These trials have conclusively shown that SGLT2 inhibitors reduce the risk of the incidence of HF, HF-related hospitalizations, and cardiovascular death in patients with type 2 diabetes and established cardiovascular disease. A strong recommendation for these agents in patients with type 2 diabetes with multiple risk factors for but without evidence of established cardiovascular disease is made despite the lack of reduction in cardiovascular death.

We considered the large relative benefit observed, the strong clinical priority for reduction of HF hospitalization, and the lack of any similar benefits associated with other antidiabetic agent in preventing incident HF.

The strong recommendation for SGLT2 inhibitors for patients with type 2 diabetes and HFrEF reflects the large clinical benefit observed in this population and the current availability of these agents for patients with type 2 diabetes. A second, conditional recommendation for patients with HFrEF without concomitant diabetes is made because regulatory approval for this patient population in Canada is not currently available, and further data from the DAPA-HF trial regarding

Table 2. Clinical trial results regarding the impact of SGLT2 inhibitors on HF and other cardiovascular outcomes

Relevant clinical trial	Number of patients	Hospitalization for HF Only, HR (95% CI)	Hospitalization for HF and cardiovascular death, HR (95% CI)	Major adverse cardiac events, HR (95% CI)	Cardiovascular death, HR (95% CI)
Type 2 diabetes and multiple risk factors (no known cardiovascular disease)					
EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58	13,672	0.64 (0.48-0.85)	0.84 (0.69-1.01)	1.00 (0.87-1.16)	1.02 (0.80-1.30)
Type 2 diabetes and known cardiovascular disease					
EMPA-REG OUTCOME, CANVAS-R, DECLARE-TIMI 58	20,650	0.71 (0.62-0.82)	0.76 (0.69-0.84)	0.86 (0.80-0.93)	0.80 (0.71-0.91)
Type 2 diabetes and albuminuric chronic kidney disease					
CREDENCE	4401	0.69 (0.57-0.83)	0.61 (0.47-0.80)	0.80 (0.67-0.95)	0.78 (0.61-1.00; $P = 0.0502$)
Stable heart failure and reduced left ventricular ejection fraction irrespective of diabetes					
DAPA-HF	4744	0.70 (0.59-0.83)	0.75 (0.65-0.85)	N/A	0.82 (0.69-0.98)

CANVAS-R, **CAN**agliflozin cardio**V**ascular **A**ssessment **S**tudy—**R**enal; CI, confidence interval; CREEDENCE, **C**anagliflozin and **R**enal **E**vents in **D**iabetes With **E**stablished **N**ephropathy **Cl**inical **E**valuation; DAPA-HF, **Dapa**gliflozin on Incidence of Worsening **H**eart **F**ailure or Cardiovascular Death in Patients with CHF; DECLARE-TIMI 58, **D**apagliflozin **E**ffect on **C**ardiovascu**lar** **E**vents -**T**hrombolysis **i**n **M**yocardial **I**nfarction 58; EMPA-REG OUTCOME, **Empa**gliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients - **R**emoving **E**xcess **Gl**ucose; HF, heart failure; HR, heart rate; N/A, not available.

glucose status in those without diabetes might be clinically impactful.

These medications are well tolerated and associated with an acceptable side effect profile within the clinical trials studied, with a low risk of genital mycotic infections, diabetic ketoacidosis or hypoglycemia, provided other antidiabetic medications are adjusted appropriately. The efficacy of this medication class is unproven at eGFR levels < 30 mL/min/1.73 m^2. Table 3 summarizes practical issues surrounding initiation of SGLT2 inhibitors.

Practical tip. It is worth emphasizing that SGLT2 inhibitors are currently contraindicated for patients with type 1 diabetes.

Practical tip. The most common adverse effect of this class of medications are genital mycotic infections (GMIs). Women (10%-15% risk), those with previous GMIs, and uncircumcised men are at highest risk. Typically, GMIs can be managed with antifungal drugs and do not require discontinuation of therapy.

Practical tip. SGLT2 inhibitors might result in temporary reduction of eGFR up to 15%, which generally resolves within 1-3 months. SGLT2 inhibitors have also been associated with acute kidney injury and increased monitoring is warranted in those at risk.

Practical tip. SGLT2 inhibitors do not cause hypoglycemia in the absence of concomitant insulin and/or secretagogue therapy. Background therapies might need to be adjusted to prevent hypoglycemia.

Practical tip. SGLT2 inhibitors should be held in the setting of concomitant dehydrating illness as part of "Sick Day" management. Patients should be educated on "Sick Day" management.[56]

Practical tip. These agents have been associated with diabetic ketoacidosis (incidence 0.1%). Patients might present

Table 3. Practical issues surrounding initiation of SGLT2 inhibitors

Issue	Concomitant diabetes	No concomitant diabetes
Glycemic control	• Collaboration with diabetes team if available • Concomitant insulin or sulfonurea therapy: no adjustment necessary with poorly controlled glucose, consider 25% reduction of each medication • Reinforce glucose monitoring • SGLT2 inhibitors contraindicated in type 1 diabetes	No concerns for hypoglycemia
Volume control	• Euvolemia: optional to reduce loop diuretic by 25-50% • Volume overloaded: no need to reduce concomitant loop diuretic • Hypovolemia: do not start until volume depletion corrected	Same as with diabetes
Renal function	Safe with eGFR 30 mL/min/1.73 m^2. Early 20% decrease in eGFR acceptable. With larger change in eGFR, evaluate clinically, consider reduction of loop diuretic	Same as with diabetes
Peripheral vascular disease	Caution with history of amputation or active peripheral arterial ulcer	Caution with history of amputation or active peripheral arterial ulcer
Perineal hygiene	Careful local hygiene—single dose of fluconazole typically effective in event of fungal infection	
Urinary tract infection	SGLT2 inhibitors might lead to increased urinary frequency but not directly associated with infection. However, urinary tract infection might occur independently of SGLT2 inhibitor use, and requires index of suspicion	Same as with diabetes
Diabetic ketoacidosis	As per CDA guidelines, this medication is on the "Sick Day" list. High index of suspicion for DKA required during clinical deterioration. Direct serum anion gap measurement suggested. In addition to volume-depleting conditions, hold for concomitant infection, trauma, surgery, or other major physiologic stressor	Hold during volume depleting intercurrent illness until oral intake adequate DKA not specifically recognized as a risk in nondiabetic patients

CDA, Centers for Disease Control and Prevention; DKA, diabetic ketoacidosis; eGFR, estimated glomerular filtration rate; SGLT2, sodium glucose cotransport.

with normal or only modestly elevated blood glucose level (< 14 mmol/L). On rare occasions, SGLT2 inhibitors might be associated with normal anion gap acidosis, which is best detected with measurement of serum ketones. Nonspecific symptoms associated with diabetic ketoacidosis include: shortness of breath, nausea, vomiting, abdominal pain, confusion, anorexia, excessive thirst, and lethargy.

Practical tip. Caution should be exercised when combining SGLT2 inhibitors, ARNI, and diuretics because of their concomitant effects to promote diuresis.

Conclusions

The definition of optimal care for patients with HF continues to evolve. Identifying the exact diagnoses and the best treatments for patients with HF can be challenging and health care providers must strive to maintain knowledge on new therapies that can improve the lives of these patients. These guidelines are aimed to provide a timely evidence-based brief update on topics currently at the centre of the changing face of HF management. Practitioners will continue to make the best clinical judgements and decisions with their patients.

Acknowledgements

The authors acknowledge the contribution of Christianna Brooks from CCS for her continued support throughout the guideline update writing process and thank the CCS Guideline Committee reviewers for providing insightful comments. The authors also acknowledge the volunteer contributions of panel members, organizations, and individuals involved in the creation and dissemination of best practices since the inception of the guidelines process.

References

1. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
2. Andrews J, Guyatt G, Oxman AD, et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719-25.
3. Cioffi G, Tarantini L, De Feo S, et al. Functional mitral regurgitation predicts 1-year mortality in elderly patients with systolic chronic heart failure. Eur J Heart Fail 2005;7:1112-7.
4. Glower DD, Kar S, Trento A, et al. Percutaneous mitral valve repair for mitral regurgitation in high-risk patients: results of the EVEREST II study. J Am Coll Cardiol 2014;64:172-81.
5. Schillinger W, Hunlich M, Baldus S, et al. Acute outcomes after MitraClip therapy in highly aged patients: results from the German TRAnscatheter Mitral valve Interventions (TRAMI) Registry. EuroIntervention 2013;9:84-90.
6. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol 2013;62:1052-61.
7. Nickenig G, Estevez-Loureiro R, Franzen O, et al. Percutaneous mitral valve edge-to-edge repair: in-hospital results and 1-year follow-up of 628 patients of the 2011-2012 Pilot European Sentinel Registry. J Am Coll Cardiol 2014;64:875-84.
8. Kortlandt F, Velu J, Schurer R, et al. Impact of mitral valve treatment choice on mortality, according to aetiology. EuroIntervention 2019;14:1733-9.
9. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018;379:2297-306.
10. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307-18.
11. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography developed in collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr 2017;30:303-71.
12. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159-95.
13. Metze C, Matzik AS, Scherner M, et al. Impact of frailty on outcomes in patients undergoing percutaneous mitral valve repair. JACC Cardiovasc Interv 2017;10:1920-9.
14. Piriou N, Al Habash O, Donal E, et al. The MITRA-HR study: design and rationale of a randomised study of MITRACLIP(R) transcatheter mitral valve repair in patients with severe primary mitral regurgitation eligible for high-risk surgery. EuroIntervention 2019;15:e329-35.
15. Ezekowitz JA, O'Meara E, McDonald MA, et al. 2017 Comprehensive update of the Canadian Cardiovascular Society guidelines for the management of heart failure. Can J Cardiol 2017;33:1342-433.
16. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med 2003;349:583-96.
17. Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation 2005;112:2047-60.
18. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. Trends Cardiovasc Med 2018;28:10-21.
19. Rapezzi C, Merlini G, Quarta CC, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation 2009;120:1203-12.
20. Benson MD, Buxbaum JN, Eisenberg DS, et al. Amyloid nomenclature 2018: recommendations by the International Society of Amyloidosis (ISA) nomenclature committee. Amyloid 2018;25:215-9.
21. Pereira NL, Grogan M, Dec GW. Spectrum of restrictive and infiltrative cardiomyopathies: part 1 of a 2-part series. J Am Coll Cardiol 2018;71:1130-48.
22. Pinney JH, Whelan CJ, Petrie A, et al. Senile systemic amyloidosis: clinical features at presentation and outcome. J Am Heart Assoc 2013;2:e000098.
23. Gertz MA, Brown ML, Hauser MF, Kyle RA. Utility of technetium Tc 99m pyrophosphate bone scanning in cardiac amyloidosis. Arch Intern Med 1987;147:1039-44.
24. Hutt DF, Quigley AM, Page J, et al. Utility and limitations of 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in systemic amyloidosis. Eur Heart J Cardiovasc Imaging 2014;15:1289-98.
25. Bokhari S, Castano A, Pozniakoff T, et al. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the

transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging 2013;6:195-201.

26. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016;133:2404-12.

27. Grogan M, Scott CG, Kyle RA, et al. Natural history of wild-type transthyretin cardiac amyloidosis and risk stratification using a novel staging system. J Am Coll Cardiol 2016;68:1014-20.

28. Maurer MS, Grogan DR, Judge DP, et al. Tafamidis in transthyretin amyloid cardiomyopathy: effects on transthyretin stabilization and clinical outcomes. Circ Heart Fail 2015;8:519-26.

29. Ikram A, Donnelly JP, Sperry BW, et al. Diflunisal tolerability in transthyretin cardiac amyloidosis: a single center's experience. Amyloid 2018;25:197-202.

30. Rosenblum H, Castano A, Alvarez J, et al. TTR (transthyretin) stabilizers are associated with improved survival in patients with TTR cardiac amyloidosis. Circ Heart Fail 2018;11:e004769.

31. Cappelli F, Martone R, Taborchi G, et al. Epigallocatechin-3-gallate tolerability and impact on survival in a cohort of patients with transthyretin-related cardiac amyloidosis. A single-center retrospective study. Intern Emerg Med 2018;13:873-80.

32. Solomon SD, Adams D, Kristen A, et al. Effects of patisiran, an RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis. Circulation 2019;139:431-43.

33. Benson MD, Waddington-Cruz M, Berk JL, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. N Engl J Med 2018;379:22-31.

34. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. N Engl J Med 2018;379:1007-16.

35. Dunlay SM, Roger VL, Redfield MM. Epidemiology of heart failure with preserved ejection fraction. Nat Rev Cardiol 2017;14:591-602.

36. Redfield MM. Heart failure with preserved ejection fraction. N Engl J Med 2016;375:1868-77.

37. Solomon SD, Zile M, Pieske B, et al. The angiotensin receptor neprilysin inhibitor LCZ696 in heart failure with preserved ejection fraction: a phase 2 double-blind randomised controlled trial. Lancet 2012;380:1387-95.

38. Solomon SD, McMurray JJV, Anand IS, et al. Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction. N Engl J Med 2019;381:1609-20.

39. Solomon SD, Rizkala AR, Gong J, et al. Angiotensin receptor neprilysin inhibition in heart failure with preserved ejection fraction: rationale and design of the PARAGON-HF trial. JACC Heart Fail 2017;5:471-82.

40. McMurray JJ, Packer M, Desai AS, et al. Angiotensin-neprilysin inhibition versus enalapril in heart failure. N Engl J Med 2014;371:993-1004.

41. Fitchett D, Zinman B, Wanner C, et al. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME(R) trial. Eur Heart J 2016;37:1526-34.

42. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117-28.

43. Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644-57.

44. Neal B, Perkovic V, Matthews DR, et al. Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study-Renal (CANVAS-R): a randomized, placebo-controlled trial. Diabetes Obes Metab 2017;19:387-93.

45. Radholm K, Figtree G, Perkovic V, et al. Canagliflozin and heart failure in type 2 diabetes mellitus. Circulation 2018;138:458-68.

46. Wiviott SD, Raz I, Bonaca MP, et al. The design and rationale for the Dapagliflozin Effect on Cardiovascular Events (DECLARE)-TIMI 58 trial. Am Heart J 2018;200:83-9.

47. Wiviott SD, Raz I, Bonaca MP, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347-57.

48. Kato ET, Silverman MG, Mosenzon O, et al. Effect of dapagliflozin on heart failure and mortality in type 2 diabetes mellitus. Circulation 2019;139:2528-36.

49. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. N Engl J Med 2019;380:2295-306.

50. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. Lancet 2019;393:31-9.

51. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995-2008.

52. Verma S, McMurray JJV. SGLT2 inhibitors and mechanisms of cardiovascular benefit: a state-of-the-art review. Diabetologia 2018;61:2108-17.

53. Zelniker TA, Braunwald E. Cardiac and renal effects of sodium-glucose co-transporter 2 inhibitors in diabetes: JACC State-of-the-Art Review. J Am Coll Cardiol 2018;72:1845-55.

54. Verma S, Rawat S, Ho KL, et al. Empagliflozin increases cardiac energy production in diabetes: novel translational insights into the heart failure benefits of SGLT2 inhibitors. JACC Basic Transl Sci 2018;3:575-87.

55. Lytvyn Y, Bjornstad P, Udell JA, Lovshin JA, Cherney DZI. Sodium glucose cotransporter-2 inhibition in heart failure: potential mechanisms, clinical applications, and summary of clinical trials. Circulation 2017;136:1643-58.

56. Lipscombe L, Booth G, Butalia S, et al. Diabetes Canada 2018 clinical practice guidelines for the prevention and management of diabetes in Canada. Can J Diabetes 2018;42:S316.

57. Tang HL, Sudbodh V. Two randomized clinical trials on the treatment of secondary mitral regurgitation—contradictory or complementary? JAMA Cardiol 2019;4:311-3.