Knowledge Translation in Heart Failure

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Abstract
The treatment of heart failure has expanded over the past three decades with large numbers of new medications and healthcare innovations available for these patients. At the same time, the prevalence of heart failure continues to increase across Canada and these patients are managed by a variety of clinicians from differing backgrounds in both primary care and hospital settings. Despite national recommendations advocating uptake of these new therapies, their utilization remains limited and inconsistent across the country. This review discusses the importance of knowledge translation in heart failure and examines the barriers to implementation of new therapies and models of care, providing a range of solutions to facilitate the delivery of guideline-directed care for heart failure patients.

Resume
Le traitement de l'insuffisance cardiaque s'est développé au cours des trois dernières décennies grâce à un grand nombre de nouveaux médicaments et d'innovations en matière de soins de santé disponibles pour ces patients. Dans le même temps, la prévalence de l'insuffisance cardiaque continue d'augmenter dans tout le Canada et ces patients sont pris en charge par divers cliniciens d'horizons différents, tant dans le cadre des soins primaires que dans les hôpitaux. Malgré les recommandations nationales préconisant l'adoption de ces nouvelles thérapies, leur utilisation reste limitée et inégale dans tout le pays. Cette étude traite de l'importance de l'application des connaissances en matière d'insuffisance cardiaque et examine les obstacles à la mise en œuvre des nouvelles thérapies et des nouveaux modèles de soins, en proposant une série de solutions pour faciliter la prestation de soins guidés pour les patients souffrant d'insuffisance cardiaque.

Heart failure (HF) management has been revolutionized over the past three decades and now includes several classes of drugs that inhibit the various pathological neuro-hormonal pathways,[1] as well as non-pharmacological interventions such as cardiac resynchronisation therapy (CRT),[2] implantable cardioverter defibrillators (ICD),[3,4] cardiac transplantation, and mechanical circulatory support. In Canada alone, the age-standardised all-cause mortality rate in HF patients has decreased from 78.4 per 1,000 in 2000-01, to 57.8 per 1,000 in 2012–13.[5] Improvements in treatment require implementation into everyday practice and integration into the local context of healthcare. This process of knowledge translation is critical to ensuring successful uptake of new discoveries that will reduce the morbidity, mortality and cost of healthcare associated with HF. This review focuses on strategies for successful knowledge translation to improve the care pathway of HF patients while highlighting current challenges.

Clinical Vignette (Part 1)

Jennifer, a 74-year-old female living in a small town in rural Ontario, presented to her family doctor with insidious exertional dyspnoea for three months, with reduced exercise capacity and poor sleep. She had been previously diagnosed with hypertension that was well controlled on amlodipine 5 mg but had no other comorbidities. She previously smoked, but stopped 40 years ago, and rarely drinks alcohol. She has noticed that she cannot walk as far as she was able to last summer, being limited by breathlessness. She denies any chest pain. She has noticed a cough over the last couple of weeks.

Examination reveals a heart rate of 110/minute, respiratory rate of 20/minute and arterial blood pressure of 98/60 mmHg, with normal heart sounds, no murmurs and fine inspiratory crepitations at the lung bases. The jugular venous pressure is not easily seen and there is bilateral ankle swelling which the patient reports as being long-standing.

The clinical suspicion is of congestive heart failure, with a differential diagnosis of possible lung pathology (emphysema or pulmonary neoplasm).

Making a Diagnosis of Heart Failure

Given the broad range of possible presenting symptoms, it can be a challenge to diagnose HF. Many symptoms are not specific to HF and there is often an overlap with other cardio-pulmonary pathologies. In this patient, there is a history compatible with HF, although the symptoms could be compatible with hypertensive heart disease or coronary artery disease, and respiratory diagnoses are also possible. Guidelines direct that possible HF diagnoses should be investigated with echocardiography, and possibly with biomarkers such as B-type natriuretic peptide (BNP) or N-terminal-pro-BNP.[6]

Access to Investigations

The diagnostic process proves difficult on a number of fronts. Firstly, despite evidence of benefit in making the diagnosis of HF using biomarkers, they are not widely available across Canada. Some provinces, such as British Columbia, have had access to BNP testing since 2012; nevertheless, a large number of barriers exist in requesting the test in appropriate populations.[7] A retrospective cohort study in Alberta showed that geographic location played a large part in the ability to access biomarker testing, as did physician specialty.[8] Access to echocardiography can also be a challenge; in our patient, the local hospital does offer echocardiography, but not necessarily a cardiology service. Therefore, the expertise available to primary care providers (PCPs) may vary greatly. Finally, several campaigns have tried to ensure diagnostic investigations are organised for appropriate patients, such as the *Choosing Wisely* campaign,[9] however, these could potentially dissuade clinicians from requesting tests when appropriate.[10] Natriuretic peptides can also be used for monitoring response to therapy, allowing family doctors and other non-specialists to better track disease progression over time and be used to refer to specialists for advanced therapies. The Canadian Cardiovascular Society (CCS) guidelines provide a framework for appropriate use of biomarker testing[6] (See Figure 1).

To further ensure consistency of approach, computerized clinical decision support systems and clinical care pathways can be

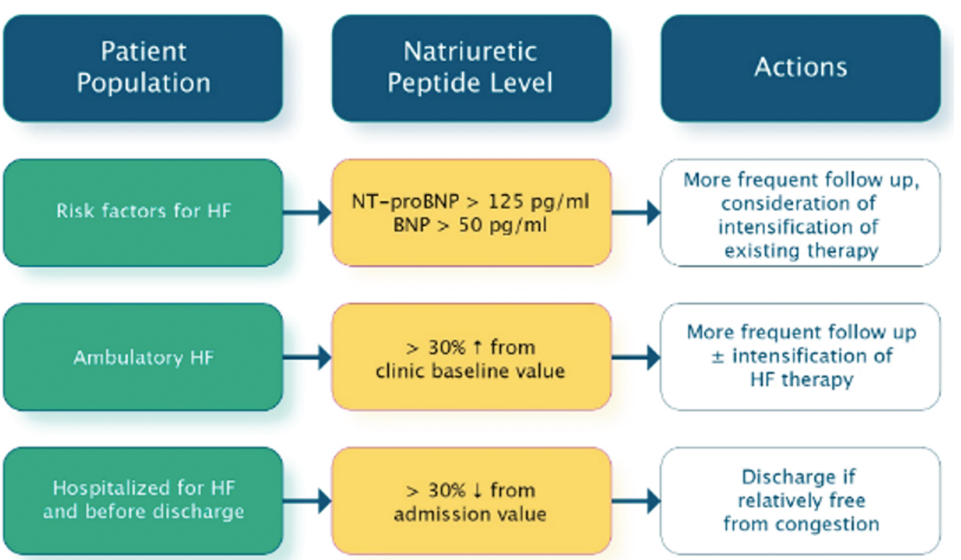

Figure 1. The Canadian Cardiovascular Society algorithm for the use of natriuretic peptides in different heart failure-related clinical scenarios.
BNP = B-type natriuretic peptide; NT-proBNP = N-terminal propeptide B-type natriuretic peptide.

a means to ensure appropriate assessment and diagnostic testing take place.[11,12] These interventions are generally cost-effective and result in fewer complications. However, these approaches are not widely used in current Canadian clinical practice, but could be a way to improve adherence to guidelines.

Risk Mismatch in Heart Failure

The CCS guidelines emphasise the use of formal risk scoring.[6] The risk mismatch paradox was described more than a decade ago in patients enrolled in the EFFECT registry (1999-2001).[13] It demonstrated that angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARB) and beta-blockers were more likely to be prescribed to lower risk patients at discharge from hospital after admission for decompensated HF. The effects of this lasted for at least a year after discharge, and even when accounting for contraindication to therapy, low-risk patients were more likely to receive ACE inhibitors or ARBs (adjusted hazard ratio [HR], 1.61; 95% confidence interval [CI], 1.49-1.74) and beta-blockers (HR, 1.80; 95% CI, 1.60-2.01) compared with high-risk patients (both $p<0.001$).[13] This has been corroborated by subsequent studies in different populations in the U.S. as part of the *Get With The Guidelines* programme that argue effective strategies need to be developed for high risk patients to receive more effective treatment.[14] Formal risk stratification can ensure that patients wrongly assumed to be low risk can be managed more quickly and aggressively to improve their outcomes, as higher risk patients are often eligible for more therapeutic interventions.

The risk mismatch paradox may be partly explained by inaccuracies related to estimating risk both by physicians and patients, as well as the impracticality of using formal risk calculators. An American study examined patients' self-assessment of one-year risk alongside the same assessment by their treating physicians.[15] Patients perceived their own risk of death, need for transplant or a ventricular assist device (VAD) to be 14% at one year, compared to their physicians who estimated it to be 69%. During follow-up, more patients had died in the physician-assessed high-risk category than the low-risk category, but more of the low-risk patients had transplantation and VAD implantation. Importantly, neither physicians, nor patients, were accurate at predicting risk, and the disagreement between the two groups may have created barriers in discussions around the appropriateness of advanced therapies. Using formal risk scoring and patient education can more accurately inform patients about prognosis and facilitate effective application of appropriate therapy to those at highest risk along with advanced care planning.

There are several possible scoring systems, but they often require both echocardiographic and hematological parameters alongside patient symptoms and biometric data. These can be unwieldy and often require electronic software to calculate, leading to underutilization of this aspect of HF management. Furthermore, there is a concern about how relevant risk stratification is for an individual patient, in whom the outcomes are often binary, whereas they are more useful on a population level, where they can assist with provision of services.[16,17]

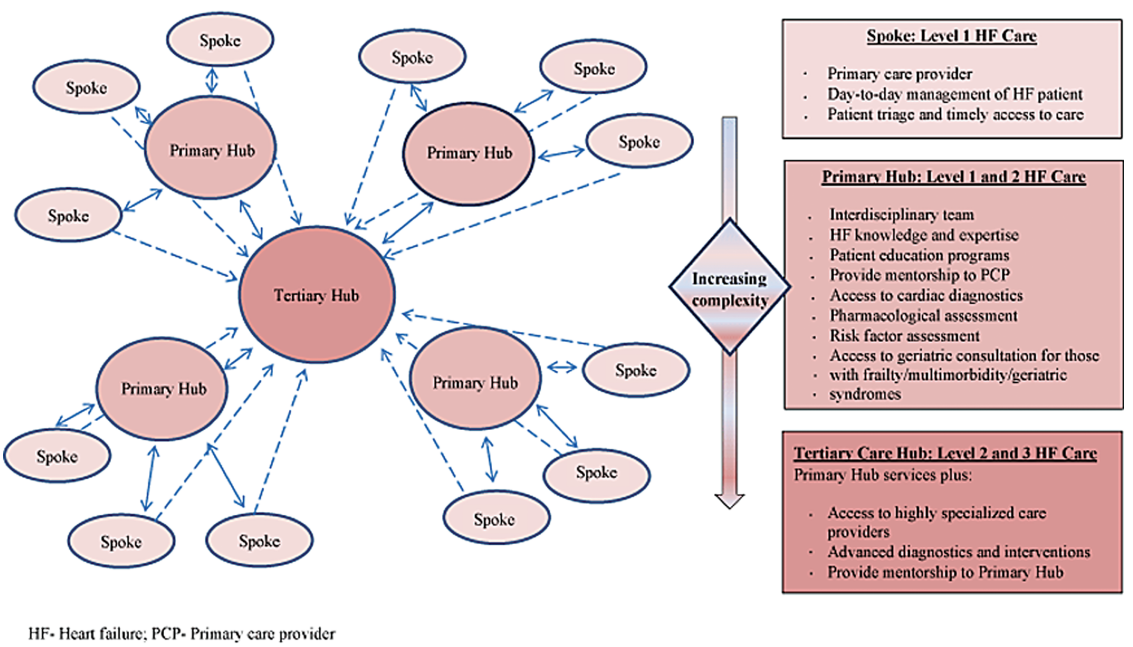

Figure 2. The hub and spoke model of care proposed by Harkness et al.[18] Reproduced with permission

Organization of Heart Failure Care

Jennifer, the patient in our vignette, lives in a rural town that has no cardiology support in its local hospital. Once the diagnosis of HF is made, it can be a challenge to access HF services. Whilst some locations may have access to cardiology services, PCPs may have trouble deciding who should be referred. Unlike surgical referrals that largely result in a discreet encounter to determine the need for intervention, HF specialist consultations often result in a management plan to be enacted locally, requiring ongoing interaction between the specialist and primary care team. The partnership between clinicians is key to successful management, with patients preferring local care that does not necessitate repeated visits to tertiary centres. Some have proposed a hub and spoke model, with delegation of responsibility and expertise down from the large tertiary centres that can focus on dealing with complex, advanced HF or symptoms refractory to usual treatment, leaving local hospital hubs able to deliver most of the hospital care to HF patients and support the PCPs in the day-to-day management of HF patients.[18]

PCPs often have close relationships with patients over many years, and are likely to be best placed to alter HF therapy given the need for repeated assessment of treatment efficacy and surveillance for side-effects such as hypotension and renal dysfunction. Advice and guidance from the HF specialist needs to be communicated to the local provider, and this can be a challenge depending on the clinical and geographic setting.[19]

Role of Opinion Leaders and Continuing Education

There is also proven benefit of outreach to community setting by "opinion leaders" who can promote and advise on implementation of best practice as guided by evidence.[20] A Cochrane systematic review suggests that education meetings can improve professional practice and healthcare outcomes for patients,[21] and others have identified the elements that need to be incorporated in a HF curriculum for primary care continuing medical education.[22] These two mechanisms can complement alternative strategies for knowledge translation into the primary care setting, increasing the confidence of primary care specialists in providing high-quality HF care close to the patient.

Communication After Hospital Discharge

A commonly reported breakdown of communication occurs at the transition from inpatient care to discharge into the community. Both patients and PCPs feel that the communication could be improved, with better guidance as to the role of the PCP, after HF hospitalisation has occurred.[23] One U.S. study showed cost-savings through reduction in hospital readmissions after focussed training for hospital providers involved in discharging patients into the community. By employing a full-time HF nurse coordinator, 30-day readmissions were significantly reduced from 23.1% to 16.4% (adjusted odds ratio [OR] = 0.64, 95% CI: 0.42–0.97).[24] Effective and timely local strategies for multi-disciplinary communication seem to be key in forging stable healthcare environments for HF patients.

Clinical Vignette (Part 2)

Jennifer was commenced on oral diuretic therapy, furosemide, 40 mg daily, and referred for an echocardiogram. This revealed a dilated left ventricle, with global hypokinesis and an ejection fraction estimated at 17%. There was no significant valvular stenosis, or regional-wall motion abnormality, and mild-moderate mitral regurgitation was noted due to dilatation of the mitral annulus. An internal medicine physician reviewed the patient after the echocardiogram, and organised a CT coronary angiogram which showed no coronary disease. The patient was diagnosed with non-ischaemic, idiopathic, dilated cardiomyopathy and commenced on ramipril, 2.5 mg daily. The patient was referred back to the family doctor with advice to continue titration of guideline-directed medical therapy.

Uptake of Guideline Directed Medical Therapy

Prescription of Medical Therapy

Jennifer has been diagnosed with HF with reduced ejection fraction (HFrEF) due to dilated cardiomyopathy, and current guidelines recommend "triple-therapy" with ACE inhibitors or ARBs, beta-blockers and mineralocorticoid receptor antagonists (MRA)(6). The evidence itself is persuasive, with numbers-needed-to-treat as low as 8 for beta-blockers to prevent all-cause mortality at 5 years.[25]

Patients are routinely being commenced on these medications as shown in a number of international studies. In a prospective U.S. cohort of 15,177 patients with HFrEF, part of the IMPROVE HF study, 80% of patients enrolled were on ACE inhibitor/ARB therapy, 87% on beta-blockers and 35% on an MRA at baseline.[26] This is comparable to the European Society of Cardiology (ESC) HF survey of 12,440 patients published in 2013, where prescription of ACE inhibitor/ARB, beta-blocker and MRA was 92%, 93% and 67% respectively.[27] No comparable Canadian data have yet been published; however, unpublished sub-analyses of the QUALIFY registry[28] show that 87% of patients were prescribed ACE inhibitor/ARB, 95% beta-blocker and 50% MRA.

Accordingly, our patient would usually be commenced on appropriate beta-blocker medication, such as bisoprolol, and an MRA such as spironolactone. The next issue is the titration of the medication to the doses studied in clinical trials and recommended in guidelines.

Medication Optimization to Target Doses

The ESC survey showed that despite high rates of prescription of each drug class, patients were only on target doses of these medications 30% of the time, with two-thirds having documented reasons for not being on higher doses (including being in the process of dose optimization).[27] U.S. data looking at patients on beta-blockers prior to admission for decompensated HF showed that those on beta-blockers were often at less than half the guideline recommended target dose.[29]

The guidelines for medication optimization are compelling, but the knowledge translation gap prevents them from impacting patient. Some have argued that while guidelines are now better at summarizing evidence behind recommendations, they do not always lend themselves to being easily implemented, lacking information to facilitate discussions with patients, summaries for different users of guidelines, whether in different professions or in different healthcare settings.[30] A meta-analysis of 38 studies focussing on HF guideline intervention found that clinical pathways, multidisciplinary teams and multiple interventions were the most effective means to implement recommendations within guidelines.[31] Here we briefly consider strategies for improving HF medication optimization.

Multidisciplinary Clinics

Nurse-led titration clinics have been suggested as means of improving prescription of guideline target doses of HF therapy. An Australian randomised trial showed faster titration of beta-blockers, with more patients reaching higher doses with nurse-led titration clinics compared to usual care.[32] More recently, a Cochrane review looked at the role of nurse-led titration clinics, with 1,684 participants across 7 studies in their analysis.[33] When hospitalization was considered (4 studies, 556 participants) there was a lower rate of hospital admission (relative risk [RR] = 0.80, 95% CI: 0.72 to 0.88, high-quality evidence) and fewer HF hospitalizations (RR = 0.51, 95% CI: 0.36 to 0.72, moderate-quality evidence) in the nurse-titration clinic population compared to the usual-care group. Six studies (902 participants) examined all-cause mortality which was also lower in the nurse-led titration group (RR = 0.66, 95% CI: 0.48 to 0.92, moderate-quality evidence) compared to usual care. Patients were also significantly more likely to be on target doses of medical therapy.[33]

A U.K.-based initiative of using a protocol-driven HF titration clinic staffed by nurses and specialist pharmacists showed a significant increase in patients on guideline directed medical therapy and at higher doses after 6 months, with the proportion of patients on "medium" or "high" doses of beta-blockers increasing from 18 to 57%, and an increase from 55 to 86% for ACE inhibitors/ARB. There was also a reduction in the severity of HF in patients, with the proportion of severe HF (NYHA Class III and IV) declining from 40 to 23%.[34] A pharmacist-based intervention in the ambulatory HF clinic of a U.S. hospital also showed a significant increase in the number of patients reaching target doses of ACE inhibitors/ARB (52.9% versus 31%, $p = 0.007$) and beta-blockers (49% versus 24.7%, $p = 0.012$).[35]

Outpatient Disease-Management Programmes

Another opportunity to optimize medications occurs when patients are attending appointments for other reasons. An Australian study based saw the use of a disease-management program with a physician supported multi-disciplinary team, including specialist nurses and clinical pharmacists, educate patients on HF and optimize their medication as they attended exercise rehabilitation classes.[36] The program included 216 HFrEF patients and was associated with a significant increase in the proportion of patients on optimal ACE-inhibitor/ARB doses from 38% at enrolment to 52% at 6 months ($p = 0.001$) and on optimal beta blocker dosage from 23 to 49% ($p < 0.001$).

The same authors developed an iterative structured medication titration plan that could be used to target medication optimization after discharge from hospital prior to HF exacerbation. Patients could choose community-based nurses or their own primary care physician (if they agreed) to supervise titration of medications, with a single point of support from the HF disease management staff based in secondary care if needed. After two rounds of implementation, there was a significant increase in the number of patients on target doses of ACE inhibitors and beta-blockers after six months in the program.[37]

Financial Incentives

A large review has demonstrated that financial incentives to providers can improve the delivery of care in chronic conditions. Financial incentives showed an improvement in referral and also in optimizing the processes of care.[38] No evidence currently exists on the effect of financial incentives on direct patient outcomes. Evidence from a systematic review of statin prescription amongst family doctors suggests that patients can become sceptical of the motives behind medication prescription if there is a financial incentive to do so.[39] A U.S. study demonstrated that providing financial incentives to both patients and physicians significantly improved adherence to statin therapy and reduced LDL cholesterol levels, when compared to incentives to either physician or patient alone, or neither.[40] While these have never been studied HF patients, it is an important consideration that could potentially assist with implanting guideline medical therapy.

Computerised Decision Support Systems

Computerised clinical decision support systems can assist in the prescription of medicines in a safe and effective manner, ensuring that pre-requisites are met and that changing a medicine dose is appropriate. Research suggests that such support systems can improve process of care, but are rarely effective in improving patient outcomes.[41] Without this evidence of benefit, they are not yet routinely available for use in HF management.

What Does Optimal Treatment Look Like?

One of the unanswered questions in HF management relates to what individually optimized HF medical management should look like. Given that the various trials have layered one therapy on another, first with ACE-inhibitors, then beta-blockers before MRA use, additional therapies are often added on top of these treatments. The landmark ICD trials were conducted in an era when MRAs were not routine treatment for HFrEF, and CRT was not widely used. The 2005 SCD-HeFT trial recruited 2,521 patients (a mixture of ischaemic and non-ischaemic cardiomyopathy) who were randomised to either placebo, amiodarone or ICD implantation, demonstrated a significant reduction in mortality with an ICD compared to placebo.[42] When these trials were repeated in the era of CRT and MRA use, the investigators of the 2016 DANISH study found no reduction in all-cause mortality between groups randomised to ICD therapy when compared to no ICD implant.[43] Similar to the earlier DEFINITE trial, there was a significant reduction in sudden cardiac death alone and not all-cause mortality.[44]

In an era when guideline directed medical therapy also includes neprilysin inhibitors, I_f channel blockers, sodium-glucose transport protein 2 (SGLT2) inhibitors and a number of different device therapies, it can be challenging to navigate which drug should be added at which time, and whether one drug should be titrated upwards over another.

This is further complicated by the different patient phenotypes in real-world clinical practice compared to those enrolled clinical trials, who are predominantly young males with few additional co-morbidities such as renal dysfunction, hypotension and diabetes which may limit use of medical treatments. A review of the Euro Heart Survey in 2005 demonstrated that only 11% of patients in this "real-world" registry would be eligible for the original ACE inhibitor, beta-blocker and MRA trials in HFrEF.[45] More recently an analysis of a European ambulatory clinic showed only 42% of their patients would be eligible for entry into the PARADIGM-HF study, which investigated the efficacy of sacubitril/valsartan in HFrEF patients, based on inclusion criteria and contraindications.[46] This poses unique challenges in knowledge translation to health care providers who may have limited experience in using these drugs and understanding who may be the most likely to benefit or be harmed by these medical interventions.

Clinical Vignette (Part 3)

Jennifer has been stabilised on daily doses of ramipril 10mg, bisoprolol 7.5 mg and spironolactone 50 mg. She was unable to tolerate higher doses of the beta-blocker due to bradycardia. She remains symptomatic with NYHA Class II symptoms. Her ECG shows a narrow QRS complex, and after review in the regional heart function centre, she declined the offer of ICD implantation for primary prevention of sudden cardiac death. Repeat echocardiography shows severely impaired left ventricular function (ejection fraction 29%). She is commenced on sacubitril/valsartan as an alternative to ramipril. During a follow-up clinic visit, she asked about any other therapies that might improve symptoms.

Delays in Applying Novel Therapies

A large number of treatments have been developed for the management of HFrEF, but there is always a lag between the emergence of evidence and the uptake of treatments in routine clinical practice. For example, in Ontario, there was a delay of 5 years in getting eplerenone funded by the Ontario Drug Benefits program after the EMPHASIS trial had shown efficacy of this drug in NYHA Class II HFrEF patients.[47,48] There may be additional delays in the provincial approval for funding once Health Canada has approved a drug, leaving a gap where only those with private insurance or sufficient wealth to self-fund can access these life-saving therapies.[49]

Despite the pivotal CHAMPION trial being published in 2011, demonstrating a 37% reduction in HF-related hospitalisation (HR =0·63, 95% CI: 0·52–0·77) in patients with NYHA class III symptoms, regardless of ejection fraction, the device remains unfunded and can only be implanted through research trials or through charitable donations. It remains the only proven strategy in managing HF patients with preserved ejection fraction.[50]

A possible solution to expedite new drug approvals might be a way to "fast-track" medications that have significant improvements in survival. In the U.K., the Medicines and Healthcare Products Regulatory Agency has an early access to medicines scheme which allows expedient access to pharmacologic therapies for life threatening or seriously debilitating conditions.[51] Sacubitril/valsartan was available for HFrEF patients within 9 months of publication of the PARADIGM-HF trial through this scheme, the first non-cancer medicine given this designation.[52,53]

Future Directions

A number of exciting propositions are on the horizon for improving knowledge translation in HF. While many countries use

audit and quality improvement to judge how well guidelines are being implemented, there is currently no Canada-wide means to assess adherence to recommendations.[54] Information is variably collected at a provincial level, but often the data sets are different between provinces precluding a comparison between healthcare providers across Canada.[49,55] The U.K. National Heart Failure Audit was first established in 2007 and is used to assess all HF hospitalizations and whether they meet published clinical standards.[56] The use of a nation-wide reporting tool for individual provider-level data has seen improvement in guideline implementation by demonstrating how clinics are performing compared to other providers. This needs to be an area of priority for HF policy makers to ensure best practice is followed in all parts of the country.

Several technological improvements are gaining momentum, and remote monitoring is a fundamental part of global HF care.[57] Where some have tried medication optimization through telephone follow-up, the use of technology to monitor patients using smartphones lends itself well to being able to have a therapeutic dialog and alter HF medications in ambulatory patients without the need for in-person evaluation.[58] The Medly programme is a remote monitoring system that uses algorithmic decision support; it has over 300 patients enrolled and is administered by a single nurse practitioner.[59] A new, randomised trial will use the same remote monitoring technology to titrate medications remotely, comparing time to complete titration, maximal medicine dose achieved and number of clinic visits against usual in-office care. This could represent a scalable, automated, computer-assisted strategy of optimisation of HF medicines which may improve adherence to guidelines by circumventing some of the challenges of knowledge translation.

Conclusions

There are many delays in translating scientific discovery into elements that can be delivered as part of a HF management program. A large effort is required to communicate novel ideas to care providers dealing with HF. While patients currently resist increases in medication, HF specialists need to educate and empower patients to be more involved in their own management, and this is likely to require a change in mindset, where patients have better education around the risks of suboptimal medical management. Finally, from a nationwide perspective, the ability to monitor performance through a national audit should drive up quality of care and presumably inspire earlier approval and funding of proven HF medications and technologies.

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