CaReMe; reaching a consensus in shared care.

Cardio renal metabolic syndrome

Cardio-renal metabolic syndrome (CaReMe) can be defined as a group of interactive cardiovascular, renal and metabolic conditions, (Ronco, Bellasi and Di Lullo, 2018). Cardiovascular diseases (CVDs) are a group of disorders of the heart and blood vessels. They include atherosclerotic disease of the heart, brain and peripheral circulation, heart valve dysfunction, and congenital malformations of the heart structure (WHO 2021). Whilst all forms of CVD are prevalent, atherosclerotic cardiovascular disease (ASCVD) remains the most dominant form of CVD. Heart Failure (HF), the most common CVD associated with Chronic kidney disease (CKD) and metabolic disorders co-exists in approximately 20% and 40% of the CKD and Diabetes population respectively, (Dunlay, Redfield, Weston et al. 2009, Van Deursen, Urso, Laroche et al, 2014). These co-morbidities independently affect response to treatment, influence disease severity and HF outcomes such as hospitalisation, quality of life and mortality, (Bhatt, Ambrosy, Dunning et al, 2020, Pandey, Vaduganathan , Arora et al, 2020, Horiuchi , Tanimoto , Latif et al, 2018, Manemann, Chamberlain, Roger et al, 2018, Joyce, Chung, Badloe et al, 2016, Lawson, Solis-Trapala, Dahlstrom et al. 2018, Manemann, Chamberlain, Boyd et al, 2016).

Traditionally, the term renal disease has been used to describe disorders of the renal system, however, the term kidney disease is now preferred to describe such conditions following the findings of the Kidney Disease Improving Global Outcomes (KDIGO) Consensus Conference (Levey et al 2020). The change in terminology reflects a move towards the use of more patient focussed language. Kidney conditions can be acute or chronic in nature. Acute Kidney Injury (AKI) is present when the patient's Glomerular Filtration Rate <60 ml/min per 1.73 m2, or there are markers of kidney damage for <3 months or decrease in GFR by ≥35% or increase in serum creatinine by >50% for ≤3 months. Chronic Kidney disease (CKD) refers to a GFR <60 ml/min per 1.73 m2 or other markers of kidney damage that have been present for >3 months (Levey et al 2020).

Metabolic syndrome encompasses insulin resistance, impaired glucose tolerance, central obesity, hypertension, and dyslipidaemia, which are not conducive to adaptation, (Reaven,1998, National Cholesterol Education Program (NCEP) 2002, Obunai, Jani and Dangas, 2007, Sowers, Whaley-Connell, Hayden, 2011, Chaudhary et al, 2013, Whaley-Connell and Sowers, 2014). The mechanisms of metabolic syndrome can increase the risk

of inter-related conditions such as CVD, CKD, diabetes and HF. The co-dependent relationships and reciprocal nature of CaReMe diseases can in turn perpetuate a vicious cycle, whereby the presence of one dysfunction can lead to a decline in another.

Prevalence

Cardiovascular disease (CVD) continues to dominate as a burden of ill health globally, with 523 million cases worldwide and an estimated 17.3million out of 54 million deaths attributed to CVD, (Roth et al, 2019, Benjamin et al, 2017). In the UK alone this equates to 255 deaths per 100,000 population, (Statistica, 2019). Whilst CVD mortality rates are falling in high income countries, it is estimated that by 2030 more than 80% of CV-related disability and death will occur in low and middle-income countries (Global Burden of Disease, (GBD), 2017). Moreover, cardiovascular related hospital admissions remain high, (Bhatnagar et al, 2016). Diseases of the circulatory system ranked ninth as cause for hospital admissions in 2018/2019 in the U.K., there were 947,224 admissions, and 436,376 people were admitted under a cardiology specialism, (NHS Digital statistics, 2018/2019), highlighting the financial burden that these diseases places on health systems.

Heart failure is one of the most prevalent forms of cardiovascular disease, often occurring as a consequence of underlying hypertension, ischaemic or valvular heart disease and is a common precursor of CaReMe, affecting 64 million people worldwide, (GBD, 2017). In the United Kingdom, the authors of the National Heart Failure Audit (NHFA) have reported that almost 70,000 patients were admitted to hospitals across England and Wales in 2019/2020 with almost one in ten (9%) of those patients dying in hospital (NHFA, 2021). HF is responsible for 1–3% of international health care costs and is estimated to grow because of increased HF prevalence and hospitalisation, (Lloyd-Jones e al, 2010, Cook et al, 2014). HF patients are best managed by specialist teams. Cleland and colleagues in 2011 reported that in-hospital mortality rose from 5% for those treated in a cardiology ward to 15% for those on general medical wards (Cleland et al, 2011). The latest U.K. HF audit supports these previous findings demonstrating lower mortality rates of 6% for those cared for in cardiology ward and 9% for those on other wards, (NHFA, 2021). Masri et al's (2018) US cohort study identified high readmission rates for patients with a HF diagnosis placed under short stay observation as opposed to those admitted onto an inpatient ward. They concluded that cardiac and all cause readmissions contradict the assumption this patient group can merely be observed and classified as low risk, particularly with the complexity of crossover of CaReMe diseases.

CKD affects around 700 million people globally, an increase of 29.3% since 1990, (Cockwell and Fisher, 2020). Global prevalence is estimated to be 13·4% (11·7–15·1% 95% CI), (Hill et al 2016). However, studies have found that due to the asymptomatic nature of CKD, approximately 44% of people living with the condition remain undiagnosed and may not be detected until the more advanced stages, at which point comorbidities may already be present (Hirst et al, 2020, Lv et al, 2013). In 2017 1.2 million people died from CKD globally and in the UK in 2020/2021, there were 127,476 admissions to nephrology wards (Bikbov et al, 2017, NHS Digital statistics, 2020/2021).

Diabetes is the most prevalent metabolic disorder globally, estimated at 8.8% for age groups 20- 79 years, expected to increase to 9.9% by 2045, contributing to 6.7 million deaths in 2021 and responsible for approximately USD 966 billion in global health expenses for the same year, (Standl et al, 2019, Cho et al, 2018, International Federation of Diabetes, 2021). In England in 2017 it was estimated over one million people with diabetes were admitted to hospital, whilst international studies communicate more than half of all acute inpatient hospital admissions and health care costs result from diabetes, (NHS England, 2019, Choi et al, 2021). Diabetes contributes to CVD, microvascular complications, reduces quality of life and is considered a worldwide epidemic as a non-communicable disease, cultivated by an unhealthy modern lifestyle, (World Health Organisation, (WHO) 2016). However, it is also estimated that 40% of CKD globally occurs as a result of Diabetic kidney disease (DKD), (Banerjee et al, 2022).

The concept of multi morbidity refers to individuals having two or more long term health conditions which increases their risk of hospitalisation, (WHO, 2016). Aubert et al's (2020) large cohort study compared definitions of the term multimorbidity to identify individuals classified as intense users of healthcare resources. This proved to be complex and may help to explain why figures relating to CaReMe syndrome are often difficult to determine. Inconsistencies with CaReMe syndrome recognition and symptoms may further increase the risk of mortality in this patient group if they are dependent upon input from multiple specialisms.

Such stark statistics provide evidence that each disease contributing to the multi morbidity of CaReMe cannot supersede the other. International studies recognise the high prevalence of CaReMe syndrome and its prognostic importance, acknowledging the substantial impact comorbidities may have on treatment choices, (Arnold et al, 2018). Yet it is thought that patients who have CVD risk factors are not managed efficiently, which dramatically accelerates the severity of underlying diseases, surmising that a consensus is needed to

define CaReMe syndrome to prevent patient exclusion, (Rask Larsen, et al., 2018, Neeland, Poirier, & Despres, 2018).

Manifestations and early diagnosis

CaReMe syndrome manifests itself over time and due to the crossover and complexity of conditions it is near impossible to pinpoint where the process has originated in an individual (Hatamizadeh et al, 2013). Due to the combined multidimensional nature of CaReMe syndrome and the processes that contribute to its diseases, it may be anticipated that symptoms can fluctuate and follow a nonconforming pattern. Volume overload, breathlessness, and oliguria are recognised to precede cardiac dysfunction (Kousa, Mullane and Aboeata, 2021). Additional signs such as fatigue and depression are dominant in metabolic disturbances, and as the individual's collection of symptoms grows, the potential to optimise healthcare outcomes becomes more challenging, (Capuron, 2008). Further studies indicate that due to remodelling abnormalities in the brain resulting from CaReMe syndrome, the risk of dementia is also increased, which intensifies the complexity of care (Hayden, et al, 2013). Current research into CaReMe syndrome has a clinical patient focus, nevertheless gaps are evident in relation to the patient experience, symptomology and quality of life with patient related outcome measures.

The early diagnosis and management of CaReMe syndrome is supported by developments in medical diagnostics. Blood pressure, risk factors. patient history and existing pharmacological treatments are aligned with an early diagnosis and case finding approach, (Sperling et al, 2015). Accessible minimally invasive tests available in both General Practice and Hospital care can readily establish an individual's cardio, renal and metabolic status. Cardiac biomarkers provide opportunities to identify patients at high-risk for HF and could indicate potential systematic pathways in the form of NT-proBNP (N-terminal pro-B-type natriuretic peptide) which is implicated in HF and in complicated chronic kidney disease, (Bansal et al, 2019). Pandey et al (2021) illustrated elegantly that a biomarker-based risk score (incorporating high-sensitivity cardiac troponin T, NT-proBNP, high-sensitivity C-reactive protein and left ventricular hypertrophy by electrocardiography) can help predict risk of incident HF in pre-diabetes and diabetes. McDonagh et al (2021) recommend transthoracic echocardiography as an essential diagnostic test to exclude important valve disease, detect intracardiac shunts and assess the systolic, as well as diastolic left ventricular function in suspected heart failure. With advancement in imaging modalities, cardiac magnetic resonance imaging (CMR) has an important role in clarifying aetiology of

HF (ischaemic or non-ischaemic causes, particularly infiltrative pathologies such as amyloid). CMR has the capability of earlier disease detection, to improve the intervention, monitoring, risk stratification, and to individualise management plans, (Seraphim et al, 2020). HBA1c and glucose level provide an indication of the stability of metabolic conditions. Similarly, an eGFR, and albuminuria can portend a propensity toward CKD or complications related to diabetes.

Adverse prognostic impact

A recent multinational study linked CaReMe complications and increased mortality risk with racial disparities, hindering equitable care provision (Birkeland et al 2020, Ferdinand et al 2014). It is, therefore, vital to understand the complexity of multiple disease processes that co-exist in CaReMe syndrome, and its potential adverse prognostic impact. HF and diabetes are considered to have a reciprocal relationship, with diabetes responsible for activating many pathophysiological and molecular functions contributing to heart damage, (Ghio et al, 2021). Key features point to poorer outcomes for individuals with HF and diabetes, whilst diabetes itself is an independent predictor for the development of HF, (Klajda, 2020). This may be explained by enhanced fatty acid metabolism in diabetic hearts and vascular complications derived from oxidative stress associated with diabetic obesity, (Carley and Severson, 2005, Giacco and Brownlee, 2010, Zareini et al, 2019). Dauritz et al's (2017) systematic review and meta-analysis examined the behaviour of HF and diabetes on morbidity and mortality, estimating that approximately one quarter of patients with HF have a diagnosis of diabetes. It revealed diabetes adversely affects patients with acute and chronic HF increasing the risk of hospitalisation and a 35% increased risk of all cause death over a median follow up of 3 years and reduced long term survival rates. Other studies make the association that diabetes is concomitant with substantially increased in-hospital mortality rates for both hospitalised and ambulatory patients with HF, (Targher er al, 2017, Dunlay et al, 2019). The connections made were thought to represent a challenge for future health care systems and sustainability of services given the resources needed to support a high-risk population.

Renal function is a significant factor that should be considered when calculating risk and appraising treatment strategies for HF patients. Reduced renal function is associated with increased mortality and can therefore be used to predict prognosis in patients with heart failure, (Smith et al, 2006, Zamora et al, 2014). Hakopian, Gharibian, and Nashed, (2019) observed the close association between a worsening prognosis of CKD and HF. Their

international study focused on progression of CKD analysing rates of hospitalisation, readmissions and death in patients with HF. It highlighted shared risk factors common to both disease groups and challenges in managing cardiorenal syndromes, such as, distinguishing volume overload due to exacerbation of one or both diseases. Results identified a significant trend in individuals with HF and CKD stage 4 to 5, whereby the risk of readmissions, hospitalisations and mortality increased, signifying these as indicators for prognostication and a subset best managed by multidisciplinary approaches.

DKD causes extensive microvascular complications occurring in up to 50% of individuals living with the disease and can result in end stage kidney disease (ESKD), reducing an individual's lifespan, (Park et al, 2019, Selby and Taal, 2020, Colhoun, and Marcovecchio, 2018). The severity of DKD is reflected by increased albuminuria secondary to progressive kidney damage, a functional decline in eGFR, hypertension, and cardiovascular manifestations which increase the risk of ill health and mortality, (Persson and Rossing, 2018).

Moreover, whilst CKD increases the risk of poorer outcomes with HF, a recent UK 20-year review concluded that risks increased further with the existence of T2DM, indicating multi-faceted interventions are necessary, (Satyajeet et al, 2021, Lawson et al, 2021). However, studies lack consensus on specific guidance relating to management of modifiable and non-modifiable risk factors to efficiently manage the trajectory in diabetic patients at risk of DKD and HF, (Satyajeet et al, 2021)

Treatments

The complexities of treating CaReMe syndrome stem from the overlapping contributing systems. For example, HF is managed by guidance relating to each classification of HF including heart failure with reduced ejection fraction (HFrEF), mid-range ejection fraction (HFmrEF) preserved ejection fraction (HFpEF) and end stage disease (McDonagh et al 2021), yet common HF treatments can affect an individual's renal and metabolic status so whilst prescribers should not withhold HF treatment needlessly, they should be aware of their impact on each system.

Primary drug treatments for HFrEF consist of, Beta Blockers, Angiotensin-Converting Enzyme inhibitors (ACEi), Angiotensin Receptor Blocker's (ARB), diuretics.

mineralocorticoid receptor antagonist (MRAs) and SLGT2 inhibitors (McDonagh et al, 2021). Beta Blockers affect the pulse rate and blood pressure, ACEi and ARBs affect blood pressure and kidney function, consequently an assessment of kidney function is advised one week from commencement of therapy. Diuretics relieve the congestive symptoms of HF and consequently oedema and breathlessness. Adverse effects to diuretics include derangements in electrolytes, predominantly serum potassium, which can be lowered by loop diuretics and thiazides and raised by aldosterone antagonists, (Roush, Kaur, and Ernst, 2014). Diuretics act by blocking sodium reabsorption in numerous locations within the renal tubules, therefore, the importance of balance between systems begins from the first line of treatment with many clinicians advocating a ‘go slow’ approach to titration, which can be resource and time intensive (Taylor, Moore and Flynn, 2019).

The evidence base for patients with HFmEF and HFpEF is less developed and whilst many of the treatments highlighted have been used in this patient group, until recently no treatment had been shown to reduce mortality or hospitalisation. However, the EMPEROR-Preserved (Empagliflozin Outcome Trial in Patients with Chronic Heart failure with Preserved Ejection Fraction) study that evaluated the effects of a sodium- glucose transporter 2 inhibitor (SGLT2i) in this patient group, (Anker et al, 2019) demonstrated a reduced risk of hospitalisation and deaths consistent across patients with or without diabetes, (Anker et al, 2020, Anker et,al, 2021). The SGLT2i, Empaglifozin was traditionally recognised as a treatment for T2DM. Its primary function was to improve glycaemic control in adult populations when combined with diet and exercise regimes. The transposable therapeutic benefits of medications conventionally used to treat systems in isolation is progressing, with the identification of other drugs having shared benefits.

Moreover, Valensi et al (2021) has advocated the benefits of SGLT2is in HF to prevent renal decline, improving cardiovascular prognosis whilst improving chronic kidney disease outcomes. Furthermore, Renin Angiotensin Aldosterone System inhibitors (RAASi) including ACEi, ARB, ARNI, retard disease progression and improve prognosis reducing the risk of mortality and hospitalizations in patients with HFrEF as well as in CKD, (Maddox et al, 2021). The consideration of treatments that encompass all components of CaReMe disease could reduce the risk of hospitalisations for individuals with HF and reduce cardiovascular deaths, (Valensi et al, 2021).

Indeed, focussing on a single disease alone, can prove to be deleterious, as treatments are initiated or removed at the expense of other co-existing pathologies. A classic example is the concept of "renalism” whereby prognostic HFrEF therapies are withheld or stopped at

times of transient fluctuations in serum creatinine, leading to adverse HF outcomes (re-hospitalisation and mortality), (Rangaswami et al, 2022). A major cause of instability has been observed in HF patients with 60% experiencing adverse consequences as a result of discontinuing RAASi, (Epstein et, al, 2022). In addition to this, it is conceded that whilst MRA's are stopped to lessen an individual's risk of hyperkalaemia, it can in the long-term place individuals at a greater risk of cardiovascular events and even death, (Trevisan et al, 2018). Renal drugs such as Patriomer, a novel potassium binder, successful in preserving normokalaemia may provide an opportunity in CaReMe treatment by controlling K+ levels and benefit by permitting RAASi in patients with HFrEF, (Butler et al, 2022). The complexity of treatment in CaReMe is tangible, and for diabetics or pre diabetic individuals dysglycemia increases the risk and incidence of HF, emphasising that good control is essential to improve outcomes, (Schneider et al, 2016, Pandey et al, 2021).

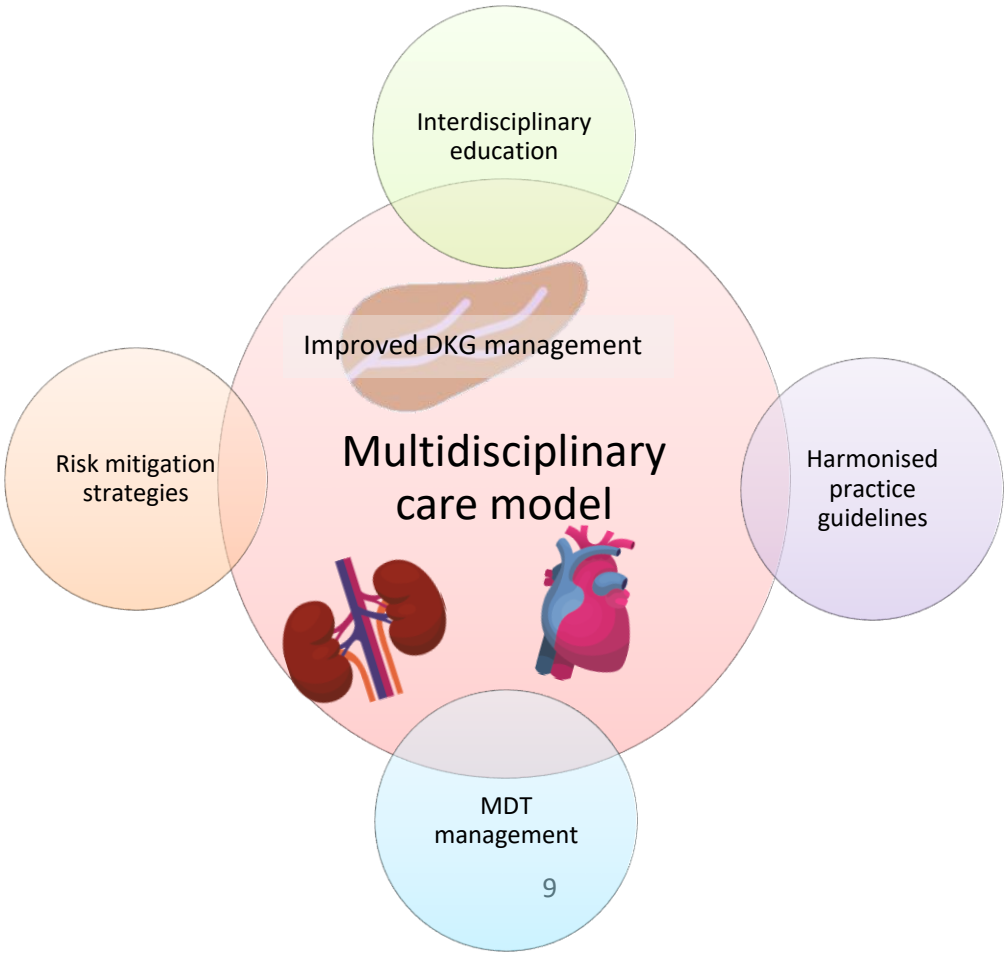
Collaborative care

NHS England (2021) endorses developing place-based partnerships, which consist of collaborative provisions designed by local and community organisations responsible for shaping health and social care services. Integrated care systems (ICSs) necessitate partnership working to deliver a vision of shared care, one which CaReMe experts aspire to emulate, (Rangaswami, Tuttle, and Vaduganathan, 2020). Shared care aims to advance population health and healthcare outcomes, confront inequalities and equity of services, to enhance productivity and cost effectiveness, and support social developments, (NHS England, 2021, The Kings Fund, 2021). It has demonstrated a reduction in emergency admissions, whilst creating a community of practice to encourage safe care delivery near home environments, and improvements in patient satisfaction and quality of life, (Chumbler, et al, 2007, Gorin et al, 2017). Cheung et al's (2021) international study of shared care models for chronic complex haematological diseases champion the benefits of providing ongoing management and supportive care through this method of delivery and indicates this may be transferrable. However, a caveat for success is the provision of dedicated resources in the form of a single point of contact, clear definition of roles and responsibilities within healthcare teams and appropriate care coordination, to ensure communication channels remain open to all, (Cheung et al, 2021).

A collaborative cardio-renal virtual MDT approach has shown that consensus decision making leads to a reduced need for multiple clinic attendances for cardio-renal syndrome, (Sankaranarayanan, Douglas and Wong, 2020). The need for multispecialty approaches is clear, necessitating a call for cardiologists, diabetologists and nephrologists

to collaborate and construct effective holistic strategies, in a bid to reduce the affliction of the CaReMe processes, (Valensi, 2021), such goals cannot be achieved without multi-disciplinary support. Rangaswami, Tuttle and Vaduganathan's (2020) paper suggests a more collegiate model of care involving physician or advanced practice provider, dietician, clinical pharmacist, care navigator, and administrative representative from all three specialties (fig1). In addition, they recommend the inclusion of individuals living with CaReMe disease and family members who will report patient level outcomes and experiences. However, they acknowledge that multi focused care delivery comes at a cost, and that most health structures are not value based, favouring quantity over quality. They identify that the practise of incorporating an integrated care system for this patient group has the potential to improve the experience of patients and their families, thus helping to develop individual therapeutic goals. Nevertheless, these outcomes will only be realised if the model in use provides the patient and their family with the resources required to self-manage their conditions.

Fig 1; Rangaswami, Tuttle and Vaduganathan (2020).



Interdisciplinary education (IPE) is heralded as a core component of the MDT care model in CaReMe management. IPE is theoretically defined as occuring when scholars from two or more professions learn together with each other, from each other, to positively influence knowledge and effectively collaborate, improving health outcomes, (WHO, 2010, Centre for the Advancement of Interprofessional Education (CAIPE), 2002). While the model seeks to establish shared care, it requires multi-level leadership and coordination of IPE across academic and practice contexts, (Schmitt et al, 2013). Guraya and Barr's (2018) systematic review and metanalysis of the effectiveness of IPE in health care demonstrated the substantial influence of IPE as an educational intervention on practitioners' knowledge, skills, and attitudes. Case-based models of IPE can improve communication and functioning of the wider team, whilst clarifying group expectations to enhance the depth of learning together, and encourage flexible, harmonious, patient–centred relationships, (Cahill et al, 2013, Barr et al, 2016). Moreover, Jones et al's (2012) evaluation of IPE for stroke self-management, determined that this shared approach led to improved team communication specific to goal setting and enhanced understanding of the support required for individuals to manage their own condition.

Promoting self-management

Self-management is often considered as the panacea of future healthcare and cited in key government policies. The 'Five year forward view' (NHS England, 2014) and 'The Long-term plan' (NHS, 2019) are examples from the U.K of the desire to promote this level of independence. It embodies the true concept of person-centred care whereby individuals can manage chronic illnesses and are empowered to promote their own health in line with personal values, beliefs, and preferences, (Heggdal et al, 2021). Allegrante, Wells and Peterson (2019) reviewed the interventions which support the self-management of chronic diseases and express three principal methods to inform chronic disease self-management programs. They promote the practise of small-group meetings to provide peer support, technological based interventions to create capacity in the delivery of knowledge and skills, alongside printed materials to build and tailor the evidence base to individual needs. Peer support is understood to improve social isolation, which is common for people with chronic conditions, and by adopting socially driven interventions, the lived experiences of others can offer a sense of connectedness and resolution in managing diseases, (Thompson et al, 2022).

However, it should be recognised that people do not exist in isolation but are part of complex family networks with competing priorities (Davies et al 2020), and their collective

actions can influence the life choices of individuals, (Birtwistle et al 2021). It is therefore important that the views of family members are considered when planning care. Whitehead et al's (2018) qualitative study focussed on the role of the family in supporting the self-management of chronic conditions and identified gaps in current research. It was denoted that families were instrumental in creating an environment that fostered family engagement, which is associated with an increased uptake in treatment and contributes to the sustenance of health behaviours and enriched clinical outcomes, (Whitehead et al, 2018, Hibbard and Gilbert, 2014). Trivedi et al (2020) emphasised the importance of distinct roles for significant others to improve the management of HF, whilst identifying tools for communication and collaboration are absent components in contemporary care. Challenges to a self-management approach include resource limitations, organisational barriers, evolving clinical knowledge and the capacity to work in a multi-professional style, (Brands and Timmons, 2021).

CaReMe patients have the additional complication of multi-morbidity which can impact self-management due to frequent modifications of treatment plans and fluctuations in one or more of its systemic components. Therefore, the potential exists for a CaReMe advanced clinical practitioner (ACP) role to manage and support people living with CaReMe diseases. ACP's have the aptitude to implement high standards of care encompassing the four pillars of advanced practice, amid current workforce shortages across primary and community care, (HEE, 2017, Edwards and Palmer, 2019). In direct correlation, 'Advancing our health: prevention in the 2020s' directs attention that reflects person centred care, integrated care models and empowerment of individuals to self-manage conditions, (Department of Health, (DOH), 2019). Evidence favourably supports the growing influence of ACPs in clinical and service-related outcomes, such as reducing waiting times, enhancing patient satisfaction, managing chronic diseases, patient education and promoting self-management, qualities which are vital to augment CaReMe care, (Htay and Whitehead, 2021).

Conclusion

Cardiovascular, renal and metabolic conditions frequently co-exist with each condition negatively affecting each other. The complexity of CaReMe syndrome with its constellation of conditions and lack of clear definition have contributed to the lack of transparency in its diagnosis and management. Frequently, patients are managed within specialty silos and consequently, treatment is considered in isolation leading to poorer clinical outcomes and patient experience. The focus on single diseases clinical guidelines

disregards the holistic approach to management advocated for those with CaReMe syndrome. An integrated multidisciplinary care model that incorporates a process of shared decision-making has the potential to overcome the deficiencies of single specialty working whilst maximising the opportunities to promote self-management. Future research that tests the efficacy of such models on patient reported outcomes measures, patient experience, symptomology and self-management is urgently required.

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