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Pushing the Envelope for Transcatheter Valve Interventions in Canada

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Abstract

Transcatheter valve interventions (TVIs) have revolutionized the treatment of structural heart disease, by providing a less invasive option to surgical valve repair or replacement for patients. Canada has been at the forefront of adopting these therapies, yet significant challenges remain. These include expanding indications, training operators, optimizing access, and integrating these rapidly evolving procedures into a government-funded single-access healthcare system. This review explores the current landscape of TVIs in Canada. We discuss the necessity for centres of excellence, training pathways for operators, and the multidisciplinary infrastructure required to ensure equitable and high-quality care.

Background

The past two decades have witnessed a paradigm shift in the management of valvular heart disease, largely driven by transcatheter technologies that offer less invasive alternatives to surgical valve replacement or repair. Initially limited to high-risk surgical candidates, appropriate indications for many transcatheter valve interventions (TVIs) are now being expanded to include lower-risk populations, supported by robust clinical trial data and real-world evidence.[1,2] In Canada's government-funded healthcare system, the integration of novel interventions must balance clinical efficacy with cost-effectiveness, resource allocation, and accessibility. Unlike other jurisdictions with private healthcare components, Canada must navigate the implementation of TVIs within a system constrained by hospital budgets, procedural caps, and regional disparities. Moreover, provincial allocation of health budgets adds an additional constraint on adopting innovative technology. As indications for transcatheter therapies expand, success will necessitate not only technological advancements but also the development of specialized hospital programs, competent trained operators, and comprehensive post-procedural care. We explore the current state of TVIs across selected key disease states while highlighting the systemic requirements for sustainable program development into the future.

Transcatheter Aortic Valve Implantation (TAVI)

TAVI has transformed the management of valvular aortic stenosis (AS), particularly among elderly and high-risk patients. In Canada, TAVI has become widely adopted, with its indications expanding to low-risk populations. Continuous development of valve platforms, device iterations, and novel procedural techniques are enabling improvements in procedural success rates and lifetime management planning.

TAVI Indications

Although initially restricted to symptomatic severe AS patients who were at prohibitive or high surgical risk, TAVI is now also indicated for intermediate and low-risk patients, following landmark clinical trials.[1,2] TAVI using both the balloon-expandable SAPIEN-3 and self-expanding Evolut R/Pro prostheses has demonstrated non-inferior outcomes to surgical aortic valve replacement (SAVR) across all surgical risk subgroups, with outcomes sustained up to 5 years, and up to 10 years in low-risk populations.[1-7] While this update is reflected in the most recent 2020 American College of Cardiology (ACC)/ American Heart Association (AHA) Heart Valve Guidelines[8] and the 2021 European Society of cardiology (ESC/European [EACTS]) Guidelines,[9] the Canadian Cardiovascular Society's 2019 Position Statement on TAVI[10] has yet to be updated to include such patients. The Canadian Cardiovascular Society's National Quality Reports have demonstrated excellent outcomes, reinforcing the need for broader access.[10]

Current international guidelines and consensus support a heart team approach with shared decision-making. According to the European guidelines, SAVR is favoured in patients under the age of 75 and for those with high surgical risk, while the American guidelines recommend shared decision-making for those between 65 and 80 years. Surgery is also favoured in patients with complex anatomical features that are not suitable for TAVI, such as bicuspid valves with heavy calcification, low coronary heights, very small or large annuli, and inadequate vascular access.[8,9]

Current TAVI Devices

At present, three TAVI valve platforms are commercially available for use in Canada, while others are available through special access or as investigational devices being evaluated in clinical trials. These include the SAPIEN (Edwards Lifesciences), the Evolut (Medtronic, Minneapolis, MN) and the Navitor (Abbott Vascular, Abbott Park, IL) valves. Among high surgical risk patients with severe symptomatic AS, clinical trials have shown that the SAPIEN and Evolut platforms have demonstrated comparable clinical outcomes and mortality rates when directly compared.[11-13] Equivalent clinical outcomes have also been observed in meta analyses and real-world studies including data from Canadian registries.[14,15] Among patients with small aortic valve annular dimensions, both Evolut and SAPIEN devices have shown equivalent clinical outcomes; however, the Evolut valve has demonstrated superior hemodynamic performance with lower rates of bioprosthetic valve dysfunction and thrombosis.[12,16] These advantages may lead to improved long-term valve durability and outcomes for these patients. The Navitor valve has demonstrated excellent short-term outcomes among high-risk patients and has achieved significant improvements in outcomes compared with its predecessor, the PORTICO valve.[17,18] However, long-term and durability data for Navitor are still pending due to its recent introduction.

Access to TAVI

At present, 31 centres across Canada offer TAVI programs **(Figure 1)**. While TAVI is available in most provinces, limitations such as procedural volume caps and geographic disparities contribute to inequitable access, particularly in remote regions. Despite the rapid uptake and widespread use of the procedure, demand has outpaced capacity, resulting in growing wait times for TAVI.[19]

Western Canada
Mazankowski Alberta Heart Institute, Edmonton AB
Foothills Medical Centre, Calgary AB
Royal Jubilee Hospital, Victoria BC
St. Paul's Hospital, Vancouver BC
Vancouver General Hospital, Vancouver BC
Royal Columbian Hospital, New Westminster BC
Kelowna General Hospital, Kelowna BC
St. Boniface Hospital, Winnipeg MB
Regina General Hospital, Regina, SK
Royal University Hospital, Saskatoon SK
Ontario
Health Sciences North, Sudbury ON
Hamilton Health Sciences, Hamilton ON
London Health Sciences Centre, London ON
Kingston General Hospital, Kingston ON
Southlake Regional Health Centre, Newmarket ON
St. Michael's Hospital, Toronto ON
Sunnybrook Hospital, North York ON
Toronto General Hospital, Toronto ON
Trillium Health Partners, Mississauga ON
St. Mary's General Hospital, Kitchener ON
University of Ottawa Heart Institute, Ottawa ON
Quebec & Maritimes
Centre Hospitalier de l'University de Montreal (CHUM), Montreal QC
Hotel-Dieu De Sherbrooke (CHUS), Sherbrooke QC
Institut Universitaire De Cardiologie Et De Pneumologie de Quebec (IUCPQ), Quebec City QC
Hospital du Sacre-Coeur-de-Montreal, Montreal QC
Montreal Heart Institute, Montreal QC
McGill University Health Centre (Glen Site), Montreal QC
Jewish General Hospital, Montreal QC
Health Sciences Centre Eastern Health, St. John's NL
St. John Regional Hospital, Saint John NB
Queen Elizabeth II Health Sciences Centre, Halifax NS

Figure 1. Canadian TAVI centres: *courtesy of Bryan Traynor, MD*, and *Akshay Bagai, MD, MHS*

In response, innovative solutions to deal with this shortfall have included the development of a Canadian TAVI triage tool to help identify and prioritize patients based on clinical urgency.[20]

Challenges and Future Directions

Expansion of Indications for TAVI: Bicuspid aortic valve patients were excluded from the pivotal randomized controlled trials due to potential anatomical challenges such as asymmetric and higher leaflet calcification, fused raphe, larger annulus size, and associated aortopathy. Initial TAVI experiences in patients with bicuspid AS reported worse in-hospital outcomes including increased paravalvular leak, device malpositioning, permanent pacemaker implantation, aortic root injury, and stroke. However, with improvements in device technology, imaging modalities, and a better understanding of bicuspid aortic valve anatomy, outcomes for TAVI in patients with bicuspid aortic stenosis have improved.[21,22] Among patients with asymptomatic severe AS, the EARLY TAVR trial has demonstrated the short-term safety of TAVI compared with close follow-up (Recently FDA approved in the United States). However, active surveillance remains an important option, particularly for younger patients where concerns such as prosthetic valve degeneration and lifetime disease management are of greater importance.[23] Several ongoing clinical trials are assessing the benefit of TAVI for patients with moderate AS, including the PROGRESS (NCT04889872) and EXPAND TAVR II (NCT05149755) trials. In contrast, the TAVR UNLOAD trial failed to show a significant benefit for TAVI in moderate AS patients with reduced left ventricular systolic function.[24]

Lifetime Management: Increasing numbers of TAVI procedures are performed in younger, lower-risk patients as the evidence base has expanded. This shift has placed a greater emphasis on considering the long-term implications following TAVI. For example, optimizing valve durability, future coronary access, and future valve-in-valve TAVI planning have now become routine components of index TAVI procedure planning. Similar long-term considerations are also becoming increasingly important for patients receiving bioprosthetic SAVR procedures.

Canadian Health System Constraints: Funding limitations for TAVI programs remains a challenge with procedural caps limiting expansion. To address rising demand, more streamlined approval processes and dedicated funding strategies are required. This will become increasingly important as the burden of AS and expected need for TAVI procedures increases with a growing and aging population. Electrocardiogram-gated Cardiac CT angiography plays a vital role in TAVI procedure planning; however, limited access to timely CT imaging remains a key challenge for many TAVI programs, which limits expansion. Procedural complication rates associated with TAVI have declined dramatically in recent years, as improvements in device technologies, procedural techniques, and planning have been made.[25] As a result, some countries have removed the need for a mandatory on-site cardiovascular surgery department when performing TAVI.[26] This practice may become more acceptable as the need for TAVI continues to increase, particularly for patients deemed unfit for surgery. In a centralized health system with limited cardiovascular surgery sites, community hospitals without surgical back-up should be allowed to perform TAVI procedures in those who are not surgical bailout. Uncertainty remains regarding the universal need for coronary angiography prior to TAVI, as well as for the benefit of complete revascularization in patients with obstructive coronary artery disease.[27] Future studies including the ongoing COMPLETE TAVR trial (NCT04634240) aim to address these questions.

Aortic Insufficiency: Unlike AS, using TAVI for aortic insufficiency (AI) remains less established due to anatomical challenges. Most TAVI prostheses have been designed for calcified AS, while pure AI typically presents with larger associated annular dimensions and lack of calcification, making valve anchoring more challenging. However, dedicated devices such as the Trilogy system (JenaValve) and the J-Valve (Edwards Lifesciences) have shown promise in addressing these challenges and advancing transcatheter treatment options for severe AI.[28,29] Canadian experience with transcatheter treatment for AI remains limited to a small number of centres performing these procedures at low volumes. Additional data are needed to evaluate the transcatheter options for AI, particularly in patients at high surgical risk. Clinical trials have demonstrated the safety and effectiveness of the Trilogy system (JenaValve),[29] while enrolment has been completed for the ongoing J-Valve study (NCT06034028). Custom-designed transcatheter solutions for AI must be integrated into the

Canadian landscape through a controlled adoption strategy supported by national registries.

Transcatheter Mitral Valve Therapies

Mitral valve (MV) disease presents a complex challenge for transcatheter interventions, given its heterogeneous etiology. Mitral regurgitation (MR) is classified as primary or organic (PMR) and secondary or functional (FMR). PMR entails an intrinsic pathology of the leaflets and/or chordae tendineae. In contrast, FMR usually entails preserved leaflets and results from either ventricular remodelling/dysfunction (V-FMR) or from left atrial dilation (A-FMR), particularly among patients with atrial fibrillation (AF). The most common cause of primary MR is myxomatous degeneration of the MV leaflets, which leads to MV prolapse. Primary MR can also occur from leaflet perforation and cleft leaflets,

Name	City and Province
Mazankowski Alberta Heart Institute	Edmonton AB
Foothills Medical Centre	Calgary AB
Royal Columbian Hosptial	New Westminster BC
St. Paul's Hospital	Vancouver BC
Vancouver General Hospital	Vancouver BC
St. Boniface Hospital	Winnipeg MB
St. John Regional Hospital	Saint John NB
Queen Elizabeth II Health Sciences Centre	Halifax NS
St. Michael's Hospital	Toronto ON
Toronto General Hospital	Toronto ON
University of Ottawa Heart Institute	Ottawa ON
Southlake Regional Health Centre	Newmarket ON
Sunnybrook Hospital	North York ON
Trillium Health Partners	Mississauga ON
Hamilton Health Sciences	Hamilton ON
Kingston General Hospital	Kingston ON
London Health Sciences Centre	London ON
Montreal Heart Institute	Montreal QC
McGill University Health Centre (Glen Site)	Montreal QC
Institut Universitaire De Cardiologie Et De Pneumologie de Quebec (IUCPQ)	Quebec City QC
Centre Hospitalier de l'University de Montreal (CHUM)	Montreal QC
Hotel-Dieu De Sherbrooke (CHUS)	Sherbrooke QC
Royal University Hospital, Saskatoon	Saskatoon SK

Figure 2. Canadian M-TEER Centres; *courtesy of Bryan Traynor, MD, and Akshay Bagai, MD, MHS*

which are deep indentations that extend to the annulus. Additionally, rheumatic disease, certain medications, radiation exposure, and connective tissue diseases can cause restricted leaflet motion due to thickening of the leaflet edges and the subvalvular apparatus. An increasing cause of MR in the elderly population is mitral annular calcification. This degenerative process starts in the posterior annulus and extends into the base of the leaflets and subvalvular apparatus, affecting both annular and leaflet function. Thus, given the varied pathologies underlying primary MR, both surgical and transcatheter MV interventions require unique and varied techniques. These include MV repair techniques such as leaflet approximation, direct annuloplasty, indirect annuloplasty, and chordal repair, as well as MV replacement. At present, in Canada, the only commercially approved transcatheter technique is leaflet approximation with edge-to-edge repair.

Transcatheter Edge-to-Edge Repair

This technique emulates the surgical Alfieri edge-to-edge leaflet repair by approximating the free edges of the anterior and posterior leaflets using clips delivered percutaneously by catheters.[30] Currently, the procedure is performed under general anesthesia using fluoroscopy and transesophageal echocardiographic (TEE) guidance.

Transcatheter Mitral Edge-to -Edge Repair Indications

Surgical intervention remains the gold standard for treating severe primary MR, with repair recommended over replacement if feasible. To date, only the mitral transcatheter edge-to-edge repair (TEER) with the MitraClip device (Abbott, Santa Clara, CA) has been evaluated in a randomized clinical trial against surgical MV repair and/or replacement. In the EVEREST II trial, which included 154 degenerative MR patients, surgical treatment was more effective than transcatheter TEER with MitraClip for treating primary MR. However, many patients with degenerative MR have multiple comorbid conditions that place them at very high or prohibitive risk for surgery. In such a cohort of 127 degenerative MR patients

Name	City and Province
St. Paul's Hospital	Vancouver BC
Vancouver General Hospital	Vancouver BC
Queen Elizabeth II Health Sciences Centre	Halifax NS
St. Michael's Hospital	Toronto ON
Toronto General Hospital	Toronto ON
University of Ottawa Heart Institute	Ottawa ON
Southlake Regional Health Centre	Newmarket ON
Sunnybrook Hospital	North York ON
Trillium Health Partners	Mississauga ON
Hamilton Health Sciences	Hamilton ON
London Health Sciences Centre	London ON
Montreal Heart Institute	Montreal QC
McGill University Health Centre (Glen Site)	Montreal QC
Institut Universitaire De Cardiologie Et De Pneumologie de Quebec (IUCPQ)	Quebec City QC
Royal University Hospital	Saskatoon SK

Figure 3. Canadian T-TEER Centres; *courtesy of Bryan Traynor, MD Akshay Bagai, MD, MHS*

from the EVEREST II and REALISM (Real World Expanded Multicenter Study of the MitraClip System) studies, who were deemed at prohibitive surgical risk, treatment with the MitraClip device was associated with safety and good clinical outcomes. These included decreases in rehospitalization, functional improvements, and favourable ventricular remodelling.[31] Accordingly, the 2020 ACC/AHA Guideline for the Management of Patients with Valvular Heart Disease considered transcatheter TEER to be a reasonable treatment option for severely symptomatic patients (classified as New York Health Association [NYHA] III/IV) with primary severe MR who are at high or prohibitive surgical risk, provided that their MV anatomy is suitable for the repair procedure.[8]

Among patients with secondary or functional MR in the context of reduced left ventricular function, the 2020 Canadian Heart Failure Clinical Trial update recommends considering mitral TEER after patients have received maximally tolerated guideline-directed medical therapy (GDMT), including cardiac resynchronization therapy and revascularization where appropriate. This recommendation is supported by findings from the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, which enrolled 614 patients after optimization of GDMT. The study showed that MitraClip therapy reduced secondary MR, and was associated with lower all-cause mortality at 2 years compared with GDMT alone.[32] Intervention with MitraClip has also been shown to reduce the risk of heart failure (HF)-related hospitalizations and significantly improve HF symptoms. These findings contrast with those of the Percutaneous Repair with the MitraClip device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trial, in which MitraClip intervention did not demonstrate a survival benefit.[33] The negative outcomes from the MITRA-FR trial have been attributed to factors such as more extensive LV dilation, less severe FMR, and the absence of forced optimization of medical GDMT prior to MitraClip therapy. More recently, the third randomized controlled trial conducted among this patient population, RESHAPE 2, showed that Mitra Clip therapy reduced the rate of first or recurrent hospitalization for HF or CV death at 24 months. Additionally, patients treated with MitraClip reported better health status at 12 months compared to those receiving GDMT alone.[34]

In Canada, the MitraClip device is being used for both degenerative and functional MR indications. A real-world observations study of 1,191 patients who underwent MitraClip across 11 Canadian centres found that MR etiology was degenerative in 41% of cases and functional in 59%. Among these patients, the rate of hospitalizations for HF dropped from 50.7% before to 10.3% within 1 year following M-TEER.[35] Although use of M-TEER is supported by data in patients with degenerative MR at high surgical risk, and in those with functional MR in the context of reduced LV function, mitral TEER use among patients with atrial functional MR (AFMR) requires additional studies. In such patients, the attribution of symptoms or a worse prognosis with AFMR is challenging. This is due to the frequent coexistence of comorbidities such as AF, heart failure with preserved ejection fraction, as well as other comorbidities such as hypertension and chronic kidney disease in these patients.

Current Mitral Edge-to-Edge Repair Devices

Two mitral TEER devices are now commercially available in Canada: the MitraClip (Abbott Vascular, Abbott Park, IL) and the PASCAL (Edwards Lifesciences). A pre-specified interim analysis from the CLASP IID trial, which included 180 patients, demonstrated that the PASCAL TEER system was non-inferior to the MitraClip TEER system in terms of both primary safety and efficacy endpoints.[36] In a recent real-world, multicenter study comparing the original PASCAL P10 device with the MitraClip NT device in the first 309 commercially-treated patients using propensity matching, both groups demonstrated high technical success. Notably, the PASCAL group achieved more effective MR reduction and lower mean mitral gradients. There were no differences in mortality or major adverse cardiac events, and both groups showed comparable improvements in NYHA functional class.[37] With two commercially available TEER devices of varying sizes, clinicians now have greater flexibility to tailor interventions to individual patient anatomy, optimizing MR reduction while balancing mitral gradients and procedure safety.

Access to Mitral Edge-to-Edge Repair

Access to mitral TEER remains limited, with 23 centres across Canada performing mitral TEER **(Figure 2)**. As the population of elderly patients with degenerative MR continues to grow, alongside the increasing number of HF patients

with functional MR, there a strong need for further expansion of the current mitral TEER programs, and to establish additional sites to meet the growing demand.

Challenges and Future Directions for Transcatheter Mitral Valve Interventions

Operator Expertise and Imaging Requirements: Transcatheter mitral interventions require advanced pre-procedural and intra-procedural TEE imaging, as well as procedural skills. In recent years, high-volume centres across Canada have begun formalizing training pathways for both cardiac imaging specialists and interventional cardiologists.

Transcatheter Mitral Valve Replacement (TMVR): Given the heterogeneity of MR etiologies, not all cases are suitable for mitral TEER (e.g., leaflet perforation, rheumatic, among others). Thus, TMVR provides treatment options for MV disease, both MR and MS, in patients at high surgical risk, or with anatomy not suitable for mitral TEER. TMVR also provides options for valve-in-valve or valve-in-ring procedures in patients with prior surgical MV replacement using a bioprosthesis or annuloplasty ring. Compared with TEER, TMVR provides complete or near-complete elimination of MR. Early feasibility studies across several TMVR platforms have shown promising results.[38,39] The transapical device, Tendyne (Abbott Vascular, Abbott Park, IL), has demonstrated efficacy in eliminating MR and improving patient outcomes.[40] Transseptal devices including the SAPIEN M3 (Edwards Lifesciences) and the Intrepid (Medtronic, Minneapolis, MN) are currently enrolling patients in clinical trials (NCT04153292, NCT03242642). While TMVR provides the advantage of being a solution that is "agnostic to the pathology", its broader application is limited by challenges with anatomic suitability, such as annular and predicted neo-left ventricular outflow tract dimensions.[41] At present, TMVR remains investigational in Canada and is available only at a small number of centres.

Transcatheter Tricuspid Valve Therapies

Tricuspid regurgitation (TR) is a common condition, affecting 4% of individuals over the age of 75.[42] TR also has several etiologies including primary valve disease, atrial functional mechanisms, ventricular function, or complications related to pacemaker/implantable cardioverter-defibrillator leads. Unlike MR, primary TR accounts for only a minority of cases, with most being functional or lead-related in origin. Traditionally, functional TR has been managed conservatively with diuretics due to the high surgical risk associated with surgical intervention.[43] However, the availability of transcatheter tricuspid therapies allows treatment of TR with reduced peri-procedural risk.

Transcatheter Edge-to-Edge Repair

Similar to mitral TEER, tricuspid TEER approximates the free edges of the valve leaflets (septal with either the anterior or posterior leaflet) using a clip delivered percutaneously via catheters. However, the tricuspid valve poses unique challenges including more complex heterogeneous anatomy, TEE imaging, and less predictable reductions in TR.

Tricuspid Edge-to-Edge Repair Indications

According to the 2020 AHA/ACC Valve Guidelines, the only class I indication for TR intervention is surgical repair among patients undergoing left-sided valve surgery. However, tricuspid TEER is likely to be included in the next version of the guidelines based upon the results of the TRILUMINATE trial. This study evaluated the safety and efficacy of tricuspid TEER in addition to medical therapy versus medical therapy alone in 572 patients with severe, symptomatic TR. At the 2-year follow-up, tricuspid TEER was shown to be safe, significantly reduced TR severity, and decreased the rate of heart failure hospitalizations, though it did not demonstrate a mortality benefit compared with medical therapy alone.[44] Thus, in general, tricuspid TEER should be considered for patients experiencing symptoms (fatigue, edema) attributable to severe TR despite optimal diuretic therapy, particularly when right ventricular function is preserved and pulmonary artery systolic pressure is <70mmHg and the valve anatomy is favourable for tricuspid TEER. However, patient selection for intervention in clinical practice is often more challenging. Many patients with TR also have multiple comorbidities (e.g., left side heart disease, renal insufficiency, AF, among others), which makes attribution of symptoms solely to the TR more challenging, and makes the response to TV intervention less predictable. In addition, the prognosis is frequently limited by their underlying comorbidities than by TR itself. Further research is needed to better identify which patients with TR

are most likely to benefit from transcatheter TR intervention.

Current Tricuspid Edge-to-Edge Repair Devices

At present, only Triclip (Abbott Vascular, Abbott Park, IL) is approved for tricuspid TEER in Canada. The PASCAL (Edwards Lifesciences) tricuspid TEER, which is available in Europe, but not yet approved in Canada, has also shown effective TR reduction and clinical improvements at 1 year, as reported in the PASTE registry of 1,059 patients.[45]

Access to Tricuspid Edge-to-Edge Repair

Access to tricuspid TEER is even further limited, with only 15 centres across Canada performing the procedure **(Figure 3)**. To date, adoption in Canada has been limited by procedural complexity, including the need for pre and peri-procedural imaging, and by a lack of funding in many regions. Recently, provincial funding for the Triclip device has expanded, with most, but not all, provinces funding Triclip. Further expansion of access will require investment in dedicated programs to develop the advanced imaging (i.e., 3-D intracardiac echocardiography) and procedural skills necessary to support safe and effective delivery of tricuspid TEER.

Challenges and Future Directions

Transcatheter Tricuspid Valve Replacement (TTVR): Although tricuspid TEER is generally safe and associated with low complication rates, its efficacy in TR reduction is limited by heterogeneity in valve morphology, intra-procedural imaging complexity, and operator experience. Orthotopic TTVR, where the replacement valve is placed in the tricuspid annulus, effectively eliminates TR and is not limited by valve morphology. Several devices using a variety of anchoring mechanisms are under development and have shown promise in early feasibility studies. Among these, only the EVOQUE valve (Edwards Lifesciences) has been recently approved by Health Canada and is available. In the TRISCEND II trial of 400 patients, TTVR with the EVOQUE device reduced TR to mild or less in 95.2% of patients and significantly improved quality of life at 1 year compared with medical therapy alone. Most adverse clinical events with TTVR were peri-procedural and included death from cardiovascular causes, severe bleeding, and conduction disorders leading to new pacemaker implantation.[46]

Given the complex nature of TR, and its severe clinical phenotypes, a one-size-fits-all approach is unlikely to succeed. Novel diagnostic tools that include artificial intelligence may offer future value by integrating multiple variables, analyzing large datasets, and harmonizing layers of knowledge to guide patient selection and procedural decision-making. Most importantly, these tools may help identify patients unlikely to benefit from transcatheter intervention. Additionally, the use of intracardiac echocardiography with image quality comparable to TEE may avoid the need for general anesthesia. Continuous improvements in current devices and new technologies will also expand treatment options and simplify procedural workflows.

Conclusion

TVIs are redefining structural heart disease management in Canada, with expanding indications across a range of valvular conditions. However, to fully integrate these therapies into the Canadian healthcare system, key barriers must be addressed, including limited access, procedural funding constraints, and gaps in operator training. By establishing centres of excellence, investing in multidisciplinary teams, and ensuring equitable distribution of resources, Canada can continue pushing the envelope for TVIs and improve outcomes for patients with valvular heart disease and remain at the global forefront of cardiovascular care.

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Role and Indications for Device Therapies in Heart Failure: Condensed Summary

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Overview of CRT and Electrophysiological Rationale

Over the past decade, the substantial benefits associated with current guideline-directed medical therapy for heart failure with reduced ejection fraction (HFrEF) have been brought into the light, as emphasized in a recent publication from our institution.[1] Despite these advances, device therapy continues to hold an important place in treating heart failure (HF), both for left ventricular (LV) remodeling (and associated prognosis) as well as for preventing sudden cardiac death (SCD).

Cardiac resynchronization therapy (CRT) is a key intervention in heart failure (HF) management, particularly for patients with left bundle branch block (LBBB), which is observed in 15–25% of patients with HF, and is associated with reduced left ventricular function.[2] CRT helps in correcting dyssynchronous ventricular contraction leading to impaired cardiac output. Although less prevalent, right bundle branch block (RBBB) and nonspecific interventricular conduction delay (IVCD) are also associated with adverse remodelling, including increased right ventricular volumes and reduced function.

Clinical Trials

Clinical trials, such as CARE-HF and COMPANION, have demonstrated the benefits of CRT in patients with symptomatic HF, left ventricular ejection fraction (LVEF) ≤35%, and evidence of electrical dyssynchrony (e.g., QRS duration >150 ms or 120–149 ms with echocardiographic dyssynchrony).[3,4] CRT has been shown to improve systolic blood pressure, increase LVEF, reduce mitral regurgitation, and decrease left ventricular end-systolic volume index, leading to reduced hospitalizations for HF and a lower mortality rate. These findings support the physiological mechanism of CRT, which aims to optimize cardiac performance by synchronizing biventricular pacing, and reducing interventricular mechanical delay.

Guidelines-Based Indications for CRT

According to the 2021 European Society of Cardiology (ESC) guidelines, the 2013 Cardiovascular Canadian Society (CCS) guidelines—with updates expected in October 2025—and the 2023 HRS/APHRS/LAHRS guideline on cardiac physiologic pacing, CRT is indicated for patients with HF who are in sinus rhythm, have an LVEF of 35% or less, and a wide QRS complex.[5-7] CRT is strongly recommended for patients with LBBB morphology and a QRS duration of 150 ms or greater. It should also be considered in patients with LBBB and QRS duration between 130 and 149 ms. For those with non-LBBB morphology (RBBB or IVICD), CRT is recommended when the QRS duration is 150 ms or greater. CRT is not indicated for patients with a QRS duration of less than 130 ms unless there is another indication for pacing. Although CRT was initially indicated after optimization of medical treatment, data showing the poorest response in patients with LBBB has suggested that earlier CRT implantation would be beneficial.[8,9]

Sex-based differences in response to CRT have been well documented. Women, who generally have smaller left ventricular dimensions, tend to benefit from CRT at shorter QRS durations compared to men. Modelling studies suggest that a QRS duration threshold approximately 10 ms shorter may be appropriate for women to derive similar benefit, reinforcing the need for sex-specific criteria in device-based therapies. Patients with non-ischemic cardiomyopathy are also known to respond better to treatment than those with ischemic cardiomyopathy.

CRT in Atrial Fibrillation

Delivering effective CRT in patients with atrial fibrillation (AF) is more complex due to the

irregular ventricular response and the presence of fusion or pseudo-fusion beats. These can significantly reduce the percentage of biventricular pacing, which is a major determinant of CRT efficacy. For patients with persistent or permanent AF who have HF and an LVEF of 35% or less, CRT is appropriate if the QRS duration is 130 ms or more and a strategy is in place to ensure a high percentage of biventricular capture (>90% at least, higher is better). In most cases, this will require atrioventricular junction (AVJ) ablation to suppress native conduction and ensure CRT efficacy (ablate and pace strategy).

In patients undergoing AVJ ablation, CRT is recommended for those with HFrEF, defined as an LVEF <40% and may be considered for those with mildly reduced EF (41–49%) and selected cases of preserved EF (≥50%). For HFrEF patients who require ventricular pacing, CRT should be preferred over right ventricular (RV) pacing to avoid pacing-induced cardiomyopathy and slow the progression of HF for patients in whom the expected percentage of pacing is more than 20 to 40% (still debated).

CRT-D vs. CRT-P and ICD Considerations

The estimated annual risk of fatal ventricular arrythmias is approximately 4–5% in primary prevention of sudden cardiac death (SCD). Implantable cardioverter-defibrillators (ICDs) are thus indicated in HFrEF with an LVEF <35%, even without prior ventricular arrhythmias, provided they are receiving optimal medical HF therapy, to reduce the risk of all-cause mortality. In the DANISH (Danish Study to Assess the Efficacy of ICDs in Patients with Non-ischemic Systolic Heart Failure on Mortality) trial, ICDs significantly reduced the rate of SCD, but did not reduce all-cause mortality in patients with non-ischemic cardiomyopathy, except in the subgroup of patients younger than 70 years. Importantly, optimal guideline-directed medical therapy for HFrEF also reduces all-cause mortality and SCD.

ICDs are well established for preventing SCD in patients with HFrEF or in selected cardiomyopathies. When patients meet indications for both CRT and ICD, the implantation of a CRT-D device is recommended. The decision to proceed with CRT-D involves a shared decision-making process that incorporates an individual risk assessment. In patients who have existing pacemakers or ICDs and subsequently develop symptomatic HFrEF and a high RV pacing burden (>20–40%), upgrading to CRT should be considered.

However, the overall benefit of ICDs for primary prevention has declined due to the decreasing incidence of SCD, now estimated at approximately 1% per year. This evolution necessitates careful patient selection while patients with ischemic heart disease tend to derive greater benefit from ICDs than those with non-ischemic heart disease, the overall rate of responders is higher in patients with non-ischemic cardiomyopathy than in those with ischemic cardiomyopathy. Other factors to consider are patient age, life expectancy, comorbidities, the presence of a genetic mutation, mechanical dyssynchrony, the presence of myocardial fibrosis on cardiac MRI, and any previously implanted devices already in place.[10]

In some patient populations, CRT-P may be favoured over CRT-D. This includes patients with non-ischemic cardiomyopathy, limited life expectancy, significant comorbidities, or advanced age. CRT-P may also be appropriate for those with poor renal function or those anticipated to undergo mitral valve intervention. Additionally, in cases of pacing-induced cardiomyopathy, where a pacemaker is already implanted, upgrading with one left ventricular (LV) lead instead of 2 leads for CRT-D may be sufficient. Additionally, patient preferences should be respected in the decision-making process, especially in light of the modest and declining benefit of ICDs for primary prevention. A frank discussion with the patient should be initiated at the time of the implant decision. CRT-P is more often used in Europe than in the United States.

Subcutaneous and Extravascular ICDs

Traditional transvenous ICD systems are associated with both short- and long-term complications including venous obstruction, vascular injury, systemic infection, lead-related problems, and lead-related tricuspid regurgitation. Subcutaneous ICDs (S-ICDs) offer an alternative that avoids the need for intravascular access, thereby reducing these risks while maintaining effective defibrillation for life-threatening ventricular arrhythmias. However, S-ICDs do not offer pacing support or anti-tachycardia pacing (ATP) and typically require a larger device generator. In the MODULAR ATP trial, the addition of a leadless pacemaker (Empower, developed by Boston Scientific) to the top of an S-ICD enabled

ATP delivery, successfully terminating 61% of ventricular arrhythmias.[11] Notably, the Empower device has not yet received approval in any country.

Extravascular ICD (EV-ICD, Aurora® from Medtronic, offer an alternative approach to avoid lead-related complications by placing the lead in a sub-sternal position. This configuration allows both ATP and defibrillation without requiring intravascular access. However, EV-ICDs do not support permanent pacing (painful) and are contraindicated in patients with a history of thoracic or cardiac surgeries (including left ventricular assist device (LVAD) patients – see below). In the Extravascular ICD Pivotal Study, which included the first 300 patients with indications for single-chamber ICDs, ATP successfully terminated ventricular arrhythmias in 77% of cases.[12]

Conduction System Pacing (CSP)

CSP is an alternative to RV pacing that preserves physiological activation of the ventricles by stimulating the native conduction system. It is particularly beneficial for patients with AV block and an LVEF below 50% who are expected to need frequent ventricular pacing (20–40%). Among CSP techniques, left bundle branch area pacing (LBBAP) has been fully adopted in recent years. Compared to His bundle pacing (HBP), the LBBAP offers greater stability (less lead dislodgement, lower pacing thresholds leading to improved battery longevity) without the need for a back-up right ventricular lead (RV lead). LBBAP may also be used in addition to a coronary sinus (CS) lead (LOT-CRT) or when the CS lead placement for CRT is unsuccessful due to anatomical constraints (bailed-out indications). Several ongoing studies are evaluating LBB pacing in patients with indications for CRT, AV block, and AVJ ablation. However, improvements in implantation materials are still needed to reduce failure rates, particularly in patients with complex anatomies. For patients with rapid AF and narrow QRS who undergo AVJ ablation, CSP may offer a viable alternative to biventricular pacing.

Cardiomyopathies and Device Therapy

Several cardiomyopathies present unique considerations when evaluating device therapy. In some cases, when a pacing indication is present, ICDs should be recommended at the time of implantation, depending on the patient's risk of SCD, to avoid unnecessary early reintervention.

In hypertrophic cardiomyopathy (HCM), AV sequential pacing with a short AV delay may reduce left ventricular outflow tract (LVOT) gradients and improve symptoms in drug-refractory patients (discordant data). Percentage of fibrosis on MRI is now part of the evaluation and recommendations for ICD indications in HCM patients.

Patients with Lamin proteins A and C (LMNA) mutations, including those with Emery-Dreifuss or limb-girdle muscular dystrophies, are at high risk for arrhythmias and may benefit from ICD implantation if they meet conventional pacing criteria and have a life expectancy exceeding one year.

Infiltrative cardiomyopathies, such as those caused by amyloidosis, Fabry disease, hemochromatosis, or glycogen storage diseases, frequently involve conduction abnormalities and both atrial and ventricular arrhythmias. Device implantation in these patients should follow standard pacing and defibrillation criteria, with special attention to amyloidosis given its strong association with SCD.

Inflammatory cardiomyopathies, whether caused by infections (e.g., Lyme disease), autoimmune conditions (e.g., sarcoidosis, giant cell myocarditis), or toxins (e.g., chemotherapy, radiation), often involve the atrioventricular node and conduction system. In cardiac sarcoidosis, pacing is recommended for both permanent and transient AV block. In patients with cardiac sarcoidosis and an LVEF below 50%, the use of CRT-D or ICD should be considered due to the significantly elevated risk of ventricular arrhythmias (VA) and sudden cardiac death.[13]

LVADs and Device Integration

For patients with advanced HFrEF who are not eligible for heart transplant, LVAD therapy offers a life-sustaining option. Prior to LVAD implantation, it is essential to optimize device-based therapies such as CRT and ICD to ensure clinical stability. In patients with CRT indications, CRT and/or CSP may be considered before or after the LVAD. Strategic decisions on lead selection and placement strategies, including epicardial versus endocardial routes, and MRI compatibility are important considerations when planning durable mechanical support. For patients with a narrow QRS and no indications of pacing,

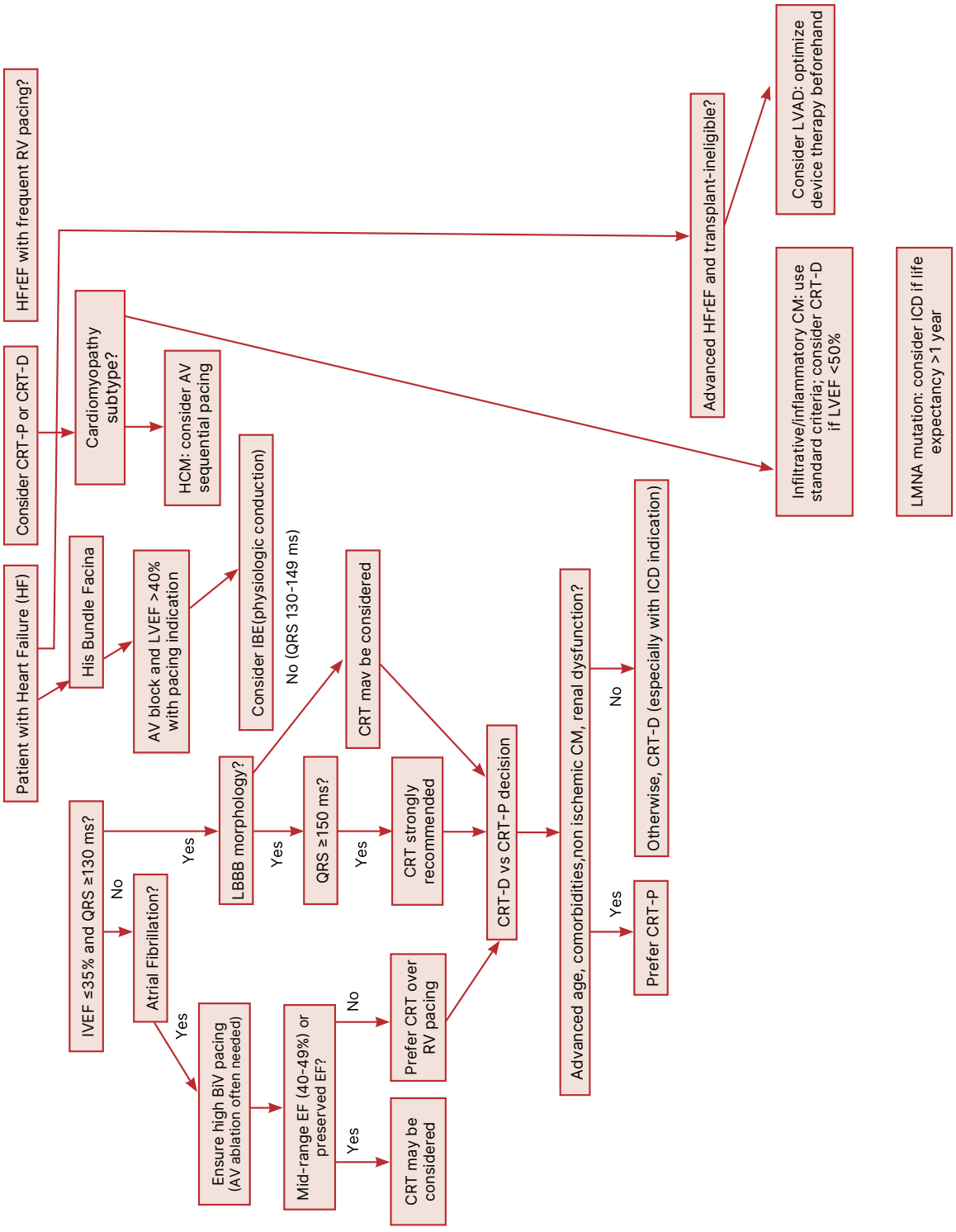

Figure 1. Decision Tree for Device Therapy in HF; *courtesy of Eileen O'Meara, MD, Blandine Mondésert, MD, FCHRS*

Abbreviations: HFrEF: heart failure with reduced ejection fraction; **CRT-D:** cardiac resynchronization therapy with defibrillator; **CRT-P:** cardiac resynchronization therapy with pacemaker; **IVEF:** Indexed left ventricular ejection fraction; **AV:** aortic valve; **LVEF:** left ventricular ejection fraction; **LBBB:** left bundle branch block; **HCM:** hypertrophic cardiomyopathy; **EF:** ejection fraction; **RV:** right ventricular; **ICD:** implantable cardiac defibrillator; **LMNA:** Lamin proteins A and C; **LVAD:** left ventricular assist device; **CM:** cardiomyopathy

using ICDs for primary prevention remains controversial.[14] In such high-risk populations, S-ICDs may help reduce lead-related and infectious complications, although electromagnetic interferences with the Heart Mate 3 pump have been observed. Meanwhile, EV-ICDs remain contraindicated in this population.

Conclusion

Device therapies are essential components in managing heart failure, offering symptom relief, reverse remodelling, and reductions in hospitalization and mortality in appropriately selected patients. The indications for CRT or CSP and ICD (transvenous or non-transvenous) must be tailored based on factors such as QRS morphology, cardiac rhythm, LVEF, comorbidities, and patient-specific factors including age, genetic profile, and personal preferences. As new evidence emerges and technologies evolve, a patient-centred, guideline-informed approach remains the cornerstone of optimal device-based therapy in HF.

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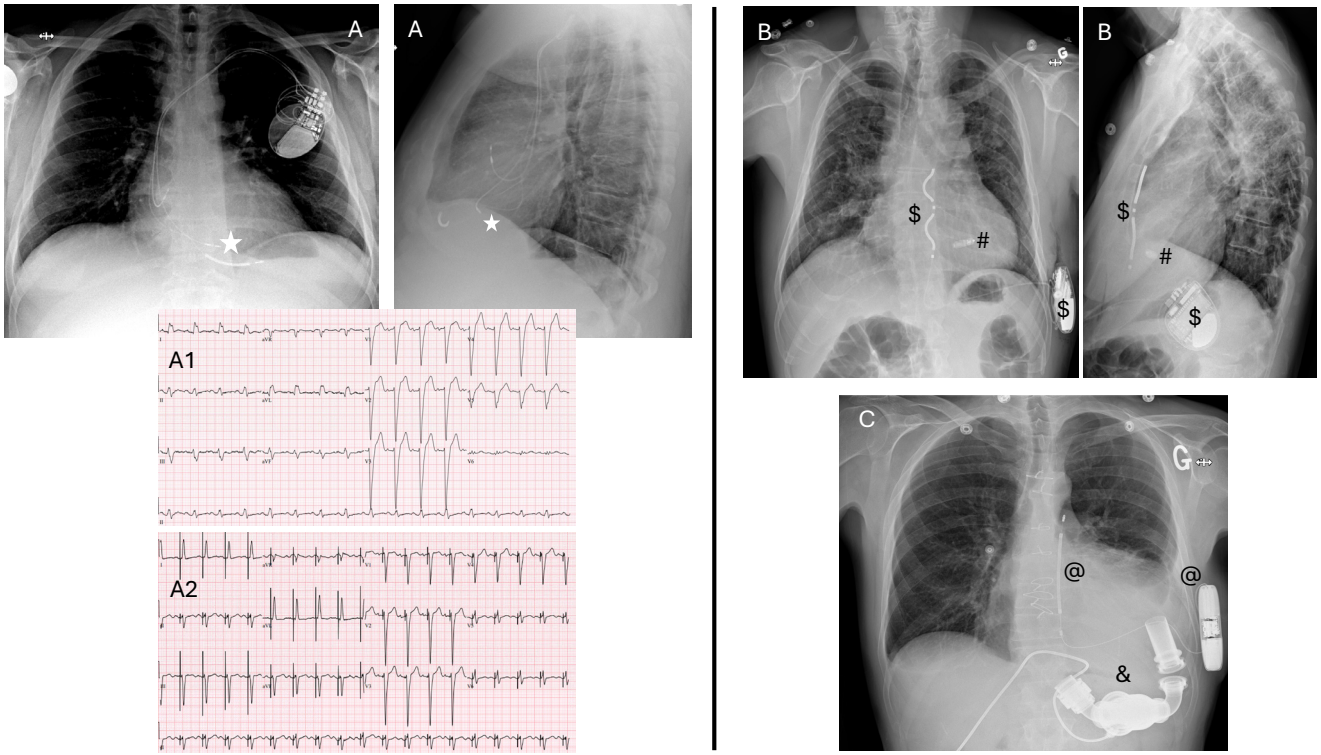

Figure 2. Examples of Devices Implanted in Heart Failure Management:
A- A 42-year-old patient with non-ischemic cardiomyopathy and left bundle branch block has undergone a failed CRT implantation. As a bail-out strategy, an LBBAP-defibrillator was successfully implanted, resulting in QRS narrowing. A: PA and lateral chest X-ray views *: LBBAP lead A1: LBB A2: LBBAP, characterized by a positive and narrow QRS in leads I and aVl, with a small R wave at the end of the QRS in V1
B- A 62-year-old patient with sarcoidosis-related cardiomyopathy, experienced multiple complications following several previous transvenous ICD procedures. The final solution involved implantation of an extravascular ICD (with the lead positioned beneath the sternum) (Medtronic Aurora®), along with a leadless AV Micra® pacemaker (Medtronic)
C- A 35-year-old patient with non-ischemic cardiomyopathy supported by an LVAD with a subcutaneous ICD (S-ICD, Boston Scientific Emblem®); *courtesy of Eileen O'Meara, MD, Blandine Mondésert, MD, FCHRS*

Abbreviations: CRT: cardiac resynchronization therapy; **ICD:** implantation cardioverter defibrillator; **LBB:** left bundle branch; **LBBAP:** left bundle branch area pacing; **LVAD:** left ventricular assistant device; **PA:** posteroanterior; **S-ICD:** subcutaneous implantation cardioverter defibrillator

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Contemporary Management of Heart Failure with Preserved Ejection Fraction: What is Current and What Lies Ahead?

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Introduction

In Canada, the incidence of heart failure (HF) among adults ≥40 years has increased from 521 per 100,000 to 601 per 100,000 from 2013 to 2023,[1] and is expected to rise further in the coming decades.[2] HF is the second leading cause of death in Canada, with an age standardized all-cause mortality rate of 5,761 per 100,000 compared to people without HF at 913 per 100,000.[3] HF with preserved ejection fraction (HFpEF), defined as the clinical syndrome of HF with left-ventricular ejection fraction (LVEF) ≥50%, comprises approximately half of all HF diagnoses. Contemporary data published this year suggests one- and five-year mortality rates for HFpEF are similar to those seen in heart failure with reduced ejection fraction (HFrEF).[2]

The Canadian Cardiovascular Society (CCS) endorses the universal definition of HF, which classifies HFpEF as having an LVEF cutoff of 50% and emphasizes markers of increased left ventricular (LV) filling pressures as a reflection of the underlying pathophysiology.[4] HFpEF is associated with both functional and structural cardiac abnormalities, including diastolic dysfunction, ventricular and atrial remodelling, LV hypertrophy, and fibrosis.[5] In addition, systemic inflammation, endothelial dysfunction, altered myocardial energetics, and abnormalities in skeletal muscle are increasingly recognized as important contributors to HFpEF pathophysiology and serve as therapeutic targets.[5]

Comorbid conditions including type 2 diabetes mellitus (T2DM), obesity, atrial fibrillation, chronic kidney disease, pulmonary hypertension, obstructive sleep apnea, and iron deficiency have been associated with the development and progression of HFpEF.[6] Furthermore, there is growing interest in identifying distinct HFpEF phenotypes to better characterize patient populations beyond their comorbid conditions, with the aim of personalizing prognosis and treatment options. In a recent study, three distinct HFpEF phenotypes were identified, including a younger group with primarily New York Heart Association (NYHA) II symptoms, a higher prevalence of smoking, and a lower prevalence of diabetes and chronic kidney disease; another consisting of older age individuals (mean age 77 years), predominantly women with atrial fibrillation and chronic kidney disease; and a third group of intermediate age (mean age 66 years) with a very high prevalence of obesity and diabetes, greater functional impairment, and elevated inflammatory markers.[7] Notably, the patients in this latter phenotype, with a very high prevalence of obesity and diabetes, were most likely to be hospitalized for HF along with having an overall mortality risk comparable to those patients classified in the older, atrial fibrillation, chronic kidney disease phenotype, despite their younger age.[7]

Guideline Directed Medical Therapy

Sodium Glucose Cotransporter 2 Inhibitors (SGLT2i)

SGLT2i inhibit the active reabsorption of glucose in the proximal tubule of the kidney, thereby reducing blood sugar levels. Several mechanisms of action have been proposed to explain their cardioprotective effects. At the cellular level, SGLT2i improve cardiac energetics through a hypoxic-like transcription paradigm and reduce inflammation and oxidative stress by decreasing epicardial adipose tissue and altering adipokine signalling.[8] At the structural level, they improve diastolic function by reducing myofilament stiffness and promoting extracellular matrix remodelling. In addition, they support cardiac workload and function through natriuresis and osmotic diuresis.[8]

The DELIVER (Dapaglaflozin Evaluation to Improve the Lives of Patients with Preserved Ejection Fraction Heart Failure) and EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart Failure with Preserved Ejection Fraction) trials evaluated the effect of two SGLT2i in outpatients with HF and an LVEF of ≥40%, with or without type 2 diabetes mellitus (T2DM) on clinical outcomes **(Table 1)**.[9,10] Both trials showed a significant reduction in HF hospitalization (HFH) or cardiovascular (CV) death compared to a placebo, driven predominantly by reduction in HFH. In both trials, the effect of SGLT2i was independent of diabetes status. Additionally, the PRESERVED-HF (Dapagliflozin in Preserved Ejection Fraction Heart Failure) trial showed that dapagliflozin improved patient reported symptoms, physical limitations, and exercise function, when compared to a placebo.[11]

SGLT2i should strongly be considered for the treatment of HFpEF, barring cases of absolute contraindications, which should be documented by clinicians, given their positive impact in reducing morbidity and mortality.

Steroidal and Nonsteroidal Mineralocorticoid Receptor Antagonist (MRA)

MRAs block the binding of aldosterone to the mineralocorticoid receptor, which prevents the downstream effects of sodium retention, potassium excretion, and water retention, contributing to lower blood pressure. MRAs also help reduce cardiac fibrosis by inhibiting the upregulation of pro-fibrotic and inflammatory cytokines, which leads to improved diastolic function.[12] In addition, MRAs exert vascular effects by reducing arterial stiffness, thereby reducing afterload.[12] Steroidal MRAs, including spironolactone and eplerenone, bind non-selectively to various steroid receptors, which can contribute to hyperkalemia and hormonal disturbances –most notably anti-androgenic effects in men, particularly with spironolactone.[13] In contrast, nonsteroidal MRAs, such as finerenone, exhibit greater selectivity for mineralocorticoid receptors, offer greater potency, and have a slightly lower risk of hyperkalemia.[13]

The TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) trial demonstrated a significant reduction in HFH in patients with LVEF ≥45% who were in the spironolactone group compared to placebo.[14] Although the overall TOPCAT trial did not show a significant reduction in the primary outcome, a post-hoc analysis of TOPCAT found a significant reduction in the composite primary outcome of CV death, aborted cardiac arrest, or HFH among participants from North America and South America that was attributed to regional differences in patient characteristics.[15] The lack of definitive evidence from TOPCAT led to heterogeneity in the use of MRAs in HFpEF patients. Recently, the FINEARTS-HF (finerenone in Heart Failure with Preserved Ejection Fraction) trial enrolled patients with HF and LVEF ≥40% to receive finerenone versus standard of care including 13-14% of patients on SGLT2i. The trial demonstrated a significant reduction in the composite primary outcome of total worsening HF events (including first and recurrent unplanned hospitalizations or urgent HF visits) and CV death compared to placebo.[16]

Prior to the FINEARTS-HF trial, the CCS issued a weak recommendation, based on moderate-quality of evidence, for the use of MRAs in HFpEF with an updated guideline anticipated later this year.[17] Given the additive findings from FINEARTS-HF, clinicians should strive to use MRAs for managing HFpEF patients with acceptable renal function to reduce the risk of HFH.

Angiotensin Receptor Blocker (ARB) and Angiotensin Receptor Blocker Neprilysin Inhibitor (ARNI)

Angiotensin II blockade with ARBs reduces aldosterone secretion leading to decreased sodium and water retention which contributes to reduce blood pressure. In addition, ARBs mitigate the pro-fibrotic and hypertrophic effects of angiotensin II on the myocardium, thereby improving diastolic function.[18] In the CHARM-Preserved (Candesartan in Patients with Chronic HF and Preserved Left-Ventricular Ejection Fraction) trial, patients with LVEF ≥40% who were randomized to receive candesartan showed a non-significant trend in reduction of CV death and HFH, driven mostly by reduction in HFH when compared to placebo.[19] However, the I-PRESERVE (Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction) trial did not show a reduction in the primary composite outcome of all-cause mortality or CV hospitalization in patients with LVEF ≥45%.[20]

ARNIs incorporate neprilysin inhibition with angiotensin II inhibition. By preventing the degradation of natriuretic peptides, bradykinin, and substance P, ARNIs promote vasodilation, natriuresis, diuresis, and exert antifibrotic and

Trial Name Intervention and Comparator	Number of Participants per Arm	Primary Outcome	Number of Events	Effect Measure
DELIVER Dapagliflozin vs Placebo	3,131 vs 3,132	CV death or worsening HF (HFH or urgent visit for HF)	512 vs 610	HR 0.82 (95% CI, 0.73–0.92)
EMPEROR-Preserved Empagliflozin vs Placebo	2,997 vs 2,991	CV death or HFH	415 vs 511	HR 0.79 (95% CI, 0.69–0.90)
PRESERVED-HF Dapagliflozin vs Placebo	152 vs 152	KCCQ-CSS	N/A	Mean change +5.8 points (95% CI, 2.3–9.2)
TOPCAT Overall Spironolactone vs Placebo	1,722 vs 1,723	CV death, aborted cardiac arrest, or HFH	320 vs 351	HR 0.89 (95% CI, 0.77–1.04)
TOPCAT Americas Spironolactone vs Placebo	886 vs 881	CV death, aborted cardiac arrest, or HFH	242 vs 280	HR 0.82 (95% CI, 0.69–0.98)
FINEARTS-HF Finerenone vs Placebo	3,003 vs 2,998	CV death or worsening HF (HFH or urgent visit for HF)	1,083 vs 1,283	HR 0.84 (95% CI, 0.74–0.95)
CHARM-Preserved Candesartan vs Placebo	1,514 vs 1,509	CV death or HFH	333 vs 366	HR 0.89 (95% CI, 0.77–1.03)
I-PRESERVE Irbesartan vs Placebo	2,067 vs 2,061	All-cause mortality or CV hospitalization	742 vs 763	HR 0.95 (95% CI, 0.86–1.05)
PARAGON-HF Sacubitril/Valsartan vs Valsartan	2,407 vs 2,389	HFH or CV death	894 vs 1,009	Rate Ratio 0.87 (95% CI, 0.75–1.01)
PARAGLIDE-HF Sacubitril/Valsartan vs Valsartan	233 vs 233	NT-proBNP reduction	N/A	Ratio of Change 0.85 (95% CI, 0.73–0.99)
Pooled PARAGLIDE-HF and PARAGON-HF Sacubitril/Valsartan vs Valsartan	541 vs 547	Total worsening HF events and CV death	281 vs 358	Rate Ratio 0.78 (95% CI, 0.61–0.98)
STEP-HFpEF Semaglutide vs Placebo	263 vs 266	Change in KCCQ-CSS	N/A	Estimated Difference 7.8 points (95% CI, 4.8–10.9)

Trial Name Intervention and Comparator	Number of Participants per Arm	Primary Outcome	Number of Events	Effect Measure
STEP-HFpEF DM Semaglutide vs Placebo	310 vs 306	Change in KCCQ-CSS	N/A	Estimated Difference 7.3 points (95% CI, 4.1 – 10)
SUMMIT Tirzepatide vs Placebo	364 vs 367	CV death or worsening HF event	36 vs 56	HR 0.62 (95% CI, 0.41–0.95)
SODIUM-HF Restricted sodium intake vs Standard of Care	397 vs 409	CV hospitalization, CV ED visit, or all-cause mortality	60 vs 70	HR 0.89 (95% CI, 0.63–1.26)
FRESH-UP Fluid restriction vs Liberal	250 vs 254	Change in KCCQ-OSS	N/A	Mean Difference 2.17 (95% CI, -0.06–4.39)

Table 1. Summary of Contemporary Trials in Patients with Heart Failure with Preserved Ejection Fraction; *courtesy of Abdullah Malik, MD, Natasha Aleksova, MD, MSc*

Abbreviations: CV: cardiovascular; **HFH:** heart failure hospitalization; **HR:** hazard ratio; **CI:** confidence interval; **KCCQ:** Kansas City Cardiomyopathy Questionnaire; **CCS:** Clinical Summary Score; **OSS:** Overall Summary Score; **NT-proBNP:** N-terminal pro brain natriuretic peptide; **ED:** emergency department.

antihypertrophic effects, leading to overall decreased myocardial stress.[18] In the PARAGON-HF (Prospective Comparison of ARNI with ARB Global Outcomes in HF with Preserved Ejection Fraction) trial, sacubitril-valsartan did not show a statistically significant reduction in the primary composite outcome of HFH and CV death compared to valsartan in patients with LVEF ≥45%.[21] In an exploratory subgroup analysis, a statistical significant reduction in the primary outcome was seen in patients with LVEF of ≤57%. The PARAGLIDE-HF (Prospective Comparison of ARNI with ARB Given Following Stabilization in Decompensated HFpEF) trial enrolled patients with LVEF >40% within
30 days of a worsening HF event and randomized them to either sacubitril-valsartan or to valsartan alone.[22] In the ARNI group, the primary outcome of time-averaged proportional change in NT-proBNP from baseline through week 4 and 8 was decreased compared to the valsartan group. Furthermore, a pre-specified patient-level pooled analysis of these two trials demonstrated that ARNIs significantly reduced total worsening HF events and CV death compared to valsartan.[23]

In considering this class of therapeutics for heart failure, the 2017 CCS guidelines make a weak recommendation in favor of the ARB candesartan, citing evidence from the abovementioned CHARM-Preserved.[17] These guideline recommendations do not incorporate more recent evidence supporting the use of ARNIs for HFpEF however will likely do so in the future. Given their mechanism of action, ARNIs are more likely to potentiate stronger cardiorenal benefits than ARB. When considering the use of ARNIs, clinicians should adopt a more personalized approach that includes a discussion with the patient about the side effects of ARNIs, which include hypotension and angioedema, as well as cost considerations.

Nonpharmacologic Management Considerations

Previous CCS guidelines provided a weak recommendation based on low-quality evidence for restricting dietary sodium intake to 2-3 grams per day.[17] Since then, the SODIUM-HF (Study of Dietary Intervention under 100 mmol in Heart Failure) trial evaluated patients with HF and a

median LVEF of 36% (IQR 27-49) comparing a low sodium diet <1500 mg per day versus standard of care. The trial found no significant differences in the primary composite outcome of CV hospitalization, CV related emergency department visits, or all-cause mortality between the two groups.[24] In subgroup analysis comparing patients with LVEF >40% to those with LVEF <40%, there was still no difference in the primary outcome. As such, suggested sodium intake should be individualized with consideration of dietary habits and concurrent use of diuretics.

The CCS also provides a weak recommendation with low-quality evidence for restricting daily fluid to approximately 2 litres per day for patients experiencing fluid retention or congestion not easily controlled with diuretics. Recently, the FRESH-UP (Fluid Restriction in Heart Failure versus Liberal Uptake) trial randomized patients with HF and a mean LVEF of 40.3% (SD 10.9) to either a restricted fluid intake of up to 1500 ml per day or a liberal intake.[25] The primary outcome, a change in the Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OSS), was not significantly lower in the treatment group and secondary outcomes of death, HFH, and changes in loop diuretic use also showed no differences. In a subgroup analysis of patients with HFpEF, there was no difference in the KCCQ-OSS between the intervention and control groups. Given the limited evidence, tailored recommendations for fluid restriction with consideration of the specific HFpEF phenotype are prudent.

Considerations for Obesity in HFpEF

Obesity has become a growing area of interest in the HFpEF scientific community given its high prevalence in HFpEF and its involvement

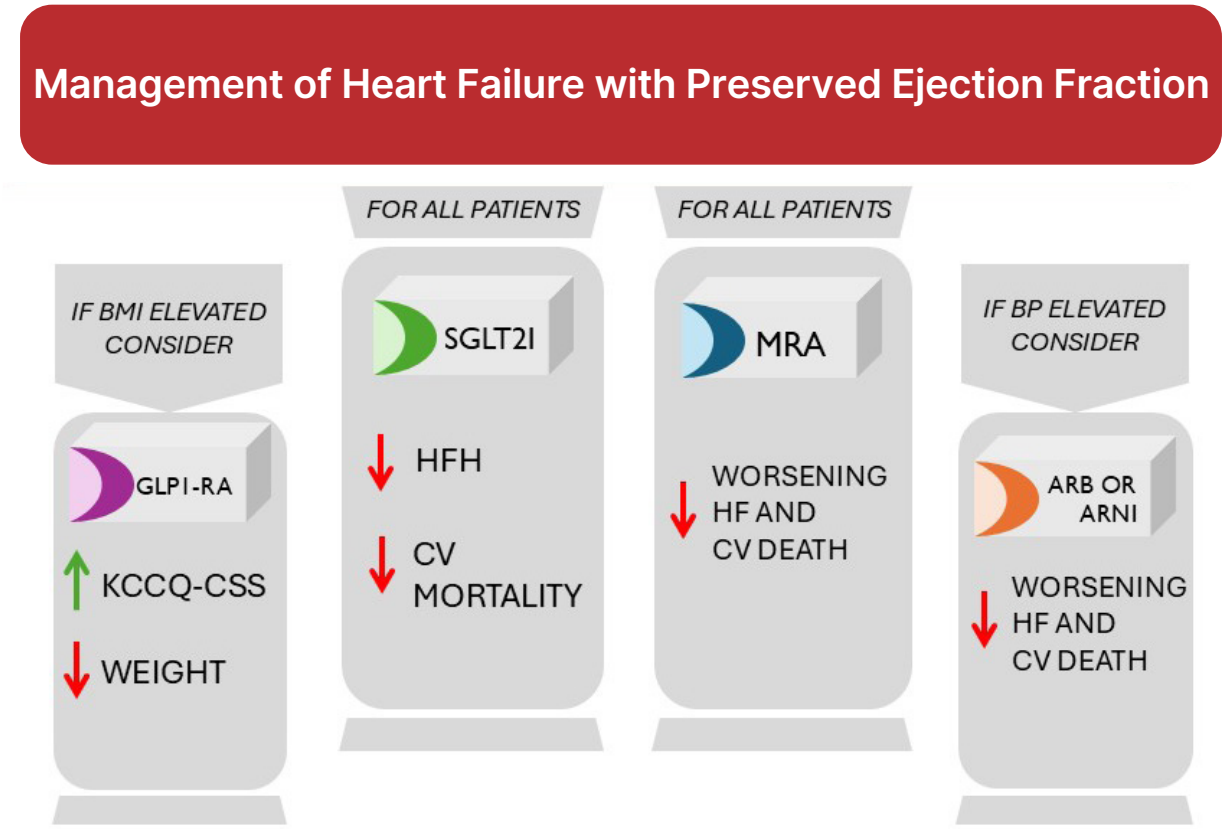

Figure 1. Summary of Pharmacologic Management Principles for Heart Failure with Preserved Ejection Fraction; *courtesy of Abdullah Malik, MD, Natasha Aleksova, MD, MSc*

Abbreviations: BMI: body mass index; **BP:** blood pressure; **GLP1-RA:** glucagon like peptide 1 receptor agonist; **SGLT2I:** Sodium Glucose Cotransporter 2 Inhibitor; **MRA:** mineralocorticoid receptor antagonist; **ARB:** angiotensin receptor blocker; **ARNI:** angiotensin receptor blocker neprilysin inhibitor; **KCCQ-CCS:** Kansas City Cardiomyopathy Questionnaire Clinical Summary Score; **HFH:** heart failure hospitalization; **CV:** cardiovascular.

in promoting a pro-inflammatory state that contributes to altered cardio-metabolic and fibrosis pathways. In the STEP-HFpEF and STEP-HFpEF DM (Effect of Semaglutide 2.4 mg Once Weekly on Function and Symptoms in Subjects with Obesity-related Heart Failure with Preserved Ejection Fraction) trials, obesity HFpEF patients with and without diabetes with LVEF ≥45% were randomly assigned to either the subcutaneous glucagon like 1 receptor agonist (GLP1-RA) semaglutide or placebo group for 52 weeks.[26, 27] At 52 weeks, the semaglutide group showed a significantly greater improvement in the KCCQ clinical summary score (KCCQ-CSS) compared to placebo along with a significant reduction in weight. In a secondary win ratio analysis of a hierarchical composite of all-cause mortality, number and timing of HF events, differences in the KCCQ-CSS, and differences in the 6-minute walk distance, semaglutide demonstrated a greater number of wins over placebo. Secondary outcomes also showed a significant improvement in 6 minute walk distance as well as a significant reduction in hsCRP. In the SUMMIT (A Study of Tirzepatide in Participants with Heart Failure with Preserved Ejection Fraction and Obesity) trial, obesity HFpEF patients regardless of diabetes status with LVEF ≥50% were randomly assigned to either tirzepatide, a combination glucose-dependent insulinotropic polypeptide receptor agonist (GIP-RA) and GLP1-RA or placebo.[28] The composite primary outcome of CV death or worsening HF events was significantly reduced in the tirzepatide group, primarily driven by a reduction in the number of worsening HF events.

Irrespective of diabetes, GLP1-RA analogues are promising therapeutic options for patients with HFpEF and obesity. Not only do they result in significant weight loss, improvement in metabolic parameters and decrease in inflammation, they offer improvements in quality of life, functional status and reduce the risk of HF events such as HFH.

Future Directions

Several ongoing trials for patients with HFpEF are targeting various pathophysiologic mechanisms related to disease origin and progression. Among these, more studies evaluating MRAs in HFpEF are on the horizon, including the SPIRRIT-HF trial investigating spironolactone and the REDEFINE-HF trial evaluating finerenone in hospitalized patients with acute decompensated heart failure and LVEF≥40%.[29] To determine if reducing inflammation can improve outcomes, ziltivekimab, a monoclonal antibody targeting the interleukin-6 ligand, is being compared to placebo in patients with LVEF >40%, focusing on a composite outcome of CV death, HFH, or urgent HF visits.[30]

Conclusion

Therapeutic options for the contemporary management of HFpEF continue to expand. SGLT2i and MRAs remain the cornerstone of treatment, while ARNIs and GLP1-RAs may be considered for specific populations of patients living with HFpEF. This highlights the need for an individualized approach to patient care **(Figure 1)**. Future research into the treatment and management of HFpEF is promising, with increasing recognition that targeting the pathophysiology associated with HFpEF may lead to improved patient outcomes.

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Secondary Prevention After Myocardial Infarction: Bridging Evidence to Practice

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Introduction

Management of acute coronary syndrome (ACS) has advanced significantly over the past years, with various strategies shown to improve patient survival and reduce cardiovascular (CV) adverse events. An expanding body of literature supports the efficacy of both pharmacologic and non-pharmacologic approaches after acute myocardial infarction (MI). This review aims to provide a comprehensive overview of the secondary prevention strategies after acute MI in the modern era, with a particular focus on recent guidelines and their application in Canadian healthcare practice.

The Non-Pharmacological Path After Acute MI

Cardiac rehabilitation (CR) remains the cornerstone of secondary prevention after MI. It is currently recommended prior to hospital discharge after an ACS event, as it has been shown to reduce death, MI, and hospital readmission. CR's multifaceted approach also aims to enhance functional capacity and patients' quality of life, whether delivered through a centre-based or home-based program.[1]

Lifestyle modification with a personalized and team-based approach is also an essential part of secondary prevention.[2] It is grounded in the following principles, designed to improve CV outcomes and reduce mortality.[2]

- The importance of complete abstinence from tobacco, using behavioural and/or pharmacologic approaches when necessary. E-cigarettes are not considered a first-line therapy for tobacco abstinence, due to unknown long-term effects.
- Limitation of alcohol intake to ≤1 drink/day for women and ≤2 drinks/day for men, as alcohol use offers no CV benefit.
- Physical activity counselling to encourage patients to engage in ≥150 minutes/week of moderate-intensity aerobic activities, and ≥2 days/week resistance training.
- Weight management in overweight or obese patients.
- Dietary modification with the adoption of a Mediterranean diet. The use of omega-3 fatty acids or dietary supplements has not shown additional CV benefit.
- Stress management and mental health counselling.

Cardiovascular risk factors should also be managed in accordance with major society guidelines, including optimal control of hypertension,[3] hypercholesterolemia and hypertriglyceridemia management,[4] and aggressive treatment of diabetes.[5]

Electrical complications should also be managed appropriately, including the use of an implantable cardioverter-defibrillator for ventricular arrhythmias when indicated, and a permanent pacemaker for irreversible advanced bradyarrhythmia.[1]

Last but not least, influenza vaccination has demonstrated a survival benefit at one year after MI and is therefore recommended to reduce death and major adverse cardiovascular events (MACE).[1] Other vaccines, such as the COVID-19 and pneumococcal polysaccharide vaccines, may also help lower the risk of post-infection complications and MACE in high-risk populations, particularly in patients with established coronary artery disease.[2]

Rewiring Recovery: Pharmacologic Approaches to ACS Care after MI

Antithrombotic therapy

Dual antiplatelet therapy (DAPT) with low-dose acetylsalicylic acid (ASA) and a P2Y12

inhibitor (clopidogrel, ticagrelor, or prasugrel) is recommended for patients undergoing percutaneous coronary intervention (PCI), coronary bypass surgery, as well as for those managed medically without revascularization for ACS. The duration of DAPT may range from 1 month to up to 3 years, depending on individual risk profiles, to reduce the risk of recurrent ischemic events.[6] In patients managed without revascularization, only ticagrelor and clopidogrel are recommended as part of the DAPT strategy. Selection and duration of DAPT therapy should be guided by a careful assessment of the patient's individual bleeding and ischemic risks.[6] Once DAPT is discontinued, lifelong single antiplatelet therapy (SAPT) with either ASA or clopidogrel is recommended, although emerging evidence suggests a potential benefit of clopidogrel over ASA for reducing recurrent ischemic events.[7]

In the COMPASS trial, combining low-dose rivaroxaban (2.5 mg twice daily) with low-dose ASA reduced the risk of MACE in patients with stable atherosclerotic cardiovascular disease (ASCVD)—including those with remote PCI—at the expense of an increased bleeding risk.[8] As such, its use may be considered for secondary prevention of ASCVD.[9]

A more detailed approach to the management and choice of antithrombotic therapy in both the acute and chronic phases following ACS is presented in **Figure 1**, incorporating the most recent evidence and guideline recommendations.

Lipid-Lowering Therapies

The treatment of dyslipidemia is considered a fundamental part of pharmacologic care after MI. Patients should all be treated with maximally tolerated dose of statins with add on therapy considered when low-density lipoprotein cholesterol (LDL-C) of ≥1.8 mmol/L, non-high-density lipoprotein cholesterol (non-HDL-C) of ≥2.4 mmol/L, and/or apolipoprotein B (ApoB) of ≥0.7 g/L.4 The European Society of Cardiology (ESC) recommends even more stringent targets, advising an LDL-C level of <1.4 mmol/L with a reduction of ≥50% after an ACS, and potentially lowering the target to an LDL-C of <1.0 mmol/L in patients who experience a second event within 2 years.[10]

Besides health-behaviour modifications, early initiation of high-intensity potent statin therapy (atorvastatin or rosuvastatin) is recommended as first-line treatment to achieve these targets and reduce MACE.[1,4] The evidence supporting their use is robust, with demonstrated benefits during both the acute and chronic phases following MI.[11,12] In both the European and American Guidelines, early reassessment of lipids post ACS and adjustment of therapy until desired lipid levels are achieved (every 4-8 weeks) are emphasized.[1,10]

In addition to high-dose statin therapy, second-line treatments include ezetimibe (if LDL-C levels remain between 1.8 and 2.2 mmol/L) or proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors in patients whose lipid parameters are further away from threshold levels (if LDL-C remains >2.2 mmol/L, ApoB >0.8 g/L or non-HDL-C >2.9 g/L). Other high-benefit patients for initiating PCSK9 inhibitors upfront after high-dose statin therapy include, among others, those within 52 weeks of index hospitalization for a recent ACS, patients with recurrent acute MI, and those with diabetes.[4]

The FOURIER and ODYSSEY OUTCOMES trials are the key clinical studies evaluating PCSK9 inhibitors for managing hypercholesterolemia in MI,[13,14] and they are cited in recent guidelines.[4] The FOURIER trial evaluated evolocumab in patients with established ASCVD, including those with prior MI, prior stroke, or peripheral artery disease, demonstrating a significant reduction in MACE when added to statin therapy (hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.79 to 0.92, P<0.001).[13] The benefits of evolocumab were reinforced in the FOURIER-OLE study which confirmed a long-term sustained reduction in MACE by 15% and CV death by 23% over a follow-up period exceeding 8 years.[15] The ODYSSEY OUTCOMES trial specifically enrolled patients who experienced a recent ACS within the preceding year and had persistent hypercholesterolemia despite receiving maximally tolerated statin therapy. In this population, alirocumab significantly reduced MACE and all-cause mortality compared to placebo, achieving a relative risk reduction of approximately 15% for the primary composite endpoint (HR 0.85, 95% CI 0.78 to 0.93, P<0.001).[14]

Ezetimibe has been demonstrated to be an effective adjunct therapy to statin post ACS. In the IMPROVE-IT trial, adding ezetimibe to statin therapy resulted in a 6.4% relative risk reduction and a 2% absolute risk reduction in MACE over a 7 year period compared to placebo (HR 0.94, 95% CI 0.89 to 0.99, P=0.016).[16]

Recent updates to the American College of Cardiology guidelines for managing hypercholesterolemia post-ACS include the

addition of inclisiran and bempedoic acid. These agents are recommended for patients on maximally tolerated statin therapy or those with statin intolerance.[1] Bempedoic acid is an ATP-citrate lyase inhibitor that provides an additional ~20% reduction in LDL-C, and has demonstrated efficacy in reducing MACE in statin-intolerant patients.[17] In contrast, inclisiran is a small interfering RNA that inhibits PCSK9 synthesis, achieving up to a 50% additional reduction in LDL-C.[18] Its advantage lies in its convenient subcutaneous administration once every 6 months. However, clinical outcome trials with inclisiran in ASCVD are still ongoing.

Beyond hypercholesterolemia management, icosapent ethyl has emerged as another therapy for cardiovascular risk reduction in high-risk patients with elevated triglycerides. It consists of a high-dose, purified eicosapentaenoic (EPA) omega-3 fatty acid (4 g/day). The REDUCE-IT trial demonstrated its efficacy in reducing CV events in high-risk patients (including those post-MI), with an elevated triglyceride level of 1.52 to 5.63 mmol/L showing a 25% relative risk reduction of MACE compared to placebo. This benefit was independent of the reduction in triglyceride levels.[19] A post hoc subgroup analysis of the REDUCE-IT trial in patients with recent ACS <12 months showed a statistically significant reduction in the primary outcome, of 37% with an absolute risk reduction of 9.3%, which is higher than that of the parent trial, without increased risk of bleeding even in patients receiving DAPT.[20]

Renin-Angiotensin-Aldosterone System inhibitors

Oral Angiotensin converting enzyme (ACE) inhibitors are a cornerstone of pharmacologic therapy for secondary prevention after acute MI, with their efficacy demonstrated in landmark trials such as ISIS-4 and GISSI-3.[21] Their benefits are particularly pronounced in high-risk patients,

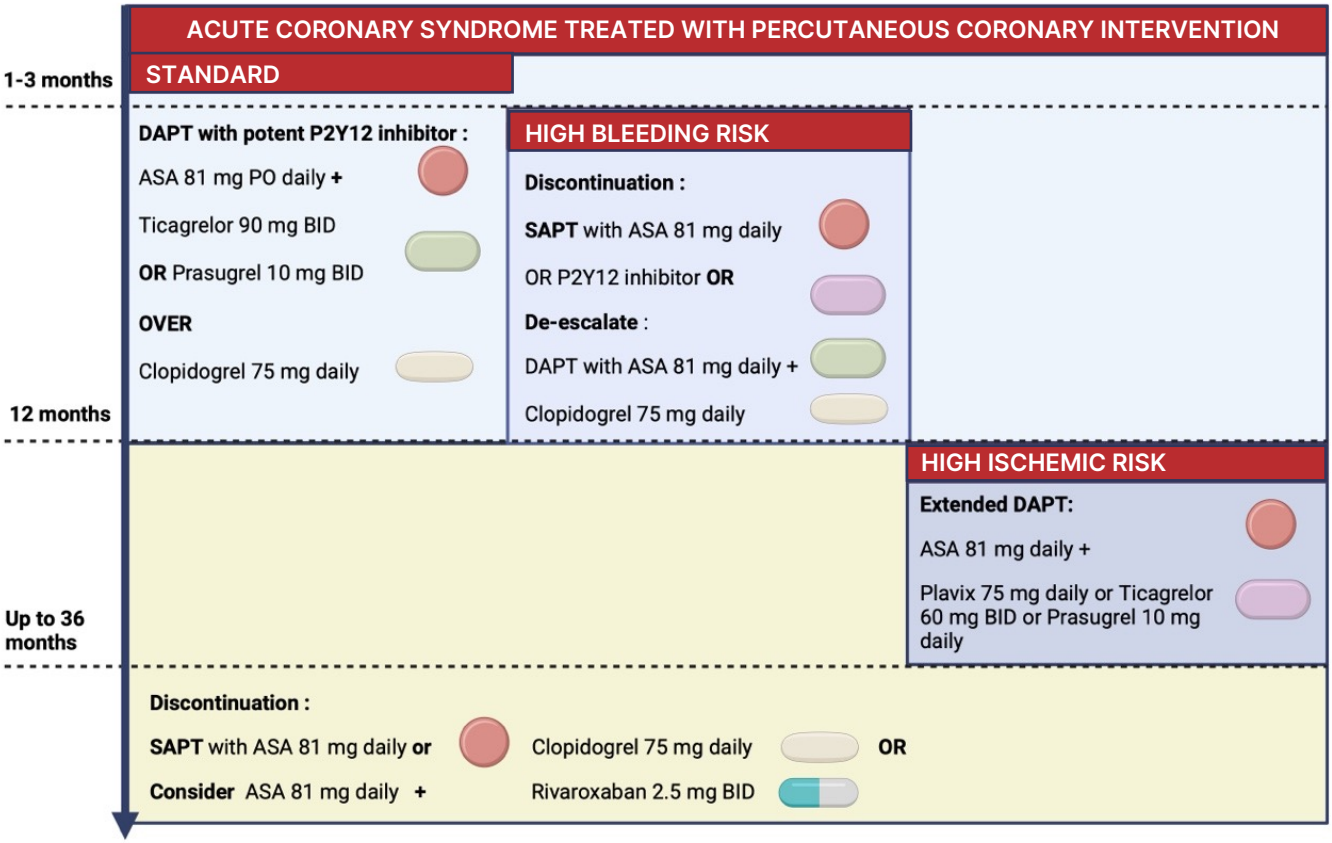

Figure 1. Recommended antithrombotic therapy following acute coronary syndromes treated with percutaneous coronary intervention; *courtesy of Kevin Haddad, MD, MSc and Laurie-Anne Boivin Proulx, MD, MSc*

Abbreviations: ASA: acetylsalicylic acid; **DAPT:** dual antiplatelet therapy; **SAPT:** single antiplatelet therapy.

including those with left ventricular ejection fraction (LVEF) ≤40%, diabetes, hypertension, chronic kidney disease, or anterior ST-elevation MI (STEMI).[1] Accordingly, ACE inhibitors or angiotensin II receptor blockers (ARB)s are recommended for patients with high-risk features after ACS, though their use remains reasonable even in lower-risk patients, given their proven benefits in reducing all-cause mortality and MACE.[1] While the angiotensin receptor–neprilysin inhibitor (ARNIs) have an established role in patients with heart failure (HF) with reduced ejection fraction (HFrEF), they have not demonstrated superiority over ACE inhibitors in reducing CV death or incident HF following acute MI.[22]

Mineralocorticoid receptor antagonists (MRA) have also been studied in the post-MI setting. Based on the EPHESUS study, patients with ACS and an LVEF ≤40% with HF and/or diabetes experienced a reduction in the primary endpoint of all-cause mortality with eplerenone, as well as in the composite endpoint of death or hospitalization from CV causes.[23] However, more recent findings from the CLEAR SYNERGY trial showed that spironolactone did not reduce MACE—defined as CV death or new/worsening HF—in an all-comers post-acute MI population.[24] These results support the use of MRAs for secondary prevention in post MI patients specifically with left ventricular dysfunction and/or HF, but not in unselected post-MI populations where no benefit has been demonstrated.

Beta-blockers

Oral beta-blockers (BB) are currently recommended within the first 24 hours after ACS, in the absence of contraindications, to reduce the risk of ventricular arrhythmias and reinfarction.[1]

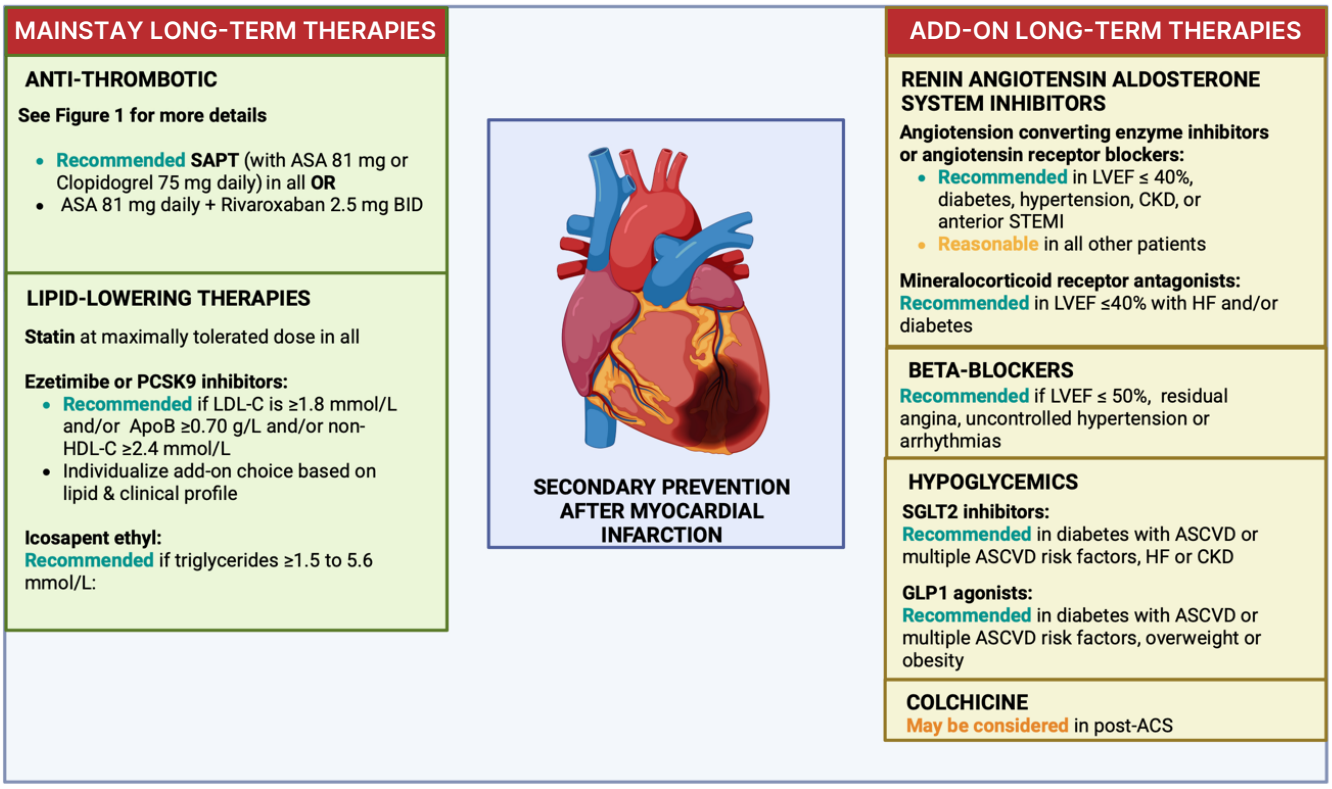

Figure 2. Recommended pharmacological treatment for long-term secondary prevention of myocardial infarction; *courtesy of Kevin Haddad, MD, MSc and Laurie-Anne Boivin Proulx, MD, MSc*

Abbreviations: ACS: acute coronary syndrome; **ApoB:** apolipoprotein B; **ASA:** acetylsalicylic acid; **ASCVD:** atherosclerotic cardiovascular disease; **CKD:** chronic kidney disease; **DAPT:** dual antiplatelet therapy; **GLP1:** glucagon-like peptide-1 receptor agonist; **HF:** heart failure; **HDL-c:** high-density lipoprotein cholesterol; **LDL-c:** low-density lipoprotein cholesterol; **LVEF:** left ventricular ejection fraction; **PCSK9:** proprotein convertase subtilisin/kexin type 9; **SAPT:** single antiplatelet therapy; **STEMI:** ST-elevation myocardial infarction.

They remain a fundamental treatment in patients with compelling and robust indications such as left ventricular dysfunction, HF, ventricular arrhythmias, and anginal symptoms. On the other hand, the benefit of using BB in patients with MI and preserved LVEF (>50%) who have undergone successful reperfusion therapy is less well established.

In the REDUCE-AMI trial, conducted in the contemporary era of early revascularization and optimal medical therapy, routine long-term BB use (median follow-up of 3.5 years) provided no additional benefit in reducing all-cause death or nonfatal MI in patients with preserved LVEF and no other indication for BB (HR 0.96, 95% CI 0.79 to 1.16, P=0.64).[25] The ABYSS trial evaluated the impact of discontinuing BB therapy in stable patients in the chronic phase following MI (median time from MI to randomization of 2.9 years), with an LVEF ≥40% and no CV events in the preceding 6 months. The study failed to demonstrate that discontinuation of BB therapy was non-inferior to continuation for the composite outcome of death, nonfatal MI, nonfatal stroke, or CV hospitalization (HR 1.16, 95% CI 1.01 to 1.33, P=0.44 for non-inferiority).[26] Additionally, interrupting BB did not lead to an improvement in quality of life.[26]

Based on recent guidelines and contemporary data, the use of BB post-MI appears to offer limited benefit in the absence of significant left ventricular dysfunction, HF, or other compelling indications such as a high arrhythmic burden, uncontrolled hypertension, or persistent anginal symptoms. However, for patients with uncomplicated MI who are already receiving chronic BB treatment, continuing BB therapy is currently recommended until new evidence emerges to guide changes in clinical practice.

SGLT2 Inhibitors and GLP1 Agonists

In addition to their established benefits in the treatment of HF and chronic kidney disease (CKD), sodium-glucose co-transporter 2 inhibitors (SGLT2is) are recommended to optimize the prevention of cardiorenal morbidity and mortality in patients with type 2 diabetes with ASCVD or multiple risk factors.[27] In this population, SGLT2is are recommended to reduce the risk of all-cause mortality, CV mortality and MACE.[27,28] Additionally, SGLT2is contribute to lowering the risk of hospitalizations for HF and to reducing the composite risk of significant decline in estimated glomerular filtration rate, progression to end-stage kidney disease, or kidney-related death.[28]

Meanwhile, glucagon-like peptide-1 receptor agonist (GLP-1RAs) are particularly recommended for reducing CV events in patients with diabetes with ASCVD or multiple risk factors. These agents have been shown to reduce all-cause and CV mortality, MACE, and may also reduce the risk of nonfatal stroke.[28] More recently, the SELECT trial demonstrated that subcutaneous semaglutide, a GLP-1RA significantly reduced MACE in patients with overweight or obesity and established ASCVD, even in the absence of diabetes.[29] Oral semaglutide was also shown to reduce MACE in patients with type 2 diabetes with ASCVD, CKD, or both.[30]

Anti-Inflammatory Therapy

Colchicine represents another class of medication that may be used in post-MI management, functioning as an anti-inflammatory agent that interferes with microtubule formation and potentially reducing the atherogenic plaque burden. Evidence supporting its use in the post-ACS setting is derived, in part, from the COLCOT trial, which showed that initiating colchicine 0.5 mg daily within 30 days of MI significantly reduced the primary composite endpoint (CV death, resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina requiring revascularization) over a median follow-up of 22.6 months. These benefits were mainly driven by reductions in stroke and urgent revascularization.[31] According to the most recent guidelines, colchicine may be considered a reasonable option to reduce MACE.[1] However, more recent data from the CLEAR SYNERGY trial failed to demonstrate a reduction in the incidence of MACE with colchicine compared to placebo at a median follow-up of 3 years in patients with acute MI undergoing PCI.[32]

Future Directions

The current molecular approach to secondary prevention post-MI is presented in **Figure 2**. Nonetheless, many unanswered questions remain to be addressed in the coming decade, requiring a concerted and active effort to clarify how best to improve patient outcomes through various secondary prevention strategies.

As recommended post-MI therapies continue to evolve, new strategies are being explored to mitigate the thrombotic and bleeding risks. One such approach involves a new class of anticoagulants—selective factor XIa inhibitors (e.g., milvexian)—which are being evaluated in

the LIBREXIA-ACS trial. These agents serve as an adjunct to antiplatelet therapy post-MI by targeting a pathway considered dispensable for hemostasis, thereby potentially offering thrombotic risk reduction while minimizing bleeding risk.[33]

In parallel, therapeutic strategies targeting other residual risks are being investigated. While no approved therapy specifically targets lipoprotein(a)—a genetic risk factor for atherosclerosis—research is ongoing. Pelacarsen, an antisense oligonucleotide that lowers lipoprotein(a) levels, is being evaluated in the ongoing HORIZON trial to determine its potential to reduce CV events in patients with established ASCVD including previous MI.[34]

Additionally, finerenone, a novel nonsteroidal MRA, has shown a reduction in HF events and CV death in patients with HF and an LVEF ≥40%.[35] However, its specific role in the post-acute MI population remains to be established.

Ongoing investigations are exploring the potential of certain anti-inflammatory and immunomodulation molecules to reduce atherosclerosis progression. These agents could offer new targets for secondary prevention in patients with a high atherosclerotic risk. The ARTEMIS trial is currently evaluating ziltivekimab, a monoclonal antibody targeting interleukin-6, for its potential to reduce recurrent events in patients post-MI.[36]

Conclusion

The journey after an ACS extends beyond discharge. Through a combination of effective medical therapies and sustained non-pharmacological approaches, secondary prevention transforms recovery into resilience—reducing CV risk, improving survival, and empowering patients to reclaim their health. Achieving this goal requires aggressive risk factor management, delivered through a personalized, team-based approach, while targeting the full spectrum of mechanisms involved in plaque disruption and disease progression.

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Financial Disclosures

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Physiologic Pacing in 2025: Guidance Made Simple

Corrado De Marco, MD

Introduction

Conventional right ventricular pacing (RVP), particularly at the right ventricular apex, has long been the standard approach for ventricular pacing in patients requiring permanent pacemakers. However, RVP has been shown to introduce electrical and mechanical dyssynchrony, resulting in adverse remodelling, atrial fibrillation, and heart failure.[1] The deleterious effects of a high RVP burden have been demonstrated in the MOST[1] and DAVID[2] trials, wherein patients with ventricular pacing >40% were identified as being at risk of increased adverse clinical outcomes, such as hospitalization for heart failure and death (hazard ratio [HR] 1.61; 95% confidence interval [CI] 1.06–2.44).[2]

In patients with baseline ventricular systolic dysfunction and left bundle branch block or a high ventricular pacing burden, cardiac resynchronization therapy (CRT) using conventional biventricular pacing (BiVP) has been shown to be superior to RVP in preventing ventricular dilation, hospitalization for heart failure, and death.[3,4] Both the BLOCK-HF trial,[3] which compared BiVP to RV pacing in patients with a left ventricular ejection fraction (LVEF) ≤50% and a high pacing burden, and the MADIT-CRT trial,[4] which compared implantable cardioverter-defibrillator therapy alone to CRT with defibrillator in patients with LVEF ≤30% and QRS duration ≥130ms, showed a reduction in all-cause mortality and heart failure events in the BiVP group (HR 0.74; 95% CI 0.60–0.90 and HR 0.66; 95% CI 0.52–0.84, respectively). However, approximately one-third of patients do not respond to conventional BiVP. Moreover, the benefits of conventional BiVP have not been consistently shown across all cohorts.[5]

To overcome the detrimental effects of RVP and the limitations of conventional BiVP, conduction system pacing (CSP) was introduced.[6] This approach harnesses the His-Purkinje system, thereby delivering stimulation mimicking native ventricular activation. The two primary CSP techniques, His bundle pacing (HBP) and left bundle branch area pacing (LBBAP), have demonstrated promise in improving both electrical synchrony and clinical outcomes.[6,7]

Historical Background and Development

HBP was first described in 2000 as a technique for maintaining physiologic ventricular activation in patients with rapid atrial fibrillation and an intact conduction system undergoing atrioventricular node ablation.[8] Despite its physiological advantages early adoption of HBP was limited by technical challenges such as high pacing thresholds and lead instability.

Introduced in 2017, LBBAP[9] involves delivering pacing impulses to the left bundle branch (LBB) or to adjacent areas within the left ventricular septum, resulting in capture of the left-sided conduction system. This technique offers near-physiological ventricular activation, while overcoming the principal limitations of HBP.

Each CSP technique manifests as narrow QRS complexes on a standard 12-lead electrocardiogram (ECG). In the case of HBP, the resultant paced QRS morphology should be virtually indistinguishable from the patient's native QRS. LBBAP, on the other hand, will be characterized by a large pacing spike (due to unipolar pacing) and a QRS morphology demonstrating a qR pattern in V1 and a short spike-to-R-wave peak time in V6 **(Figure 2B)**. The specific criterion for LBBAP will be discussed in greater detail later.

Anatomical Considerations

An anatomical understanding of the atrioventricular conduction system is essential for proper CSP implantation and subsequent interpretation of the type of physiological capture obtained. The compact atrioventricular node (AVN) lies in the triangle of Koch, which is bordered anteriorly by the septal tricuspid leaflet, posteriorly by the tendon of Todaro, and has its base at the ostium of the coronary sinus.[10] The transition from the compact AVN to the bundle of His exhibits high variability. It may occur within the triangle of Koch, at the commissure of the anterior and septal tricuspid leaflets, or in the ventricular membranous septum.[10] As the bundle of His emerges from the interventricular septal crest, it branches into the left and right bundles.[10] The LBB thereafter typically fans out into three main fascicles: anterior, septal, and inferior/posterior.[11] The LBB therefore offers a wide target zone for achieving effective physiological pacing. In fact, it has been shown that only 9% of patients undergoing LBBAP are paced at the LBB proper[12]; the remainder are paced via one of the LBB's fascicles. Slight differences in the frontal axis of the paced ECG can be observed depending on which segment of the LBB is activated by the pacing impulse **(Figure 3)**.

Implantation Technique

Due to issues associated with HBP, notably high pacing thresholds and lead instability, it has fallen out of favour at the expense of LBBAP. As such, the increased adoption of LBBAP has led to significant advances in the development of dedicated pacing leads, both lumenless and stylet-driven, as well as improvements in delivery sheath technology.

The key to successful LBBAP lead implantation is penetration of the interventricular septum at a target site likely to result in capture of the left sub-endocardial conduction system. Fluoroscopic guidance **(Figure 1)** is essential, with alternating views between the right anterior oblique (RAO) and left anterior oblique (LAO) projections to ensure an appropriate lead course. Initial penetration is usually targeted at an angle of 10-40° with respect to the horizontal plane in the LAO 30-40° view, with subsequent adjustments made using the RAO view (at approximately 10-20°) for orientation along the anterior-posterior axis.

As the lead progresses through the septum, depth of penetration and presence of conduction system capture can be assessed using several different techniques.[13]

1. The unipolar paced QRS morphology will become gradually narrower, a Qr/qR/rsR'/R morphology will appear in lead V1, and the V6 R-wave peak time (V6RWPT) will progressively shorten.
2. The presence of fixation beats, which correspond to PVCs induced by the mechanical trauma of lead advancement, correlate well with the depth of lead penetration. Fixation beats that display a terminal R-wave in V1 suggest that penetration to the left-sided conduction system is either near or achieved.
3. Unipolar pacing impedance usually rises upon initial penetration, then falls as the left ventricular (LV) endocardium is approached. A sudden impedance drop of >200 ohms is usually a sign that perforation into the LV has occurred, and that the lead should be pulled back.

4. Myocardial current of injury will demonstrate a rise (to 20-35 mV) on initial penetration, followed by a gradual decrease (to 10-12 mV) as the lead penetrates toward the LV subendocardium.

While the indicators described above strongly suggest that the LV conduction system has been attained, they do not constitute definitive proof of conduction system capture.[13] More precise criteria for conduction system capture are required, with the most commonly used being:

1. V6RWPT <75 ms (or <80 ms in patients with native conduction system disease), as illustrated in **Figure 2A**;
2. V6-V1 R-wave interpeak interval >44ms, also illustrated in **Figure 2A**;
3. QRS transition from non-selective to selective-left bundle branch pacing (LBBP) or LV septal pacing, characterized by an increase in V1 R-wave peak time (V1RWPT) >10 ms or an increase in V6RWPT >15 ms, respectively, during the performance of a pacing threshold test; and
4. LBB potential-V6RWPT equal to pacing stimulus-V6RWPT (±10 ms).

As the adoption of CSP becomes more widespread, rigorous adherence to the established criteria is essential for true physiologic pacing to ensure maximal benefit for patients.

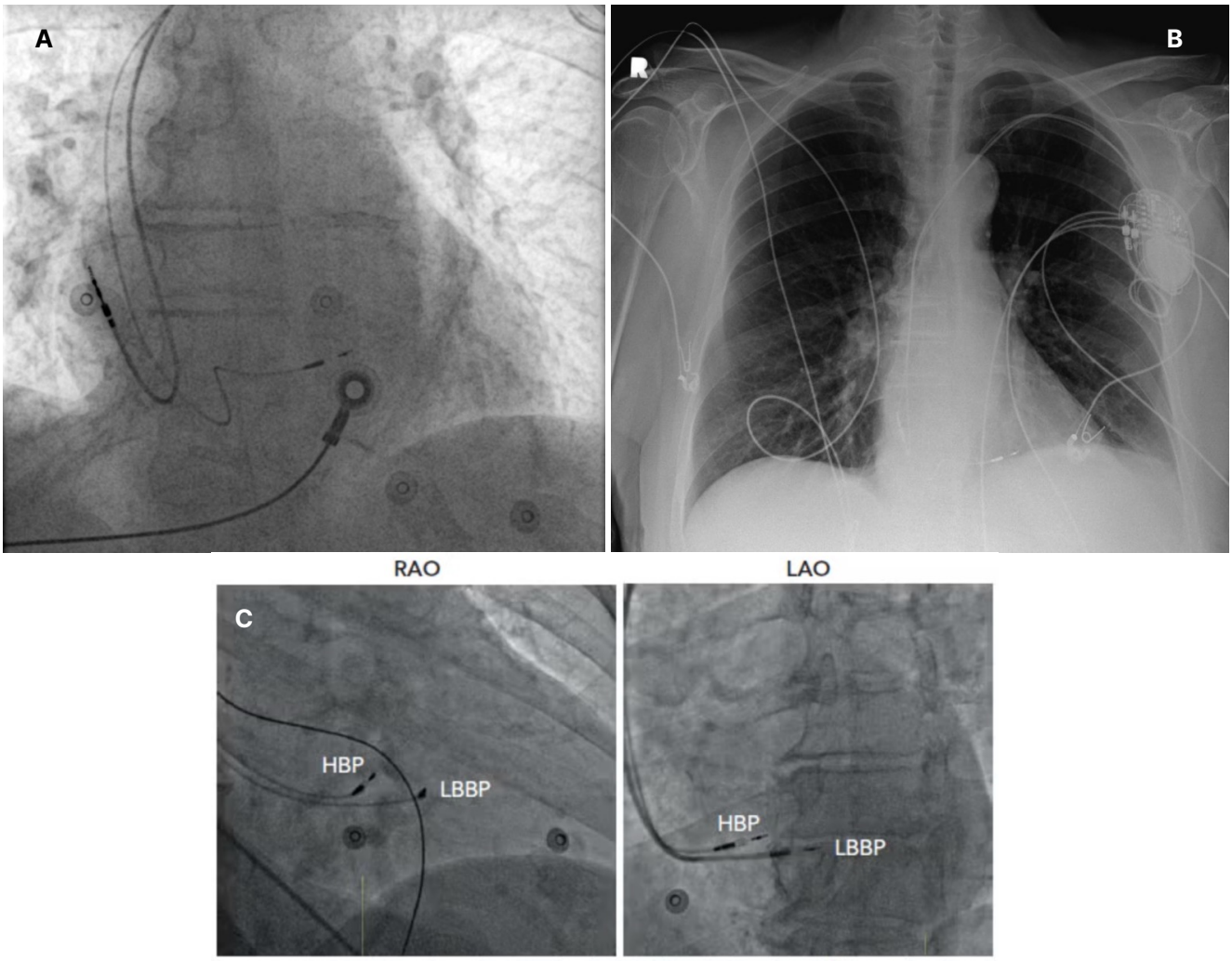

Figure 1. Panels A and B illustrate the mid-ventricular, septal position of the right ventricular lead used for left bundle branch pacing (LBBP), as seen on fluoroscopy (A) and post-procedural chest X-ray (B). Panel C shows an example of both a His bundle pacing lead (HBP) and an LBBP in the same patient, in both right anterior oblique (RAO) and left anterior oblique (LAO) projections; *courtesy of Corrado De Marco, MD*

Possible Complications

As with any new technique, a knowledge of relevant complications, both during and after implantation, is essential to ensuring optimal patient care.

Septal perforation is the most frequently encountered peri-procedural complication, occurring in up to 15% of cases.[13] It is most readily identified by a sudden drop in pacing impedance, a low current of injury (typically <2.3 mV), and/or by the penetration of contrast into the LV during septal angiogram.[13] If septal perforation is missed during implant or presenting later, after the implantation, it may manifest clinically as systemic embolism resulting from thrombus formation on a lead that has inadvertently entered the LV cavity. Therefore, any patient presenting with stroke or systemic embolism following LBBAP implantation should undergo testing aimed at eliminating this specific complication.

Septal hematomas occur more rarely, and usually asymptomatic or mildly symptomatic, and occasionally present with mild chest pain, which usually resolves spontaneously. Even more rarely, mechanical trauma to coronary vessels may occur during lead deployment, though acute coronary events are highly uncommon. In some cases, coronary venous fistula may develop due to perforation of the lead helix into a coronary vein. However, reported cases have shown that the lead position can often be maintained without adverse clinical effects, provided that a successful LBBAP is achieved.[12] Coronary artery fistulas have been reported in rare instances as well. These are generally asymptomatic and are usually incidentally noted on post-procedural transthoracic echocardiography, which may show a diastolic jet from the LV septum into the RV.

Other possible complications, similar to those encountered during standard RVP implantation,

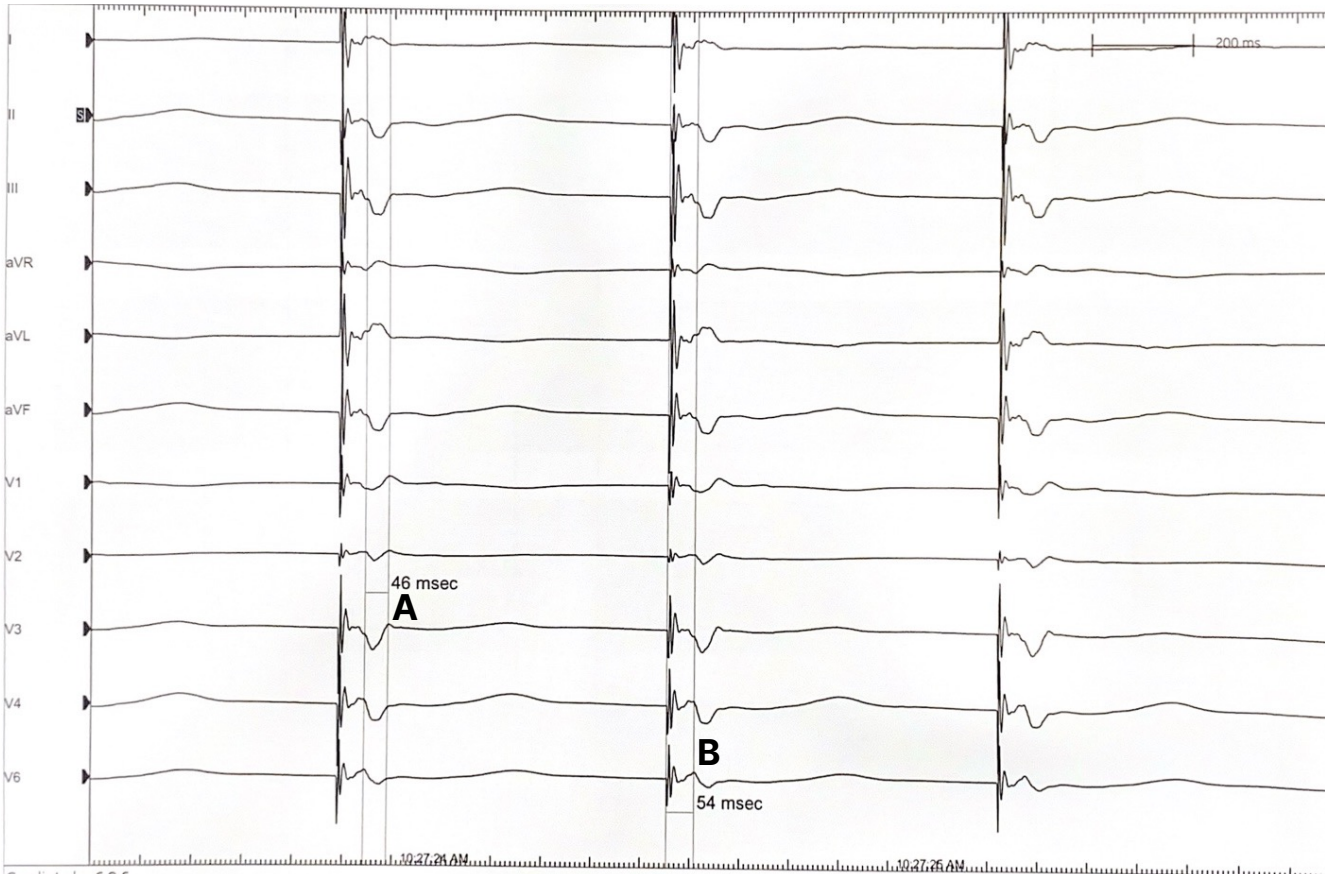

Figure 2A. Two of the most commonly used left bundle branch pacing (LBBP) criteria: a) V6-V1 interpeak (measured from the peak of the R-wave in V6 to the peak of the R or R'-wave in V1) interval >44 ms, and b) V6 R-wave peak time <75 ms in V6; *courtesy of Corrado De Marco, MD*

include tricuspid regurgitation, lead dislodgment, rise in lead threshold, or loss of capture.

Evidence in Support of Conduction System Pacing

The body of evidence in support of CSP has significantly grown in recent years. Studies have emerged comparing CSP to both RVP and BiVP. However, the existing literature at present is based almost entirely on observational data and is limited by small patient numbers.

CSP Versus RVP

Early studies comparing HBP with RVP demonstrated that HBP could prevent LV dyssynchrony, mitigate the development of mitral and tricuspid regurgitation, and preserve LVEF.[14] However, initial evidence demonstrating clinical benefits of HBP compared to RVP was scarce.

As the focus with regards to CSP has shifted to LBBAP in recent years, more data has emerged. The earliest studies demonstrated that LBBAP resulted in LV synchrony comparable to native conduction, despite a slightly wider paced QRS than the native QRS due to the delayed right ventricular activation. Notably, the degree of LV synchrony was markedly better with LBBAP than with RVP.[12]

In one of the largest observational studies comparing CSP to RVP, Tan et al. demonstrated that CSP, comprising 95 patients with HBP and 136 patients with LBBP was associated with a 47% reduction in the primary composite outcome of heart failure hospitalization, need for upgrade to BiVP, or all-cause mortality compared to 628 patients receiving RVP. This benefit was observed in patients with >20% ventricular pacing.[15]

Overall, in comparison with RVP, CSP has shown better ventricular synchrony, less marked valvular regurgitation, and improved LVEF preservation. Moreover, observational data suggests the clinical benefits of CSP over RVP are significant.

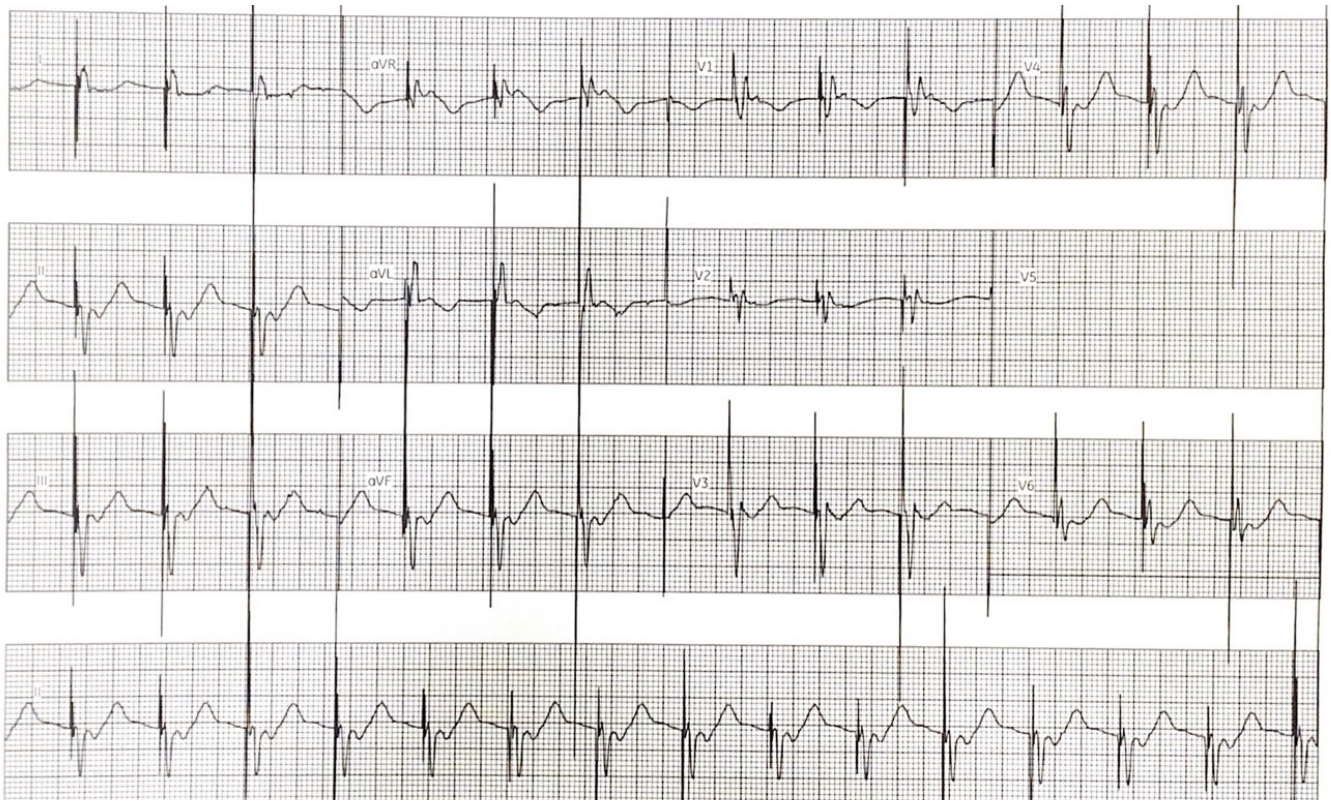

Figure 2B. The post-implant electrocardiogram (ECG) (taken with the patient still lying on the procedure table) for the same case as in *Figure 2A*. Note the hallmark features of the left bundle branch area pacing (LBBAP), most notably the large pacing spike, the qR pattern in V1, and the short spike-to-R-wave interval in V6. Lead V5 not pictured due to electrode connectivity problem during ECG recording; *courtesy of Corrado De Marco, MD*

CSP Versus Biventricular Pacing

BiVP represents a well-established cornerstone of ventricular resynchronization in patients requiring CRT. However, CSP is increasingly being employed as an alternative to traditional BiVP delivered via a coronary sinus lead.

To date, only two randomized trials have compared HBP to conventional CRT with BiVP. The HIS SYNC[16] trial compared HBP to BiVP in 41 patients, though significant cross-over between groups (48% from HBP to BiVP and 25% from BiVP to HBP) represents a significant limitation of the trial. Moreover, it found no statistically significant differences between groups in the reduction of QRS duration or improvement of LVEF. Similarly, the His-Alternative trial[17] randomized a cohort of 50 patients meeting CRT criteria to either HBP or BiVP. The trial showed no statistically significant differences in clinical and echocardiographic improvements, however, pacing thresholds were higher in the HBP group.

Similar trials have been published comparing LBBAP to conventional CRT with BiVP. As with HBP, most of these studies are retrospective and observational. A common theme that emerges is that LBBAP provides results comparable to HBP, while providing the advantage of lower pacing thresholds, reduced risk of far-field oversensing of atrial signals, and easier mastery of the implantation technique.[18] In a large, retrospective, observational study of 1,004 patients with LVEF of 36-50% and either LBB block or a need for ventricular pacing, CRT delivered via CSP, primarily via LBBP, was independently associated with a significant reduction in the primary composite endpoints of time to death or heart failure hospitalization (22% in the CSP group versus 34% in the BiVP group, hazard ratio 0.64, p=0.025).[19]

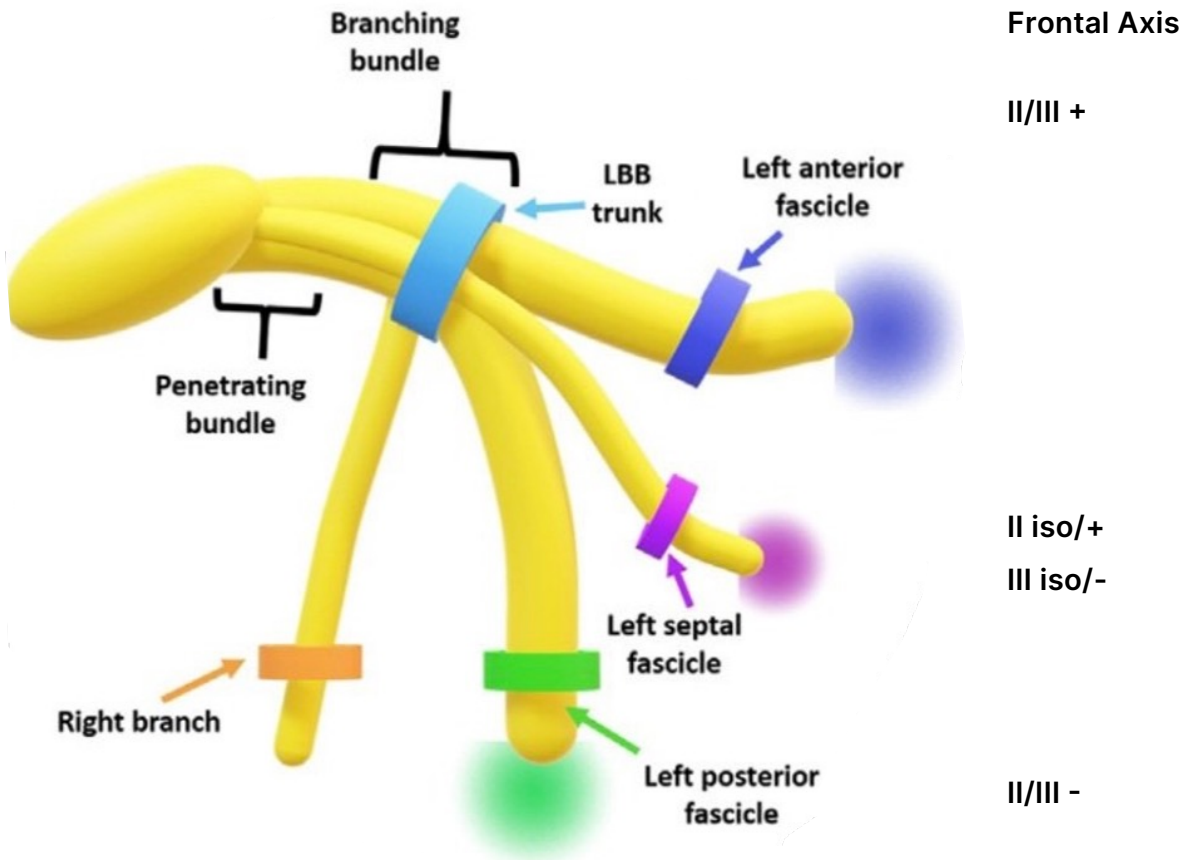

Figure 3. A schematic representation of the left bundle branch (LBB) and its fascicles: anterior (in navy blue), septal (in violet), and posterior (in green). The frontal axis (listed at right) may vary depending on the location of the pacing lead helix; *courtesy of Corrado De Marco, MD*

Nonetheless, there is a distinct lack of sufficiently powered, randomized, controlled trials comparing conventional BiVP to CSP. The ongoing Left versus Left trial is currently the largest clinical trial comparing CSP to BiVP, with a planned enrolment of 2,136 patients and follow-up extended up to three years. Until data from adequately powered randomized, controlled trials is published, CSP should be seen only as a viable bailout to conventional BiVP, and not as an alternative to clinically validated conventional BiVP. In instances when CRT is indicated, CSP should be performed in cases where BiVP implantation proves challenging provided that true HBP or LBBAP can be achieved.

Combined CSP and Biventricular Pacing

Small, observational studies have examined the benefit of combined CSP and conventional BiVP, referred to as HOT-CRT when HBP is combined with conventional BiVP, and LOT-CRT when LBBAP is combined with conventional BiVP. Both HOT-CRT and LOT-CRT resulted in LVEF improvement, QRS duration reductions, and improvements in New York Heart Association (NYHA) functional class, outcomes comparable to CSP alone and superior to traditional BiVP.[20] However, no randomized controlled trials on the subject have been published to date.

Future Directions and Conclusion

As the implantation techniques for conducting CSP continue to evolve and more clinicians are trained, the use of CSP is becoming more widespread. While it is most commonly used in cases where the burden of ventricular pacing is expected to be high, such as in complete AV block or post-AV nodal ablation, it is also emerging as a practical alternative in cases of failed traditional BiVP implantation.

The promise of CSP is undeniable, and the coming years are certain to bring a surge of evidence that will better quantify its merits. While early data are certainly encouraging, large-scale, multicenter, randomized controlled trials comparing CSP to other pacing modalities are yet to be published. Several such studies are currently underway.

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Financial Disclosures

C.M.: None declared

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