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REVIEW ARTICLE

Heart failure research paradigms using bedside observation on endothelial muscle common denominators to highlight important translational questions

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ABSTRACT

Background and Aim: Congestive heart failure (CHF) imposes a relevant burden on healthcare systems, as it is associated with high morbidity and mortality rates and considerable costs. Within the last three to four decades, there have been revolutionary advancements, particularly in the pharmaceutical industry. In addition, health services research at the population level has also delivered. A third avenue for advancing the clinical management of CHF is to explore established therapies with a new approach. In this perspective, we explore these established concepts and provide impetus for using bedside observations to find improvements in CHF outcomes.

Conclusion: There are potentially new concepts that can be brought to established solutions for CHF. Encouraging observations when delivering established guideline-directed medical therapies are issues that the evidence-based medicine community should factor alongside novel discoveries to improve CHF prognosis. An emphasis on innovating on the known can be considered as an important paradigm for discovery.

Relevance for Patients: Patients with CHF receiving current available treatments have improved outcomes; however, those not improving could be considered under evolving research paradigms.

1. Introduction

Congestive heart failure (CHF) as a syndrome has advanced considerably with the understanding of pathophysiology and in delivering prognostic treatments. The latest guidelines published by American and European cardiac societies provide a comprehensive outline of strategies and proven therapies for holistic CHF disease management [1,2]. Guideline-directed medical therapies (GDMTs) will improve outcomes, nonetheless, the debate will continue in regions where there are poorer outcomes. Thus, there is merit in reflecting on what has been achieved. In particular, understanding where and why there are gaps in achieving trial findings when GDMTs are prescribed at the population level [3-6]. Clinical translation and health services research has addressed some of these external validity factors [7,8]. A second factor on validity that may be intrinsic to patients is not easily standardised for in trials and randomisation and can be masked when data is pooled; importantly, it can be assessed at the bedside when treatments are administered, and responses are observed [9]. There is thus the intersection with post-trial prescribing in the clinical domain, and to fully capture what transpires requires a collaborative mindset and an administrative framework to deliver to patients the GDMT and learn of emerging gaps.

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There are examples of extending innovation from established therapies, from clinical intuition and exceptional bench to bedside translational research. Two such advances in the last decade are the angiotensin receptor-neprilysin inhibitors (ARNIs) as an extension of the renin-angiotensin system and sodium-glucose cotransporter-2 (SGLT-2) inhibitors and extension of incidental observations in diabetes studies [1,2]. These examples highlight the importance of post-trial observations.

Noting it can be decades between such important discoveries, clinicians will undoubtedly question who, how, and when will newer discoveries come along. Feasible contributions clinicians can make in their daily routines are interrogative bedside observations and where relevant, direct a bench connection. For this discussion, we acknowledge that the understanding of cardiovascular disease through vascular endothelium, smooth, and skeletal muscle pharmacology reminisces great achievements in medicine and is an opportunity to ignite debate on gaps and challenges. In this short communication, we first highlight a basic understanding of key CHF processes in the endothelium and skeletal muscle; in the second part, we explore key challenges in epidemiology and drug discovery; and finally, we discuss ideas that may not be traditional; however, the direction of which could be important to find research questions to expand on established therapies.

Heart failure (HF) in this review is focused on HF with reduced ejection fraction (HFrEF). Other forms of HF have different pathophysiology and are not discussed.

2. Gaps Beyond the External Validity of Delivering Guideline-directed Therapies

There are four pillars of CHF pharmacotherapies published in established guidelines (Figure 1) [1,2]. These therapies that were developed over decades are examples of successful clinically translated bench-to-bedside discoveries. CHF affects all organs and utilises many counter regulatory pathways. Some pathways play a greater role in CHF pathophysiology. Other pathways are also important and holistically contribute to chronic disease propagation. Thus, comprehensive care requires a multimodality approach including allied health participation. All established guidelines detail a framework for comprehensive care. Therapeutic response creates a new equilibrium as these pathways navigate from the disease state to the new milieu and vice versa. As there are differences in individual outcomes, if we assume GDMTs have been delivered, according to protocol, this leaves us with several questions: Do differences in response warrant a search for new therapies such as a fifth or sixth pillar; or alternatively exploring the question through renewed bedside observations may highlight pathophysiological clues on how some patients are responding? This post-trial introspective approach allows clinicians to go beyond the grouped outcome data of a trial and individualise an outcome for the patient. Thus, it can then generate new hypotheses to take back to the bench.

There are some examples of this. The A-HEFT study had important implications for treating Black patients with HFrEF [10]. The pioneering hydralazine (arterial dilator)-nitrate (venodilator) Vasodilator HF Trial (V-HeFT trial) in 1986 demonstrated improved survival in HFrEF. In 2004, the African-American HF Trial (A-HeFT trial) improved on mortality reduction of V-HEFT from 34% to 43%. The pathophysiology targeted was primarily reducing intracardiac filling pressures and altering cardiovascular negative remodeling, and secondarily increased nitric oxide (NO) availability both as a donor and with antioxidant properties [11]. In between these studies in 1997, the angiotensin-converting enzyme inhibitor (ACE-i) trials established this as the first pillar in therapy. Here, enalapril superseded the vasodilator combination in mortality. However, among the 215 black versus the 574 white patients, there was no difference in either arm. A speculation was the efficacy of ACE-I in reducing blood pressure in Black patients [12]. In the real world, observations from two studies first showed that in Black patients above 65 years, 18% had an estimated glomerular filtration rate (eGFR) of <30 mL/min/1.73 m^2 and the actual use of proven vasodilators in those who have contraindications to a CHF pillar or who qualify outright was low [10,13-15].

To advance these arguments, we draw on a simple perspective of biological systems, as they are seen as being composed of compartments. External compartments are outside the system. Internal compartments are separated by function, synergy, distance, or other barriers. Importantly, pathways beyond routine facilitation are activated to overcome barriers. Through mediators that act outside a cell or downstream through a cellular receptor counter regulatory mechanism creates the milieu and equilibrium. Several important pathways and downstream links in CHF that *have not* seen revolutionary prognostic treatments, despite playing key roles in its pathophysiology are the endothelium (excluding vasodilator studies) and skeletal muscle.

2.1. Endothelium in HF

In CHF patients, endothelium-dependent vasodilatation is blunted due to abnormal NO production and actions [16-18]. Many CHF treatments aim to restore this balance. Endothelium, the largest organ in the body, originates from embryonic mesoderm. It is a single layer of cells that lines the entire circulatory system, including the heart, blood vessels and lymphatics, and the smallest capillaries of all other organs in the body. Physiologically, vasodilator and constrictor factors, predominately NO and endothelin, regulate structure, function, and dynamism [18]. The endothelium exerts multiple biological effects through endocrine and paracrine signaling pathways. It also responds to various stimuli and has broader actions such as platelet aggregation, leukocyte activation, smooth muscle cell proliferation, neurotransmission, cardiac contractility, anti-tumor, and pathogen, and inflammatory effects, thus maintaining vascular general homeostatic control (Figure 2) [19]. Endothelial dysfunction occurs from an imbalance in vasoregulatory actions, leading to a reduction in flow-mediated dilatation or vasoconstriction in response to agonists, such as acetylcholine. Impaired synthesis and inactivation of the relevant bioactive compounds are then critical to disease development [20].

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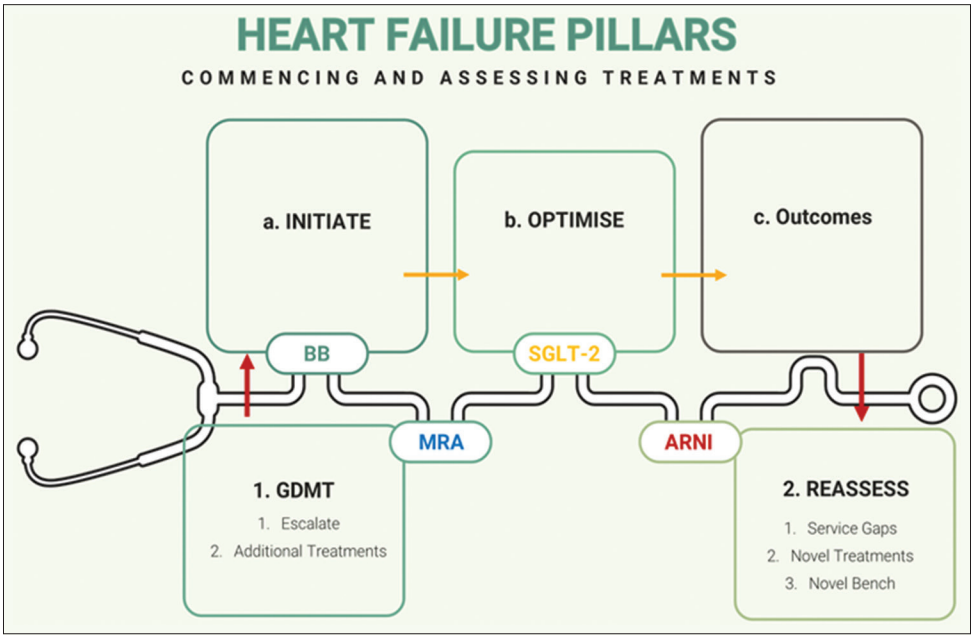

Figure 1. The four pillars of HF therapeutics. The bottom left boxes outline the GDMT: the first pillar ACE-I, now superseded by ARNI, BB, MRA, and SGLT-2 are routine first-line therapies. The top 3 boxes highlight the aim of GDMT treatment from initiation to optimisation and monitoring outcomes. The bottom right box is reassessment if outcomes are not achieved. Importantly, some patients have contraindications or comorbidities. It is vital that individual patient observations and guideline checklist be responsive to detecting gaps in outcomes. It may also be a source for the future discovery. Abbreviations: ARNI: Angiotensin receptor neprilysin inhibitors; BB: Beta-blockers; GDMT: Guideline-directed medical therapy; MRA: Mineralocorticoid receptor antagonist; SGLT2i: Sodium-glucose cotransporter-2 inhibitor.

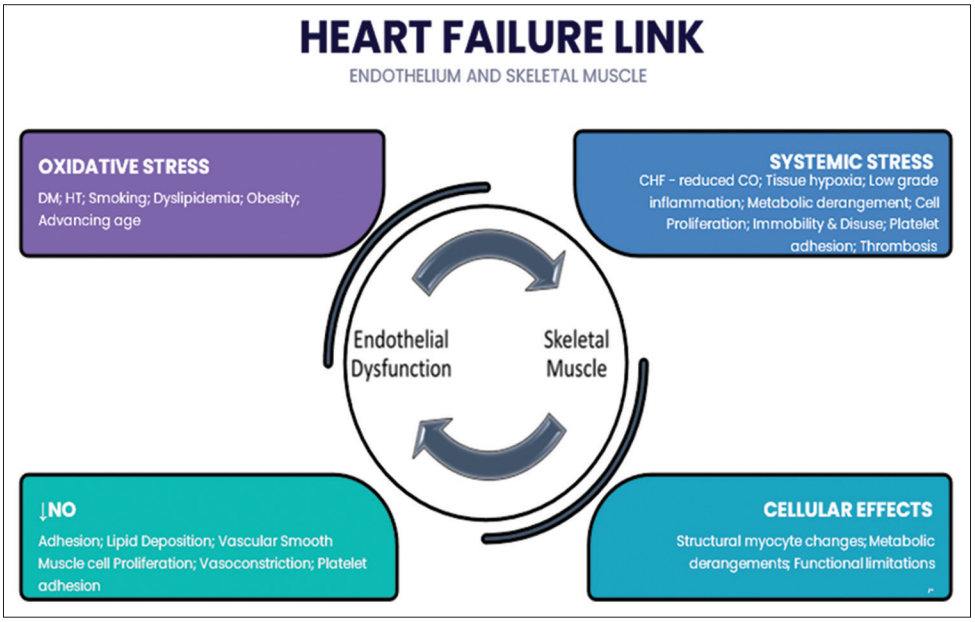

Figure 2. Endothelial skeletal muscle and heart failure (HF) links. Nitric oxide (NO) imbalance and skeletal muscle hypoperfusion and dysfunction are considerations for therapeutics that could be future HF pillars. In common, they are greatly impacted in all stages of the disease. Specifically, traditional risk factors, oxidative stress, NO deficiency, endothelial dysfunction, and skeletal muscle injury are linked in a loop that is both effectors and causes of HF propagation. Endothelial and skeletal muscle responses may potentially have significant impacts on the trajectory that determines recovery and health. The key factors in these pathways that could alter prognosis remain unknown. Bedside observation could play a critical role in identifying those who lag despite optimal care (Adapted from reference 21).

The counter regulatory pathway is NO-cyclic guanosine monophosphate (NO-cGMP). L-arginine is catalyzed by the enzyme NO synthase (NOS) to NO and L-citrulline. There are three isoforms of NOS and its production, functions, and

regulations are well described [14]. The NO-cGMP pathway requires a host of factors including a substrate (L-arginine) and cosubstrates (oxygen and NADPH), enzyme cofactors [Flavin adenine dinucleotide (FAD), flavin mononucleotide (FMN), and (6R-)5,6,7,8-tetrahydro-l-biopterin (BH4)], intermediary proteins (e.g., calmodulin [intermediary calcium-binding messenger protein]), and trace minerals (e.g., zinc). In CHF, the NO pathway is under stress and a redox state emerges. Elevated production of superoxide radicals and other oxidant species (ROS) with a decline in elimination is defined as oxidative stress. The mitochondria are the main source of ROS that inflicts cellular and DNA damage and reduced NO effects [16,21-24]. With HF, endothelial dysfunction and accumulation of ROS diminish the ability of mitochondria to perform their functions. Oxidative stress is also a common denominator between HF, endothelial dysfunction, and skeletal muscle dysfunction [25-27]. We discuss this in the next section.

2.2. Skeletal muscle and HF

HF induces skeletal muscle myopathy with inflammation, oxidative atrophy, declining strength, acute injury, and impaired regeneration. This myopathy is unique to HF and creates a loop that further declines exercise tolerance [28-31]. These factors are summarised in Figure 2. Essentially, the skeletal muscle is at the forefront of a cycle where its integrity and function are altered by reduced perfusion. In return, the reduced function impairs actions that help the movement of blood in the venous system such as those supported by muscle contraction, and one-way valves. With structural changes, cellular atrophy can lead to apoptosis or permanent dysfunction. There are critical pathways here that trigger these processes. Thus, the NO pathway and skeletal muscles have important links. Impaired blood flow also alters skeletal muscle fatiguability. Endothelial dysfunction and its contributor oxidative stress are directly associated with mitochondrial dysfunction, microvascular dysfunction, exercise intolerance, and insulin resistance in HF [32,33].

There are many contributors to exercise intolerance in CHF, and the direct symptomatic or perceived fatigue attributed to skeletal muscle fatiguability is not clear, although it likely plays a major role. Studies have shown that systolic dysfunction in isolation does not contribute to exercise intolerance or fatigue. A cascade of events with high sympathetic output and low cardiac output leads to reduced perfusion, changes in skeletal muscle metabolism and atrophy, pro-inflammatory cytokines, reduced NO availability, altered oxidation, and glycolysis [28]. Importantly, with the advent of rehabilitation, both NO and muscle changes can be addressed with the right program.

3. Perspective on Observations and Traditional Clinical Laboratory Links

Filling in the clinicopathophysiology gaps was instrumental in the development of the main CHF therapies. Guidelines weaved these therapeutic pillars with ancillary care to shape comprehensive management programs, which work for many patients with improved outcomes and quality of life. Before reflecting on these gains, two points are worth reflecting on; the epidemiology of diseases is transitioning and the risk factors, main etiologies, and demographics, among others, are evolving [5,34]. Today, diastolic HF or HF with preserved ejection fraction (HFpEF) accounts for 50% of all CHF cases and is more prevalent in older adults, particularly females [1]. Second, miscellaneous unanticipated findings can be observed when post-trial real-world data starts emerging, as discussed in the first segment [35]. These are among the strongest arguments to learn and reflect on observations.

3.1. The process of reflecting on achievements

An article published a decade ago by Atkinson highlighted that over the span of 40 years, statins constituted 25% of the top 15 best-selling drugs at the time, and 50% of these drugs entered the market more than 30 years earlier. The author highlighted possible reasons as duration of drug development from synthesis to marketing, and economics which favor copying over innovation. From these observations, Atkinson quoted “Albeit, looking at these figures, a pessimist would be tempted to say that cardiovascular pharmacologists have shown a certain lack of imagination – an optimist would say that there is a large number of potential targets out there just waiting to be discovered and developed” [36]. Whether one or the other perspective is true, here, the pessimistic argument is propagated. For the individual, diseases prosper when the efficiency of communication between any intrinsic feedback loop or extrinsic management option is unhealthy. These communication issues are factors in common for success at the bench (laboratory) and the bedside (health services). With GDMT, the achievement of pharmacotherapy addresses but one component of well-being and is thus prescribed in conjunction with multidisciplinary care and a holistic appraisal of a variety of intrinsic factors. This cannot be better emphasised by the lower attainment of outcomes with proven drugs prescribed at the population level compared to the same drug when used in controlled trials [6]. Thus, an introspection on the epidemiology of the original problem is a vital part of reflecting on achievements.

3.2. Epidemiology: Linking the past to reshaping the future

The last 5 decades have seen stellar advancements in CHF research (Figure 3). The Framingham study, a pioneering population study, was the impetus for an increased understanding of CHF epidemiology[2]. From this point, a revolution in cardiovascular medicine took form. Scientific understanding and technological advancements took many shapes. First, basic sciences led to improvements in diagnostics including cardiac catheterisation which helped improve clinical pathophysiology. This interlink in advancements opened up more areas that delivered pharmaceuticals and extended to device-based technologies. Second, the evidence-based movement (EBM) standardised this process and led to clinical guidelines. Third, from guidelines, post-trial standards were factored in, for example, process of care programs like OPTIMIZE-HF followed by Fonarow *et al.* [8]. We are currently at the point where GDMTs are significant, yet outcomes lag in some areas.

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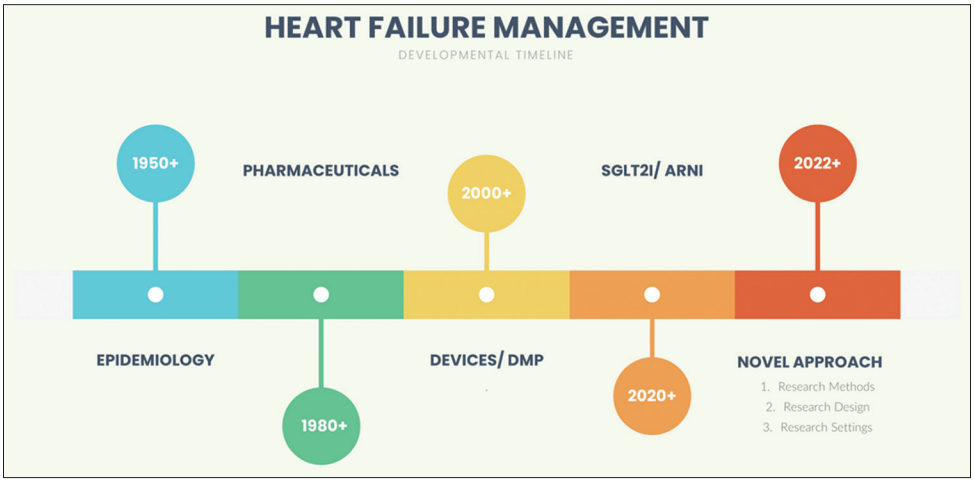

Figure 3. Timelines and potential paradigms for HF with reduced ejection fraction management. The largest gap in research methodology today has been advancing links in hypothesis-generating research and its rapid translation through benchwork. Hypothesis-generating research has its greatest strength in qualitative methodology. Linking these qualitative methods to the bench could prove beneficial to broaden the information from observations to guide the next steps in CHF research. This concept, in a new qualitative (research methodology) paradigm, could be contextualised relative to the direction in the management of chronic diseases from pharmacological, device, physical, to psychological options. Particularly, when the disease trajectory is complex and differs with individual patients. As the permutations are higher, it will thus be hard to get accurate standardisation in CHF patients and research controls. Nonetheless, balancing control, standards, diversity in general population research, or the translational phases could address many outstanding gaps.
Abbreviations: ARNI: Angiotensin receptor neprilysin inhibitor; DMP: Disease management program; SGLT-2: Sodium-glucose co-transporter-2.

In the last several years, the translation of ARNI and SGLT-2 inhibitors as novel pillars of CHF has been important. These guideline-based strategies achieved class 1A indications quickly and unequivocally improved all major cardiovascular outcomes in trials. Nonetheless, like its predecessors, global epidemiology suggests not all patients have seen the full benefits, highlighting ongoing issues in post-translational delivery that require different strategies [35,36]. Despite factoring this, it is interesting to note that however, we look at the epidemiology, the size of the problem is growing, costs are escalating and outcome improvements have not been as significant as other conditions like rheumatic and coronary heart diseases [5,6].

This then poses some questions as to linking clinical observations of the past, the present, and how we identify and shape solutions from them. Two schools of research methodology, qualitative and quantitative, as well as the mixed methods research (MMR) can be applied. There are some important acknowledgements to ponder. First, GDMTs are unequivocally based on quantitative data; second, MMR research is vital for hypothesis generation, however, in the post-trial phase, the logistics of conducting randomised controlled trial (RCTs) to prove these new hypotheses may not be feasible; third, qualitative perspectives on basic sciences, that is, *qualitative molecular epidemiology* is a missing link in this mix. Thus, the question that must be asked is why is it important and how do we link these different research schools to deliver guideline level evidence at the post-trial level?

Class 1A evidence often has a bench and clinical journey to the bedside. The early stages of research are based on the focus of one problem. The journey here is based on the traditional methodology of identifying a clinical problem, identifying a pathophysiological mechanism, and narrowing down the key factors. The result is a key biomarker or therapy that has a significant influence on the disease trajectory. However, as we are realising at a population level as one layer of a problem is unwrapped, others begin to appear. In CHF, with success in improving the acute trajectory of the illness, chronic latent states evolve and interspersed with the slow decline, are acute decompensation and costly readmissions. Let us explore a hypothetical question, to build Class 1A evidence to prevent readmissions. At the population level from current GDMT, we need to consider that there is no absolute cure for CHF. Let's take two examples that offer continuous ambulatory solutions to prevent readmissions, a clinical and invasive example. Both options can act as early identification of decompensation (biomarker) and inform early escalation of acute therapy (e.g., inotropy or diuresis). There have already been studies in this area, predominately with negative results.

i. Chronic disease self-management (CDSM) with a health service-supported model of care such as nurse lead home-based care. The addition of allied health support does improve major adverse cardiovascular outcomes; however, it is resource-intensive and has not translated globally into models of care largely from logistics. CDSM is a viable solution and gold standard trial evidence is still a while away [2,7].
ii. Device-based left ventricular filling pressure assessments are the closest predictors to decompensation. The evidence has been clouded and they are also measuring events later in the decompensation phase [2,38].

Several important lessons could be learned when translating controlled studies: A translation issue is difficult when individualising solutions, as there are many more factors to consider, and we still have lessons to learn on how to deliver evidence

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with wide benefits. This suggests that translational solutions that encompass all comers are difficult and new approaches may be needed. Beyond current GDMT, a holistic and invasive (above) approach has failed to improve outcomes, in patients receiving optimal GDMT. Thus, a holistic trial approach, at some point needs to consider individual factors such as disease chronology and severity itself, demography (age, sex, and ethnicity), and a host of unconventional factors [37]. As there are physiological differences to factor in, this could be important [38-41].

4. Defining the Translational Issue of Complex Care

In considering the issues of translating findings from RCTs and finding solutions for complex and chronic care, this can only be answered when the perspective of the question or problem is encountered and defined. Cause and effect are proven in trials; however, unforeseen gaps are identified in clinical translation. Should these gaps relate to a new disease pathophysiology, new pillars of treatment can be explored as highlighted with NO and skeletal muscle. However, it is gradually being recognised that complex care may determine responses beyond the pathophysiological pathways controlled for in trial settings. This idea could shape post-trial CHF management, and this is discussed.

4.1. Anecdotal evidence for observational paradigms in complex care

Under-representation of demography, ethnicity, gender, and complexity of cases are recognised flaws for translational goals from RCT findings [35,36]. While they are gold-standard for proving causation, the actual issue is not the result but its application when administered to untested heterogeneity, which is the norm in a real-world clinical setting. Registries and anecdotal *post hoc* data are traditional sources for identifying these issues [7]. As an example, among indigenous peoples with chronic diseases in North America and Australasia, this group represented 5.6% of the total population in 172 of 1000 studies reviewed[42]. In cardiovascular trials, from 2015 to 2019, African Americans younger than 65 years only represented 3% of clinical trial participants [39,42]. Among indigenous Australians, established genetic variation with rheumatic heart disease was identified at a locus related to immunity responses (HLA_DQA1-DQB1) [4] and with kidney diseases an uncharacteristically high susceptibility to renal stress, renal failure associated with lower nephron numbers with ACE D alleles [39]. Across the board, there is established evidence of differences in risk factors and diseases in groups of peoples (e.g., race and gender), from single nucleotide polymorphisms to multiple genetic abnormalities, to systems such as cytochomone P450 and receptors such as the adrenergic systems [39].

Specific examples of these paradigms have even come from trials and follow-through with observations in the cohort subgroups and registry of real-world recipients of the medication. The most notable subgroup (African Americans) included in A-HEFT [43] and the ALLHAT [36] study, shaped an important understanding of the pathophysiology of hypertension in this population. Hypertension was observed to be more severe and resistant, from genetic predisposition to retaining salt and water, manifesting biochemically as low renin and aldosterone and overactivity of ENaC [44,45]. Thus, in isolated CHF, as population heterogeneity increases with chronicity and greater complexity, more factors are encountered outside the trial inclusion and this requires ongoing observations to filter potentially significant findings.

4.2. Chronic illnesses and evidence-based medicine

Complex and multimorbid illnesses are confounders to finding proof of causation. Population heterogeneity that contributes to this complexity includes a higher prevalence of traditional and nontraditional risk factors, gender, age, ethnicity, sociodemographics, and multiple chronic comorbid illnesses. These comorbid conditions and demographics can influence the baseline when comparing a treatment and placebo. When we add in the cost of RCTs and the feasibility of bench-to-bedside translation in cost and time, the ability to find meaningful answers for today's chronic ailments such as CHF becomes more challenging, especially post-trial findings. The existing tools are there to allow hypothesis generation, broad observations and means to inform cost-effectiveness when evidence is established. What is different, however, is the level at which we are able to advance these topics and methodologies we utilise.

Thus, the question is how do we better employ the technology that understands pathophysiological mechanisms, for predicting decompensation, preventing readmissions, and reducing costs? What are the population level gaps for CHF? Patients who are good self-managers are invariably better at relaying information to their teams. Good self-management requires a degree of cognitive behavioral changes. However, there are confounders, treatments will improve symptoms, and comorbidities such as renal impairment, coronary artery disease, diabetes, and atrial fibrillation can aggravate HF [7,9]. Symptoms can also be confounded by these conditions and biomarkers like N-Terminal Brain Natriuretic Peptides (NT pro-BNP) can be elevated. The chronology of chronic HF can cause symptoms and biomarker levels to change at varying stages [7,9]. Thus, chronic illnesses have individual fingerprints, while acute illnesses can respond to management strategies along a more singular, universal, and GDMT line. This argument is probably the most relevant, as the health system devises models to address chronic disease cost, outcome, or cost-effectiveness. As there is no fixed baseline of health for patients at first presentation, nor are there predictable trajectories, are individual fingerprints on health needed, and is there a molecular basis for this, and for post-trial scenarios such as predicting early deteriorations?

4.3. Entropy

Could entropy in a medical sense have relevance? If so, it could help start discussions on novel post-trial observational paradigms, which include factoring common denominators in complex cases, or responses in patients with multiple comorbid conditions who demonstrate unexplained treatment responses. A simple definition of entropy is the measure of the amount of energy in a system that cannot contribute to work. Importantly, for our argument,

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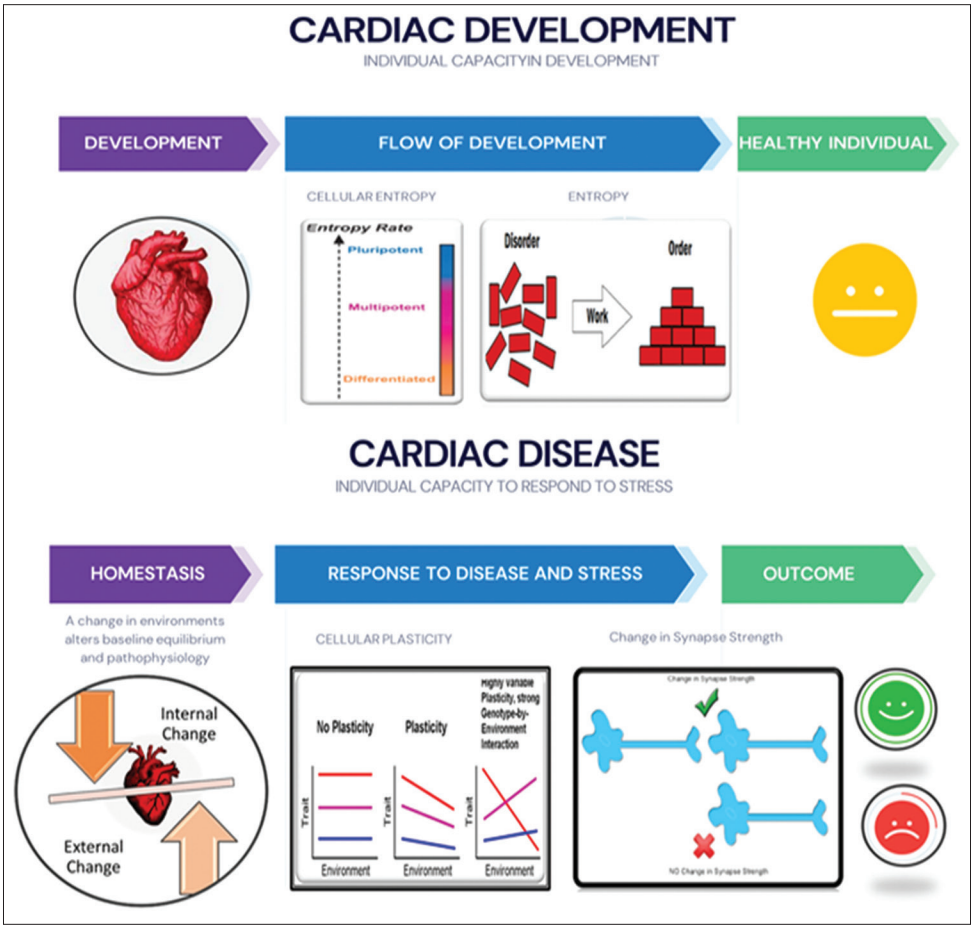

Figure 4. Summary of cellular biology and function. During embryological development cells specialise and commit to certain lineage. Populations of stem cells remain to provide plasticity for new cell regeneration when it is required. Cellular entropy describes the energy that is in the system that allows for the balance of differentiated, multipotent, and pluripotent cells. Entropy describes a systemic process where the cells exchange energy and matter to keep cells functioning normally or alternatively succumbing to external pressures. At present, there are no means to measure this from a clinical perspective. The example below shows an external stimulus that activates internal counter regulatory processes to maintain homeostasis. From the concept of entropy, cellular processes in the counter regulatory pathways have varying degrees of plasticity based on baseline entropy. The result is the ability to change synaptic strength and respond positively to the external stimulus. Wellness and illness could be influenced by entropy. This factor is close to the foundations of a common denominator for systemic health. Further study in this area could reveal useful biomarkers for chronic disease well-being.

it represents a holistic view of a disease state. In cellular development, the human body develops from one cell quickly into an organised symbiotic living organism. The trade-off from this specialisation and organ development is a loss of plasticity. This term is used to define the capability of cells in organisms to adapt to surrounding changes to continue healthy functions. Relevant to entropy are forces that maintain homeostasis. This term is used here to define self-regulation by organisms to adjust to external stimuli to maintain internal stability and function. In fact, the hypotheses we propose around chronic disease revolve around:

i. Understanding the balance between entropy and homeostatic capabilities.
ii. Inactivity and traditional risk alone do not equate to systemic ill health and risk of cardiac decompensation, for example, spinal cord injury patients who are intubated for long periods do not demonstrate worsening cardiovascular function.
iii. From this understanding, we must progressively identify the common denominators that regulate homeostasis, high cellular plasticity/entropy, and resulting low system entropy in patients who are not demonstrating similar benefits despite appropriate treatments. This is a new risk that could be explored further. As a question we can ask, what are we programmed to do at an individual level? How has exposure to factors and comorbidities shaped this response? A summary of these concepts is illustrated in Figure 4.

4.4. Observation to improve guideline-directed care treatment outcomes

What does this concept of entropy have to do with clinical care? What is the nature of the investigations that need to be done? The traditional means to use biochemistry is to identify a change compared to the reference range and associate that with the

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disease. As there can be numerous confounders, this is an example of why this approach is one-dimensional. In CHF, there are aspects of chronic disease care that cannot be mapped by traditional risk scoring. For example, any patient can be at risk of decompensation and resilience is hard to measure. Hence, it does pay to invest in high-value pathophysiological targets and explore their function in multiple dimensions. Entropy appears as a common point that shapes the direction of any individual to stress. The key question is which factor/s can be identified as the rate-limiting one, hence where is the starting point to channel research resources?

Specifically on endothelium and skeletal muscle, endothelial dysfunction alters both cardiac and skeletal muscle function. If the factor is oxidative stress which can be involved in the pathophysiology of HF in the heart as well as in the skeletal muscle; however, the downstream effects at each organ could differ. The treatment effects could also differ. The direction in which patients' well-being moves could vary based on a broader picture. Thus, where entropy is relevant, is that these processes might be predetermined, regardless of conventional risk score predictions. An ability to predict this will allow us to target the patients and deliver the intensive support that may be needed. A better understanding of these mechanisms may enable the development of novel and effective therapeutic strategies against HF, by targeting the factor least likely to respond to GDMT. More specifically, with CHF, there are pleiotropic actions of conventional cardiovascular drugs that could play a greater role.

4.5. Observations and the personalisation of GDMT

An ideal that is yet to take greater shape in medical practice is personalised health parameters, it is hoped that it will achieve optimal individualisation of care. The terminology used varies from personalised [46], customised [47], precision [48,49] care for screening, disease management, and risk prognostication. The tools at hand help phenotypic and genetic profiling and presently computer-assisted analysis of data are also possible. Leopold and Loscalzo [49] that exactness can be counterproductive, thus, as opposed to only identifying the positive, should we identify what does not work, we must invest in identifying causation. GDMT is a checklist, and this can lead to polypharmacy without the intended benefits in some cases, or lack of benefits when treatments are deemed unsuitable. If cost-effectiveness is the standard objective that guides universal systems of care, better use of medicines must be at the heart of this discussion. One place to start is the concept of entropy and identifying early common factors in the failure of therapies. The cost of inefficacious medications is a preventable cost to health systems and patients, in the latter, they can be expressed as disability-adjusted life years. We must thus be mindful of Ehrlich's predication and advance it with thinking on "*It is because we are to exact, we may also fail.*"

5. Conclusions

In this review, we discuss CHF, a chronic and complex cardiovascular syndrome, and explore the paradigm in observing the delivery of GDMT. We have cited examples where post-trial observations have shaped new directions for therapy. As a specific theoretical example, we have contextualised the argument to smooth muscle and endothelium function. An area that is novel in clinical medicine is identifying the sentinel common denominator of the effect to a treatment. This is vital for chronic diseases where there are numerous confounders. While innovation remains critical, we acknowledge that entropy in a clinical sense is theoretical, and our focus is on exploring what is known and reshaping new thinking based on evidence. Bench-to-bedside research today can address common questions and find translatable answers. The margin to maneuver, however, with clinical and basic sciences is decreasing in some areas. Cost-effectiveness remains an important consideration in health services. Specifically, in this paper, we ask the question if we can identify higher risk patients, those who may not achieve the full benefits of GDMT, and are going in the direction that is away from good health? In these cases, investment in conventional guideline care will be costly with little progress. Alternatively, a common denominator can be identified to reverse this. Is there a common denominator here for treatment direction and how do we address this? Improving health and reducing readmissions is a critical consideration as it relates to cost-effectiveness of health policies. *Simple Summary:* Trial evidence extrapolates well to large populations, it may be too complex to broaden applicability further. New concepts that encourage and vet novel observations on clinical outcomes when delivering GDMTs are vital. Entropy is a subjective common denominator to start a dialogue on the more objective pathophysiology determinants in chronic and complex care.

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Conflicts of Interest

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