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The Contribution of Psychosocial Interventions to Precision Medicine for Heart Health☆,☆☆

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ABSTRACT

This paper reviews the value of incorporating psychosocial interventions into precision medicine for heart health. First, we review the empirical literature on prevalence of common mental health comorbidities among individuals with cardiovascular disease (CVD). We then review transdiagnostic approaches for conceptualization and treatment of mental health in individuals with CVD. We highlight recent studies that have used novel methods to individualize psychosocial interventions. Finally, we propose a preliminary framework intended to support Health Care Providers in individualizing treatment, which includes: 1) assessment of patient risk factors, characteristics, and expectations; 2) consideration of transdiagnostic processes underlying several psychiatric symptoms that contribute to CVD risk; 3) patient engagement in shared decision-making for psychosocial treatment; and 4) ongoing outcome monitoring to evaluate treatment responsiveness. We anticipate that the proposed framework will evolve with the emergence of new empirical evidence; as such, future directions and challenges for research are discussed.

Contents

Abbreviations and acronyms: ACS, Acute coronary syndrome; CAD, Coronary artery disease; CBT, Cognitive behavioural therapy; CR, Cardiac rehabilitation; CV, Cardiovascular; CVD, Cardiovascular disease; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ENRICHD, Enhancing Recovery in Coronary Heart Disease Patients; HCPs, Health Care Providers; ICD, International Classification of Diseases; MDD, Major depressive disorder; MI, Myocardial infarction; OQ-45, Outcome Questionnaire 45; PHQ-9, Patient Health Questionnaire; PTSD, Post-traumatic stress disorder; QoL, Quality of life; RDoC, Research Domain Criteria; SMART, Sequential Multiple Assignment Randomized Trials.

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The Precision Medicine Initiative, a research program supported by the National Institutes of Health Research, is characterized as "an approach to disease prevention and treatment that takes into account individual variability in genes, environment and lifestyle to aid in the development of individualized care".[1] This approach stands in contrast to traditional approaches that involve the development and implementation of interventions for the average person without considering individual variation. Adopting precision medicine has numerous benefits, the most salient being the determination of which sub-groups of people respond most favourably to certain prevention strategies and treatments. Precision medicine can also serve as a bridge between medicine and the behavioural sciences through the provision of an underlying framework for interdisciplinary collaboration that targets different spheres of a patient's life (e.g., medical, social, psychological, behavioural), and thereby directly informs care that is comprehensive and tailored to the patient.

This paper provides an overview of the potential value of incorporating psychosocial interventions into precision medicine for heart health. First, we provide a review of the empirical literature on the prevalence of comorbid mental health challenges (i.e., depression, anxiety, and stress disorders) typically observed among individuals with cardiovascular (CV) disease (CVD). A review of transdiagnostic approaches for the conceptualization and treatment of mental health in the context of CVD is presented that highlights recent studies that have employed novel approaches to individualize psychosocial interventions for this population. Finally, we propose a preliminary framework to support Health Care Providers (HCPs) in implementing individualized treatment that incorporates integrating evidence-based practice, patient characteristics and preferences, and clinical expertise. This framework includes: 1) the assessment of patient risk factors, characteristics, and expectations; 2) consideration of transdiagnostic processes that underlie a range of psychiatric symptoms that contribute to CVD risk; 3) engaging the patient in shared decision-making for psychosocial treatment; and 4) ongoing outcome monitoring to evaluate treatment responsiveness. Future directions and challenges for research in this domain will also be discussed since we anticipate that this framework will evolve and expand as new evidence emerges.

CVD and common comorbid mental health challenges

There is opportunity for integrating precision medicine and psychological intervention principles in the prevention and treatment of CVD. Research has consistently reported an association between poor mental health and increased risk of CVD. For example, the authors of a recent study of 524,952 patients registered in 140 primary care practices in the UK reported that individuals with psychiatric disorders (i.e., schizophrenia, bipolar, depression, anxiety, and personality disorders) have an increased risk for various CVD risk factors, including diabetes, hyperlipidemia, and obesity.[2] Using data from a world representative sample, serious mental illness has been associated with increased risk of coronary artery disease (CAD), cerebrovascular disease, and heart failure in cross-sectional studies, and heart failure in longitudinal studies, following adjustment for potential confounds.[3] Patients with serious mental illnesses have significantly higher odds (i.e., odd ratios ranging between 1.42 and 2.10) of experiencing CVD compared to controls.[3]

Depression

Depressive disorders are characterized by low mood and/or loss of interest or pleasure in previously enjoyable activities, in addition to other symptoms such as change in weight, fatigue or loss of energy, feelings of worthlessness and guilt, difficulty thinking or concentrating, and suicidal ideation.[4] CVD patients frequently report symptoms of depression, and 31–45% of patients with CAD suffer from clinically significant symptoms of depression.[5] Meta-analytic reviews reporting on nearly 1,000,000 patients also report a relationship between depression and incidence CVD with 60–80% increase in risk.[6] Further, 20% of these patients meet diagnostic criteria for major depressive disorder (MDD),[6] approximately four times the rate of MDD observed in the general population. These high prevalence rates have important implications: the authors of a meta-analysis summarizing 25 years of research observed that, compared to patients without depression, patients with post-myocardial infarction (MI) depression had a 2.25-fold (95% CI 1.73–2.93, unadjusted) increase in risk for all-cause mortality, 2.71-fold increase in risk for CVD mortality (95% CI 1.68–4.36), and 1.59-fold (95% CI 1.37–1.85) increase in risk of recurring CVD events.[7] Moreover, while the intersection of depression and CVD has been explored primarily in patients with pre-existing CVD, individuals with MDD are also at increased risk of developing CAD and experiencing cardiac-related mortality compared to those without MDD.[3] There is a dose-dependent relationship of symptoms of depression and CVD events among patients with CAD, such that sub-clinical elevation in symptoms of depression are associated with poorer prognosis.[8]

Several potential biological and behavioural mechanisms have been identified that explain the association between CVD and symptoms of depression. Biological mechanisms include altered autonomic nervous system activity (elevated heart rate at rest and in response to stressors, and low heart-rate variability), elevated levels of catecholamines and inflammatory markers, abnormal heart-rate response to ventricular premature complex, endothelial dysfunction, and platelet dysfunction.[6] These hypothesized mechanisms only account for a small proportion of risk.[6] More compellingly, the anhedonia and avolition that characterize depression interfere with adopting and adhering to behaviours that promote heart health and longevity; thus, potential behavioural mechanisms underlying the association between depression and CVD risk include poor health behaviours, such as physical inactivity, smoking, poor diet, and medication nonadherence.[6] Persistent depression in acute coronary syndrome (ACS) is related to lower adherence to CV medications, smoking cessation, exercise, and cardiac rehabilitation (CR) attendance.[9] A multi-pronged approach that involves the treatment of depression and promotion of adherence to preventive behaviours may lead to better long-term CVD outcomes.

Anxiety

Anxiety is characterized by uncertainty, fear, and apprehension about the future, and varies in its frequency and intensity across individuals. Anxiety experienced frequently, in high intensity, and/or in inappropriate situations may represent a diagnosable anxiety disorder according to the Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5) criteria (e.g., generalized anxiety disorder, panic disorder, phobias).[4] Post-traumatic stress disorder (PTSD) has been reclassified from an anxiety disorder in previous versions of the DSM to a trauma and stressor-related disorder in DSM-5.

The links between CVD and anxiety have received less research attention than those between CVD and depression, with studies reporting mixed results. A meta-analysis assessing the longitudinal association between anxiety and risk of CAD (21 studies, N = 249,846) reported that individuals with self-reported or clinically diagnosed anxiety were at elevated risk for CAD and CVD death. This increase in risk was independent of health behaviours, biological risk factors, and demographic variables.[10] Importantly, this meta-analysis did not adjust for depression and included studies of PTSD, though results did not differ by type of anxiety. A 6-year investigation into the associations between depression and/or anxiety and CVD incidence among 2510 initially CVD-free patients with a DSM-IV diagnosis reported that concurrent depression and anxiety disorders were associated with increased incidence of CVD while having an anxiety disorder in the absence of depression was not.[11]

In contrast, a recent meta-analysis (37 citations, N = 1,565,699), with a mean follow-up period of 24 years, reported that anxiety was associated with an increase in incidence of CVD of 52%, independent of

CVD risk factors and depression.[12] While associations between anxiety and CVD have emerged over and above risk factors and health behaviours, it remains noteworthy that anxiety, like depression, is associated with poor adherence to health behaviours in individuals at risk for CVD.[13] More specifically, anxiety is significantly associated with physical inactivity in both sexes, as well as unhealthy diet and smoking habits among men only.

Up to one third of patient's self-report elevated symptoms of anxiety following MI; these symptoms persist for at least one year in half of patients.[14] Greater symptoms of anxiety at 6 months are significantly predictive of self-reported recurrent CVD events at one-year follow-up, after statistically adjusting for severity of the CAD event, sex, family income, smoking, and diabetes.[14] Feng et al.[15] focused on clinical diagnosis rather than self-reported anxiety and depression symptoms in their nationwide population-based cohort study. At 2-year follow-up, patients with MI exhibited higher risk of anxiety disorders and depressive disorders than did individuals without MI. This risk for anxiety and depressive disorders was greater among women and patients aged 45–64 years. Patients with anxiety post-MI had a 9.37-fold greater risk of recurrent MI than those without, after controlling for sex, age, socioeconomic status, and comorbidities. Relatedly, high levels of kinesiophobia (i.e., fear of movement) are endorsed by 20% of patients with CAD, and a positive association exists between anxiety and kinesiophobia.[16] Of concern, kinesiophobia is associated with reduced attendance at CR.

Stress disorders

Exposure to psychological trauma may also increase the risk of CVD and CVD-related mortality.[17] Up to 12% of patients who have experienced a MI meet diagnostic criteria for acute stress disorder.[18] Further, studies have acknowledged that MI is a risk factor for acute stress disorder, which may encompass symptoms of dissociation, intrusion, avoidance, and hyperarousal during hospitalization.[19] Longitudinal studies have identified that dissociative symptoms specifically predict all-cause mortality, such that greater levels of in-hospital dissociative symptoms reported are associated with shorter survival time.[19] A diagnosis of acute stress disorder is only applicable to the first month following exposure to the traumatic event (in this case, MI),[4] though severity of acute stress disorder symptoms during hospitalization has been linked to PTSD.[20]

PTSD is a trauma and stressor-related disorder characterized by exposure to a traumatic event and subsequent intrusive thoughts related to the trauma, attempts to avoid such reminders of the trauma, and physiological hyperarousal.[4] Individuals with PTSD have an increased risk of CVD, as well as risk factors for CVD, such as hypertension, hyperlipidemia, and obesity.[21] As with acute stress disorder, research findings have demonstrated that CVD events themselves can act as the trigger for the development of PTSD. For example, approximately 12% of patients with acute coronary syndrome develop PTSD related to an ACS event,[22] and evidence suggests that this increases the risk of additional CVD events and mortality.[23] Of note, female sex, younger age, low socioeconomic status, and ethnic minority status are demographic factors associated with acute coronary syndrome-induced PTSD.[24,25] A number of risk factors for ACS-induced PTSD have been identified, including: 1) intense fear, perceived life threat, helplessness, chest pain, lack of control, and/or dissociation during the CVD event;[26] 2) acute stress disorder and depression symptoms during hospitalization;[24] and 3) history of psychiatric disorder prior to the event.[24]

Transdiagnostic approaches to mental health in CVD

Given the variety of symptoms observed within each psychiatric diagnostic category, there are ongoing efforts to create diagnostic categories of mental illness based on biological, psychological, and sociocultural variables. As a response to the movement to capture the dimensional nature of mental health disorders using neurobiological and behavioural measures, the Research Domain Criteria (RDoC) framework[27] provides a new method of classifying mental disorders, with a focus on neurobiological characteristics.[28] The RDoC aims to address problems with current versions of the DSM and International Classification of Diseases (ICD), which have been increasingly documented in both clinical work and research.[27] The RDoC's creators assert that diagnostic categories do not align with recent findings from the fields of clinical neuroscience and genetics, these diagnostic categories do not predict treatment response, and these categories may not reflect underlying mechanisms of dysfunction. Historically, in the field of medicine, disorders once considered to belong to the same category based on clinical presentation have demonstrated heterogeneity in laboratory tests, and other disorders appearing clinically different may result from the same pathophysiological etiology.[27] To address these problems, with the end goal of improving treatment outcomes, the National Institute of Mental Health launched the RDoC project. The RDoC represents a shift from traditional categorical approaches to understanding mental disorders, emphasizing basic dimensions of function to dysfunction that apply across the diagnostic categories found in other classification systems, such as the DSM and ICD.[28] The RDoC framework is comprised of two main axes (domains of functioning—each of which can be further specified by relevant subsystems, units of analysis) and two dimensions (environmental aspects, developmental aspects). Importantly, this framework acknowledges the heterogeneity of mental health challenges and encompasses the normal and abnormal range of function.[29]

The RDoC affords advantages in terms of research and clinical practice over the widely-used categorical system of diagnosis. In terms of research, the RDoC focuses on specific processes or mechanisms that may cut across diagnostic categories, rather than linking specific symptoms to a particular diagnostic category. In a world where comorbidity is the rule rather than the exception, focusing on processes that underlie clusters of symptoms allows for greater precision in targeting treatment approaches. In essence, the adoption of a transdiagnostic framework to diagnosis and treatment shifts the fundamental unit of analysis to the individual and focuses on mechanistic processes involved in the development and maintenance of behavioural-health problems. We propose that the RDoC will play an important role in the future of precision medicine for psychosocial care in CVD since elements of the RDoC may provide more detailed and pertinent information regarding an individual's specific and unique mental health compared to diagnostic categories that encapsulate significant variability in presentations and symptoms.

Several studies in recent years have investigated neural predictors of response to psychological treatments for depressive and anxiety disorders, including the role of the hippocampus, insula, and dorsolateral prefrontal cortex in predicting response to cognitive behavioural therapy (CBT) for panic disorder[30] and neural predictors of response to psychotherapy in major depressive disorder[31] and generalized anxiety and stress disorders.[32] A systematic review and meta-analysis of neural predictors of treatment response to pharmacological and psychological treatments for depression concluded that increased baseline activation in the anterior cingulate predicts higher likelihood of treatment response, whereas increased baseline activity in the insula and striatum and decreased right hippocampal volume predict poorer treatment response.[33] The authors conclude that developing clinically-relevant, prognostic neural markers of treatment response will require high individual-level predictive accuracy.[33] Among individuals with PTSD, lower pre-treatment activation in the amygdala and rostral anterior cingulate cortex has been reported to predict improvement following CBT.[34] Additionally, there is mixed evidence regarding the association between greater pre-treatment amygdala activation and better treatment responses among individuals with generalized anxiety disorder following CBT.[34] Neural predictors of response to psychosocial interventions in the context of CVD and comorbid mental health challenges has yet to be investigated, representing a future direction within precision medicine.

Emerging evidence points to the importance of adapting psychotherapy to patient characteristics. This approach, commonly referred to as treatment adaptation and responsiveness, and often denoted by patients as personalized treatments[35], has the goal of enhancing the effectiveness of treatment by adapting it to each individual's unique situation. The third interdivisional American Psychological Association Task Force on Evidence-Based Relationships and responsiveness recently performed a meta-analysis of >300 studies, summarizing the evidence for common elements of the therapeutic relationship across treatment approaches and relevant treatment adaptations based on patients' characteristics.[35,36] Effect sizes were generally medium to large and ranged between standardized mean differences of 0.40 to 0.80. The authors concluded that adaptations based on culture (race/ethnicity), religion/spirituality, and patient preferences have demonstrated effectiveness, and adaptations based on reactance level, stages of change, and coping style are likely effective. Adaptations based on attachment style show promise but warrant further investigation, and adaptations based on gender identity and sexual orientation represent an important area of future investigation and a current gap in the research literature.

Examples from the empirical literature demonstrate the importance of considering patient characteristics when delivering psychosocial interventions. For instance, the Enhancing Recovery in Coronary Heart Disease Patients (ENRICHD) trial allocated post-MI patients experiencing symptoms of depression to a CBT-based psychosocial intervention (supplemented by selective serotonin reuptake inhibitors in cases of severe depression) or usual care. Although the treatment group experienced greater reduction in symptoms of depression and increase in perceived social support compared to control, there were no significant differences between groups in recurrent nonfatal MI, cardiac-related death or all-cause mortality.[37] A secondary analysis of the ENRICHD trial elucidated a potential reason as to why the intervention failed: patients whose depression did not respond to treatment were at higher risk for late mortality (i.e., ≥6 months following MI) relative to patients characterized as responders.[38] This effect points to the need for determining predictors of depression treatment response in trials like ENRICHD to identify precision medicine targets in psychosocial care. Further, this suggests that it may be important to monitor indicators of psychological treatment response with the same frequency as heart health outcomes while also adopting transdiagnostic approaches to treatment.

Despite the potential advantages of transdiagnostic and individualized approaches, the adoption of dimensional frameworks such as RDoC provide challenges, perhaps most obviously at the clinical level. Currently, RDoC is a vision for the future and will rely heavily on findings in clinical neuroscience to increase its utility in clinical diagnosis. Additionally, while dimensional tools are widely available and widely used (e.g., inventories of depression, anxiety symptoms), adoption of a new system of diagnosis would represent a significant change in clinical practice and involve change to provider's existing practice. However, given that the RDoC aims to more accurately capture clinical diagnoses, it is possible that this approach will align more closely with the way HCPs perceive psychopathology, increasing potential for buy-in to this novel system.

A potential solution: moving toward an idiographic approach

A potential means of addressing important patient differences is to embed precision medicine within evidence-based practice[39] by: 1) adopting evidence-based treatments recommended by clinical practice guidelines; 2) choosing treatments with the needs of each individual patient in mind (e.g., patient preference, patient characteristics); and 3) tailoring treatments to an individual's situation based on clinical expertise and prior experience. In the context of psychosocial interventions for heart health, this may involve increased complexity and the consideration of factors beyond the presenting mental health concern, such as CVD-specific treatment considerations and interdisciplinary collaboration when appropriate (e.g., to address adherence to medical regimens).

Such an approach has recently shown promise in reducing symptoms of depression in patients with CVD; this strategy moves away from treating the average person and incorporates patient preference and stepped-care.[40,41] A core tenant of stepped-care is shared decision making. HCPs work alongside their patients and involve them in decisions surrounding their care (e.g., initiation of medication and/or psychotherapy). Response to treatment is continuously monitored and patients are involved in decisions to maintain, intensify, or discontinue treatment based on outcome data, potential risk, and availability of alternative approaches. In a stepped care approach, patients are first offered the lowest-intensity evidence-based treatment that is likely to generate a treatment response while being systematically monitored to determine if intensification or discontinuation of treatment is needed.

There is preliminary evidence for moderate efficacy of stepped-care approaches for the treatment of depression. For example, Davidson et al.[40] investigated stepped, patient preference-based treatment among participants who endorsed elevated symptoms of depression 2 to 6 months after an acute coronary syndrome. The treatment group ($n = 73$) participated in 6 months of care for depression, which was provided according to patient preference (problem-solving treatment provided via telephone or the Internet, pharmacotherapy, both, or neither). Treatment was stepped every 6 to 8 weeks. The control group ($n = 77$) received usual care, involving physician notification of the participant's symptoms of depression. Compared to control, those in the treatment group reported greater improvements in symptoms of depression. Further, promoting a collaborative relationship between patients and HCP's is another aspect to consider when individualizing patient care. Huffman and colleagues[41] investigated a collaborative care intervention to treat depression, generalized anxiety disorder, and panic disorder among individuals hospitalized for an acute CVD event. The collaborative care intervention spanned 24-weeks of telephone-based stepped-care to provide therapeutic interventions as appropriate; this was compared to "enhanced" usual care, involving the serial notification of medical providers when participants required support. Those randomized to collaborative care demonstrated greater improvements in mental health-related quality of life at 24-weeks, as well as improvements in symptoms of depression. Symptoms of anxiety did not differ between groups. Importantly, response rates among different mental health disorders and adherence between intervention and control groups did not differ. More research is required to compare treatment effects observed within stepped-care approaches to high intensity therapy at baseline and cost-effectiveness of stepped care models for depression.

Despite reported improvements in symptoms of depressed mood following collaborative care treatments, these treatments do not seem to significantly affect long-term cardiovascular risk. For example, a recent systematic review and meta-analysis synthesized the evidence of collaborative care for depression among individuals with comorbid CAD and depression.[42] Across six RCTs that met inclusion criteria, collaborative care resulted in better short-term reduction in symptoms of depression and anxiety and better mental health related quality of life (QoL) relative to control. Collaborative care led to a significant reduction in major adverse CVD events in the short-term but was not sustained ≥12-months after treatment. It should be noted that long-term outcomes were based on two trials reporting on 157 patients ($n = 80$ in collaborative care). Moreover, no data was available for symptoms of depression ≥12-months after treatment which represents a significant confound for the assessment of long-term outcomes (i.e., there is no way to guarantee that depression did not recur). Another approach to individualized precision treatment of mental disorders in CVD is by pinpointing subtypes of depression, which can be differentially targeted with treatments with the best success rates for each variant. Current guidelines classify the treatment of depression according to severity,

recommending that mild depression be targeted with psychotherapy and moderate to severe symptoms treated with antidepressants,[43,44] but do not offer more specific recommendations based on various presentations of depression commonly seen in patients with heart disease. To illustrate, situational depression following a heart event may be particularly responsive to behavioural activation in the context of CBT, while persistent depressive disorder (dysthymia) with atypical features may require more intensive treatment with therapy and antidepressant medication.[45]

Precision medicine in the context of CVD and anxiety has been less well-studied compared to CVD and depression. While anxiety disorders contribute to CVD risk, the authors of a recent review concluded that no study has demonstrated that treatment for anxiety disorders offsets CV risk.[17] Thus, treatment for anxiety disorders in individuals with CVD should currently be conceptualized as a strategy to improve QoL, or to address anxiety-related avoidance of health behaviours associated with CVD risk (e.g., avoiding physical activity due to high levels of kinesiophobia), but not necessarily to offset risk of CVD events or disease.

Psychological treatments for comorbid PTSD and CVD are also not well understood due to a lack of empirical studies. A single randomized controlled trial of CBT using imaginal exposure in individuals with PTSD resulting from a life-threatening CVD event demonstrated no differences between treatment and control groups in terms of safety (i.e., patients' pulse and blood pressure before and following every study appointment; deaths, hospitalizations, subsequent MIs, invasive procedures).[46] Importantly, the treatment group did not demonstrate significant improvement in symptoms of PTSD or depression, or overall illness severity following treatment. Of interest, a subgroup of participants with acute unscheduled CVD events and high symptoms of PTSD at baseline did demonstrate improvement in PTSD symptoms. Taken together, these results suggest that treatment for PTSD in individuals with comorbid CVD is safe and may be an effective means of treating PTSD symptoms for some individuals. Overall, there is a paucity of research exploring psychological treatments in patients with CVD and PTSD,[17] representing an important future direction for this line of work.

Future directions and challenges

A precision medicine framework for psychosocial care in heart health

HCPs are expected to maintain familiarity with an ever-increasing scope of practice guidelines for one-size-fits-all approaches to treatment. It is cause for concern that HCPs could become overwhelmed by advances in precision medicine, which will require retention and integration of increasingly complex clinical decision-making algorithms. An efficient implementation framework for best-practice in precision medicine is especially important given that provider adherence to clinical guidelines is already alarmingly low (<50%) across chronic illnesses, including CVD.[47] Successful implementation of precision medicine principles into routine clinical practice will not only depend on providing professionals with adequate training opportunities but must also target provider motivation and self-efficacy for change in practice, consider provider expectations, and address environmental barriers, such as time constraints and inadequate access to HCPs. To this end, we propose a preliminary framework for psychosocial care in CVD for clinicians that are based on principles of precision medicine (Fig 1). We anticipate that the proposed components of this framework will continue to expand as further evidence emerges.

Assess patient risk factors

A combination of biological (e.g., genetic markers, hypertension, insulin sensitivity, hypercholesterolemia), psychological (e.g., depression, anxiety, trauma), and social (e.g., available supports, social stress, determinants of health) factors should be considered when assessing CVD risk. Routine clinical interviews that focus on biological factors can be supplemented with questions about psychosocial factors (e.g., mood or social support), or through the administration of short screening questionnaires such as the 9-item Patient Health Questionnaire (PHQ-9; www.phqscreeners.com) to assess severity of depression symptoms. As research on predictors of treatment outcomes continue to evolve, HCPs will have access to information about the synergistic effects of CVD risk factors within an individual's profile to prescribe the treatment with greatest likelihood of success. For example, based on recent evidence from an RCT with 157 CV patients, thyroid axis function (thyroxine T4) predicted depression treatment response to CBT, while inflammatory markers (c-reactive protein, interleukin-6 and tumor necrosis factor), sleep quality and physical functioning did not.[48]

Assess patient characteristics and expectations

In addition to illness-specific risk factors, patient characteristics should be considered when conceptualizing a treatment plan. These could include patient knowledge, preference for treatment, capacity and motivation to adhere to treatment, and self-efficacy to implement behavioural change. Recent work by Hundt et al. reported that baseline mental health symptoms, physical health impairment, and self-efficacy are significant predictors of improvement in symptoms of depression and anxiety after a brief CBT intervention, such that patients with greater impairment in physical functioning and lower self-efficacy experienced less improvement.[49] In addition, it is pertinent to inquire about patient expectations for treatment success, given that expectations for recovery in patents with significant obstructive CAD is associated with improved likelihood of long-term survival and functioning.[50] Development of various assessment methods beyond the traditional clinical interview is ongoing, including testing the use of neuroimaging, behavioural lab-based measures, virtual reality and smartphone sampling to assess patient self-regulation targets for behaviour change.[51]

Consider transdiagnostic processes of psychiatric symptoms that contribute to risk

The differential influence of transdiagnostic factors characterizing mental health conditions often comorbid with CVD should also be assessed in the context of psychosocial care. Work is ongoing through initiatives like the RDoC framework to identify molecular, genetic, and behavioural features of emotional, cognitive, social, and regulatory systems that underpin psychopathology. Underpinning factors relevant to CVD populations with comorbid mental health concerns may include genetic predisposition to mood disorders, avolition (i.e., decreased motivation to initiate self-directed behaviour) affecting treatment engagement and adherence, fear-related avoidance of physical activity (i.e. kinesiophobia), helplessness or hopelessness, and level of acceptance of medical diagnoses. Though yet to be tested in the context of CVD, a transdiagnostic psychological treatment for anxiety disorders – the Unified Protocol[52] – has demonstrated efficacy for four anxiety disorders (panic disorder, generalized anxiety disorder, obsessive-compulsive disorder, and social anxiety disorder). Following treatment with the Unified Protocol, patients reported reductions in symptom severity that remained statistically significant at 6-month follow-up.

Engage patient in shared decision-making algorithm

Decision-making tools are important resources for clinicians working with CVD patients to accurately evaluate risk, make clinical decisions about how risk should be managed, and assess the likelihood of improved clinical outcomes based on data about heterogeneous treatment responses.[53] Utilizing simplified decision-making algorithms improves provider adherence to recommendations made by practice guidelines for CVD prevention, such as improved compliance with prescription of antihypertensive medication.[54] This process would also involve consultation with practice guidelines and adapting evidence to patient needs and the clinical context. Such simplification and support

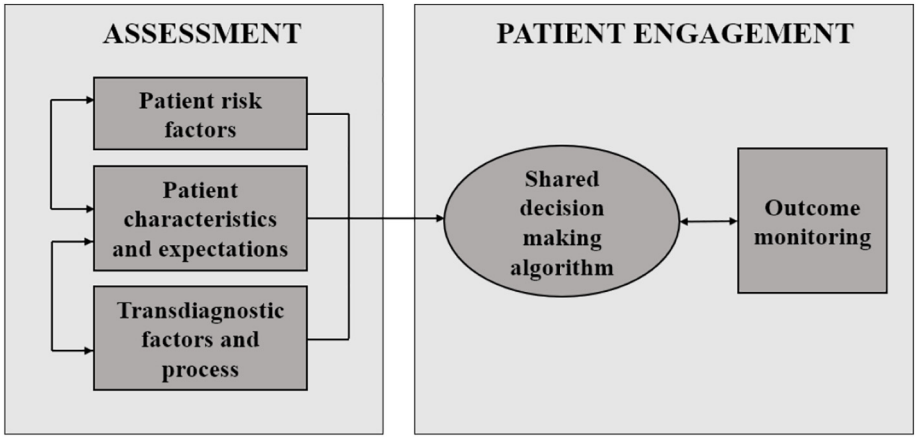

Fig 1. Precision medicine framework for psychosocial care in heart health.

are necessities given the breadth of information that is required to practice precision medicine. These tools could also be used to engage patients in collaborative decision making about their care and this, in conjunction with treatment outcome monitoring described below, will serve as a continuous form of reinforcement and provide opportunities to discuss patient concerns, including difficulty with adherence to treatment.

Ongoing outcome monitoring to evaluate treatment responsiveness

Setting and following through with a plan for tracking key clinical outcomes that are sensitive to treatment responses will help provide evidence that would signal the need to intensify or change the treatment. Ideally, monitoring would incorporate validated measures that have the sensitivity to assess clinically meaningful indices of change for CVD patients (i.e., the smallest change in the treatment outcome considered as meaningful improvement in an individual's condition), such as the Hospital Anxiety and Depression Scale.[55] Further, some psychotherapy outcome progress monitoring tools, such as the Outcome Questionnaire 45 (OQ-45)[56] have integrated a Reliable Change Index to assess whether the differences between scores of an individual's scores at two points in time is statistically significant. These thresholds and decisions should also incorporate patient risk factors and characteristics. Routine monitoring will likely engage the patient further and serve as source of motivation to persist with treatment, especially if clinicians also track outcomes that have been flagged as important for QoL of individual patient (e.g., illness-specific symptoms interfering with physical, psychological or social functioning).

Future directions and challenges in research

Most psychosocial and medical research evaluates treatment effectiveness in RCTs by assessing the average treatment effect in a representative sample of the target population. However, precision medicine requires evaluation approaches that predict how an individual participant will respond to the treatment. Specific statistical approaches for predicting individual treatment effects within RCT designs exist and will make it possible for researchers to quantify the heterogeneity in treatment responses which can then be used to predict the characteristics of individuals who will be helped or harmed by the intervention.[57] Another data-driven approach to determine the optimal intervention for individual patients is the N-of-1 trial study design, in which the patient becomes the unit of analysis. These studies use a multiple crossover design in which comparative treatments are administered in random order within each patient, rather than patients being randomized to single treatment arms, with clinical outcomes assessed throughout. Results can then be reviewed with a clinician to determine which treatment to continue to treat the target condition. This design lends scientific rigor to the trial-and-error or wait-and-see approaches often used to treat depression or anxiety disorders in patients with cardiovascular disease, while providing treatment estimates based on the interaction of patient characteristics, which is impossible between-subject designs. Pooling of results of multiple N-of-1 trials would also provide insight into the heterogeneity of the treatment effect and enhance our understanding of who may benefit from these interventions.[58]

Another approach to studying behavioural interventions from a precision medicine lens are via Sequential Multiple Assignment Randomized Trials (SMART) designs,[59] developed specifically to allow researchers to investigate and build optimal, adaptive interventions. SMART designs allow for the study of sequential, individualized treatment approaches, in which treatment is adapted and re-adapted multiple times in response to the individual's unique needs and evolving status.[59]

Other innovative approaches to research include models such as that employed with the ENGAGE Study.[51] The ENGAGE study is a research project that engages self-regulation targets in order to understand mechanisms of behaviour change and improve mood and weight outcomes for individuals with obesity and comorbid depression. Ultimately, the authors aim to identify profiles of self-regulation among the participants to tailor intervention strategies in this population. This study provides a guide for studying precision medicine within the context of comorbid mental and chronic health conditions. The ENGAGE study integrates neuroscience and behavioural science to understand self-regulation mechanisms of behaviour change associated with improvements in mood and weight outcomes among adults with comorbid depression and obesity. The authors are developing a prototype for determining underlying self-regulation mechanisms of behaviour change and the application of these mechanisms in optimizing intervention strategies for multiple chronic diseases. The ENGAGE study embodies an Experimental Medicine[60] approach to research, which emphasizes targets or mechanisms of change, with the aim of identifying and validating targets, and understanding how and when targets are optimally engaged. From an individualized perspective, Experimental Medicine seeks to understand what strategies are conducive to behaviour change, for which individuals, and under what circumstances.

Research on the identification of techniques and mechanisms of behaviour change represents a new and emerging field. A recent synthesis of the literature by Carey and colleagues aimed to identify behaviour change techniques – theorized to be the "active" components of interventions via which behaviour change occurs – and their mechanisms of action.[61] The authors identified 277 articles on behaviour change interventions, extracting hypothesized links between behaviour change techniques and mechanisms of action. A total of 2636 links were identified in total, with each article averaging 9 links. Importantly, the links

identified have yet to be tested empirically and are solely theory-based at this time. A key next step is the systematic investigation of empirical support for these behaviour change techniques and mechanism of action links. Researchers at Science of Behavior Change (http://scienceofbehaviourchange.org) are dedicated to understanding the mechanisms behind behaviour change, with the goal of understanding why behaviour change occurs in some individuals but not in others. Developing a clearer understanding of these links will help both researchers and HCPs select the most appropriate behaviour change techniques for both the target behaviour(s) and the individual receiving the intervention. Broadly, an intervention may be tailored to the target behaviour if mechanisms of action are empirically linked to behaviour change techniques, and, more specifically, certain mechanisms of action may hold greater or lesser relevance to the individual patient. As such, behaviour change techniques could then be strategically selected and implemented via a precision medicine approach.

Conclusions

The overlapping symptomatology in depression, anxiety and stress-related disorders, which commonly co-occur with CVD, points to the need for considering transdiagnostic factors during assessment and treatment. Key ingredients to consider when adopting a precision medicine framework for treating these conditions in cardiac patients include understanding patient preferences and expectations, engaging in collaborative consultation practice with patients, knowledge of stepped care models, and predictors of treatment outcomes. Several new and promising research designs are well suited to help further the evidence base on tailored psychosocial and behavioural interventions, such as N-of-1 and SMART trials. There is exciting potential for psychosocial interventions to play a role in precision medicine for heart health.

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