Towards precision medicine in heart failure

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Abstract | The number of therapies for heart failure (HF) with reduced ejection fraction has nearly doubled in the past decade. In addition, new therapies for HF caused by hypertrophic and infiltrative disease are emerging rapidly. Indeed, we are on the verge of a new era in HF in which insights into the biology of myocardial disease can be matched to an understanding of the genetic predisposition in an individual patient to inform precision approaches to therapy. In this Review, we summarize the biology of HF, emphasizing the causal relationships between genetic contributors and traditional structure-based remodelling outcomes, and highlight the mechanisms of action of traditional and novel therapeutics. We discuss the latest advances in our understanding of both the Mendelian genetics of cardiomyopathy and the complex genetics of the clinical syndrome presenting as HF. In the phenotypic domain, we discuss applications of machine learning for the subcategorization of HF in ways that might inform rational prescribing of medications. We aim to bridge the gap between the biology of the failing heart, its diverse clinical presentations and the range of medications that we can now use to treat it. We present a roadmap for the future of precision medicine in HF.

The number of available therapies for heart failure (HF) has doubled over the past decade, and several new therapies are likely to reach the clinic in the coming years, meaning that physicians who are treating patients with HF are suddenly faced with an abundance of choice. Indeed, we are on the verge of a new era in HF, in which physicians will have to look beyond single-agent trials to maximize individual benefit for their patients.

In this Review, we discuss a framework for understanding how the biology of myocardial disease can be matched to an understanding of the genetic predisposition in an individual patient with HF to inform precision approaches to therapy. Specifically, we provide a roadmap for the future of precision medicine in HF. We first discuss the cellular biology of HF, highlighting the latest discoveries in HF genetics, pharmacogenomics and proteomics, together with the known mechanisms of action of traditional and novel therapeutics. We explore the Mendelian genetics of cardiomyopathy, the complex phenotype of HF and the polygenic risk that contributes to both. Finally, we discuss applications of machine learning for the subcategorization of HF in ways that might inform rational prescribing of medications.

The biology of the failing heart

Structure and function

The structure of the heart is intricately linked to its function, but the clinical presentation of HF has a consistency that contrasts with the diversity of molecular and cellular remodelling that leads to it. The form and structure of the adult heart is inextricably linked to cardiac development, a complex cellular process orchestrated by developmental transcriptional programmes[1–4]. Formation of the embryonic myocardial heart tube occurs early in development (days 20–25 in human development), and this heart tube is composed primarily of contractile myocardial cells. These cells undergo proliferation and the addition of differentiating cells from the visceral mesoderm; the tube then elongates and loops, forming the fundamental structure of the heart chambers and conduction system[1,3,5,6]. The cardiomyocyte proliferative capacity is lost early in life[7–9], after which the continued increase in heart size in early childhood occurs as a result of myocyte hypertrophy, with fibroblast and vascular proliferation[10]. With estimates that the adult human heart has 2–4 billion cardiomyocytes, this organ is unusual in its extremely limited regenerative potential[10,11].

Ever since a positive relationship between filling volume and the strength of cardiac contraction was first described in 1895 by Otto Frank[12], investigators have sought to define the physiology of the human heart in normal and diseased states[13–15]. Fundamental work by Starling and Visscher in dog models further showed that cardiac work is directly related to diastolic ventricular filling volume and that myocardial oxygen consumption is linearly related to cardiac work[16]. Furthermore, cardiac output is related to systemic vascular resistance

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https://doi.org/10.1038/s41569-021-00566-9

Key points

- The number of therapies for heart failure with reduced ejection fraction has nearly doubled in the past decade, with new therapies for hypertrophic and infiltrative disease emerging.
- We are on the verge of a new era in heart failure, in which basic biology can be matched to an understanding of genetic predisposition to inform precision therapy.
- The precision model of treatment for Mendelian disease is focused on treating the underlying mechanism, for which genetic therapy is increasingly in clinical development; genetic variants can also function as strong modifiers of complex disease, which might inform precision-based treatment of heart failure in the future.
- Important precision medicine approaches for the diagnosis and treatment of myocardial hypertrophy caused by hypertrophic cardiomyopathy, amyloidosis, Fabry disease or Noonan syndrome are available today but are underutilized.
- Machine learning tools to evaluate large clinical, biological and genetic data sets can be used to phenotypically group patients and improve prediction of response to therapy, providing an important mechanism to guide precision approaches to therapy.
- We aim to bridge the gap between the basic biology of the failing heart, its diverse clinical presentations and the range of medications we can now use to treat heart failure.

and overall blood pressure (afterload); classic studies in human volunteers identified that a reduction in systemic vascular resistance by administration of sodium nitrite leads to an augmentation in cardiac output to maintain blood pressure until circulatory collapse is observed[17]. This relationship has been further characterized clinically, whereby decreases in systemic vascular resistance, such as in sepsis, cause an increase in cardiac output[18]. Ventricular systolic pump function has been modelled as time-varying elastance, in which the ventricle acts as an elastic structure that stiffens during systole[15]. In an attempt to define myocardial systolic performance, investigators have demonstrated a highly linear relationship between stroke work and preload, a relationship that is independent of afterload, giving rise to the concept of preload-recruitable stroke work[14]. Similarly, a linear relationship exists between the time derivative of left ventricular (LV) pressure (dP/dt) and LV end-diastolic volume, the slope of which is increased with infusion of dobutamine[15]. This end-systolic pressure–volume relationship is characterized by slope and volume axis intercept and not only increases with positive inotropism and sympathetic activation, but also decreases with negative inotropism, ventricular dyssynchrony, myocardial ischaemia and myocardial infarction, further highlighting that this relationship is a reflection of cardiac performance[15,19].

These pressure–volume relationships were further corroborated in patients with dilated cardiomyopathy (DCM), highlighting that DCM is physiologically characterized by impaired contractility with compensatory increased filling pressures[20] (FIG. 1). This situation is in contrast to that in patients with clinical HF with a restrictive physiology and preserved ejection fraction (HFpEF), in which both end-diastolic and end-systolic LV pressures are higher, as are measures of ventricular stiffness and dyssynchrony[21] (FIG. 1). With this increased ventricular stiffness, systolic and diastolic performance in response to dobutamine infusion is also impaired, highlighting an inadequate reserve function[21]. This ventricular stiffness is demonstrated by the end-diastolic pressure–volume relationship, which is a non-linear relationship that reflects the passive mechanical properties of the ventricle[19]. Ventricular stiffness and overall ventricular performance are also influenced by the rate of ventricular relaxation, or lusitropy, whereby impaired relaxation affects ventricular filling[19]. Increased LV filling pressures with restrictive physiology are also a hallmark of hypertrophic cardiomyopathy (HCM) and other infiltrative cardiomyopathies; importantly, in obstructive HCM, LV outflow tract obstruction is dynamic and worsens with increasing ventricular contractility[22]. Despite distinct cardiac physiologies when comparing the heart with impaired systolic function to that with restrictive physiology, the similarity of clinical presentation — vascular congestion, fluid volume overload and dyspnoea — is striking. This clinical presentation drives diagnosis, hospitalization and often the initiation of therapies.

Systemic responses to HF

Since the 1950s, clinical HF has been known to be characterized by a systemic response that includes an increase in systemic pro-inflammatory factors, such as C-reactive protein[23]. In the 1960s, the systemic inflammatory response in patients with HF was also found to include an increase in circulating levels of neurohormones, and these neurohormones might have a pathogenic role in HF[24–26]. Subsequently, the systemic response to HF has been characterized in further detail as an increase in the levels of circulating factors such as angiotensin II, aldosterone, noradrenaline, adrenaline and atrial natriuretic peptide, and these factors are associated with HF mortality[27,28]. These factors contribute to further impairment in myocardial performance through direct effects on the cardiomyocytes and by driving myocardial fibrosis and promoting a depressed coronary flow reserve through coronary microvascular rarefaction[29–32] (FIG. 1).

Excitation–contraction coupling

The biological underpinnings of HF first manifest at the level of the cardiomyocyte (FIG. 1). Cardiac muscle is striated, with the basic unit being the sarcomere[33,34]. The sarcomere generates force by a complex interaction between thin filaments, composed of actin, tropomyosin and troponin complexes (made up of troponin T, troponin I and troponin C), and thick filaments, composed of muscle myosin II, which contains four myosin light chains and two myosin heavy chains (FIG. 1). In series, these sarcomeres comprise the myofibril and generate contractile force by myosin–actin interactions that are principally governed by Ca^{2+} binding to troponin C, followed by displacement of tropomyosin, allowing myosin to bind to actin. As the cardiac action potential opens voltage-gated L-type Ca^{2+} channels on the sarcolemma, the influx of Ca^{2+} (I_{CaL}) stimulates Ca^{2+} release from the sarcoplasmic reticulum (SR) via ryanodine receptor 2 (RYR2), which produces a transient rise in intracellular Ca^{2+} concentration, and the Ca^{2+} binds to troponin C. This binding initiates myosin–actin interactions, which continue until the Ca^{2+} is subsequently sequestered back into the SR to facilitate

sarcomere relaxation (FIG. 1). The pumping of intracellular Ca^{2+} back into the SR is mediated by sarcoplasmic–endoplasmic reticulum Ca^{2+} ATPase 2 (SERCA2). This physiological process fundamentally links electrical excitation of myocytes to the contraction of the myocardium; Ca^{2+} is the direct activator of the myofilaments, and Ca^{2+} mishandling is a central cause of impaired cardiac performance[35].

Failing or hypertrophied cardiomyocytes have smaller Ca^{2+} transients, with weaker contractions due to a reduced capacity of the I_{CaL} to trigger Ca^{2+} release from the SR[36]. This impairment in excitation–contraction coupling in the failing myocardium is characterized by Ca^{2+} leak from the SR via RYR2 (REF.[37]), impaired Ca^{2+} sequestration secondary to decreased SERCA2 expression[38], as well as maladaptive Ca^{2+}-dependent signalling, including activation of calmodulin, Ca^{2+}/calmodulin-dependent protein kinase II (CAMKII) and calcineurin, and subsequent transcriptional activation mediated in part by nuclear factor of activated T cells[39]. This impairment in excitation–contraction coupling is further driven by ultrastructural changes of the contractile dyad between the L-type Ca^{2+} channel and RYR2 (FIG. 1). As the dyad distance increases,

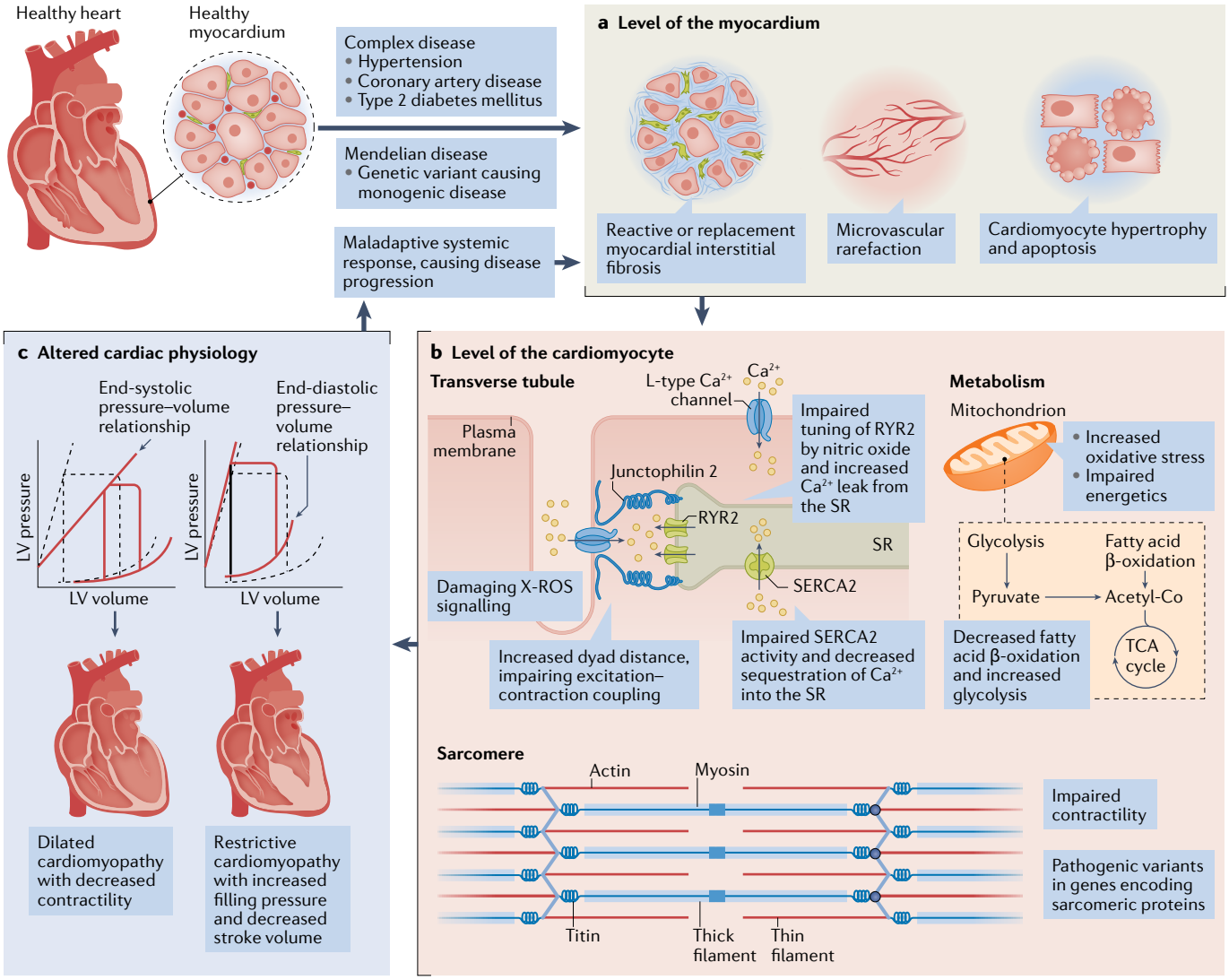

Fig. 1 | **Mechanisms and physiology of the failing heart.** The initiation of heart failure occurs at the level of the myocardium and fundamentally at the level of the cardiomyocyte, secondary to complex and/or Mendelian disease. **a** | Pathology within the myocardium can include reactive or replacement myocardial interstitial fibrosis, microvascular rarefaction characterized by a decrease in microvascular density, and cardiomyocyte hypertrophy and apoptosis. **b** | At the level of the cardiomyocyte, important mechanisms include decreased excitation–contraction coupling with impaired Ca^{2+} handling, changes in energetics with decreased fatty acid β-oxidation and increased glycolysis, increased oxidative stress and damaging X-reactive oxygen species (X-ROS) signalling, and impaired contractility secondary to pathogenic variants in genes encoding sarcomeric proteins. **c** | These pathogenic changes lead to structural remodelling of the heart, including dilatation or hypertrophy of the left ventricle, causing a dilated cardiomyopathy (characterized by reduced contractility of the myocardium) or a restrictive cardiomyopathy (with increased filling pressures and decreased stroke volume), respectively. These pathogenic changes lead to further maladaptive systemic responses and disease progression. LV, left ventricular; RYR2, ryanodine receptor 2; SERCA2, sarcoplasmic–endoplasmic reticulum Ca^{2+} ATPase 2; SR, sarcoplasmic reticulum; TCA, tricarboxylic acid.

the efficiency of RYR2 activation decreases, a finding observed in the cardiomyocytes of infarcted hearts, dilated hearts and in ischaemic cardiomyopathy without infarction, in which the volume density and surface area of cardiomyocyte transverse tubules decreases, with accompanying decreases in coupling between the transverse tubules and the SR[40–42]. The structure of the dyad is maintained by junctophilin 2, and this ultrastructural change in HF is associated with a reduction in junctophilin 2 expression[41,42] (FIG. 1). As junctophilin 2 is cleaved in cardiomyocytes by the Ca^{2+}-dependent protease calpain, the N-terminal truncate translocates to the nucleus and binds to DNA, modulating transcription[43]. The N-terminal junctophilin 2 is a TATA-binding protein and modulates MEF2-mediated transcription and thereby attenuates the hypertrophic response and HF, further suggesting junctophilin 2 cleavage and N-terminal junctophilin 2 as potential novel therapeutic targets[43].

Myocardial energetics

With the human heart cycling 6 kg of ATP every day, cardiomyocyte force generation requires an enormous amount of ATP. Under non-ischaemic conditions, 60–70% of ATP hydrolysis is used by myosin ATPase to fuel contractile shortening, whereas the remaining 30–40% is used by SERCA2 and other ion pumps (such as the Na^+–K^+ ATPase)[44–46]. Although ATP generation in cardiomyocytes relies on oxidative phosphorylation in the abundant mitochondria, the myocardium is uniquely flexible in its use of metabolic substrates to meet its energy demand[44,46]. Energy is transferred from carbon-based fuels via reducing equivalents (NADH and $FADH_2$) to the electron transport chain. NADH and $FADH_2$ are generated primarily by dehydrogenation reactions in the tricarboxylic acid cycle, which is fed by acetyl-CoA from fatty acid β-oxidation together with dehydrogenation of pyruvate derived from glycolysis (FIG. 1). Interestingly, in the myocardium, pyruvate is generated in equal parts by glycolysis and oxidation of lactate, and the oxidation of lactate to generate pyruvate produces a small amount of reducing equivalents directly[46]. When ATP is produced in the mitochondria, it is inaccessible to cytosolic enzymes unless it is shuttled to the cytosol through the mitochondrial phosphotransfer system, which utilizes phosphocreatine, with mitochondrial and cytosolic forms of creatine kinase[44]. This system of phosphate shuttling works as an energy buffer and prevents an increase in cytosolic levels of ADP; even during periods of increased cardiac workload, energetic phosphates are maintained at a stable level[44].

Given the high energy demand of cardiomyocytes combined with high mechanical stress and limited regenerative potential, how cardiomyocytes maintain mitochondrial homeostasis was uncertain. In a fascinating discovery, cardiomyocytes have now been shown to eject dysfunctional mitochondria in dedicated membranous particles (exophers), which are then actively taken up by macrophages[47,48]. Cardiac stress stimulates this mitochondrial transfer, and loss of the macrophage phagocytic receptor (MERTK) inhibits exopher uptake and leads to accumulation of dysfunctional mitochondria and impaired cardiac function[47].

The cardiomyocyte is termed a 'metabolic omnivore' owing to its flexibility in the use of metabolic substrates: 60–90% of ATP production arises from fatty acid β-oxidation and the remaining 10–40% arises from pyruvate oxidation, with a small amount of ATP generated from alternative fuel sources, including ketone bodies and amino acids[44]. Dynamic shifting between substrates occurs with rapid changes in workload. Increases in workload cause a shift to glucose oxidation as a means to generate pyruvate, thereby increasing the relative contribution of ATP from glycolysis and pyruvate oxidation. Additionally, ketone bodies are thought to become a primary source of energy during prolonged fasting or poorly controlled diabetes mellitus[44]. A stoichiometric link exists between the rate of oxidation of carbon fuels, electron flux through the electron transport chain, oxidative phosphorylation, ATP hydrolysis, actin–myosin interactions and subsequent cardiac power[46]. Given these dynamic changes in cardiac power, flexible and efficient substrate utilization is crucial[44–46,49].

Severe metabolic derangement in the failing myocardium is a hallmark of disease. In animal models of HF, free fatty acid utilization is decreased, which is associated with decreased protein expression of free fatty acid transporters in overt LV systolic dysfunction as well as in early and compensated states of LV hypertrophy[49]. A similar finding has been observed using PET in patients with non-ischaemic cardiomyopathy, in whom myocardial free fatty acid uptake and metabolism were significantly lower and glucose uptake was significantly higher than in healthy control individuals[50], a finding that was also observed when evaluating myocardial tissue from patients with end-stage HF, which also revealed increased ketone body utilization[51].

The performance of the myocardium is directly linked to its substrate utilization, energy metabolism and maintenance of mitochondrial homeostasis, with evidence that each of these factors is deranged in the failing myocardium. Understanding the energetic mechanisms of HF will be crucial in identifying and implementing novel treatments for this condition.

Redox balance

HF results in increased oxidative stress within the myocardium and in the plasma, and oxidative injury negatively affects cardiomyocytes, leading to hypertrophy, impaired contractility, arrhythmia and cell death[52,53]. Although these effects have led to substantial interest in the potential to use antioxidant supplements as a treatment for HF with reduced ejection fraction (HFrEF), randomized trials of antioxidant therapies have not shown a benefit and, indeed, indicate potential harm with this approach[54,55]. These findings highlight the concept of the antioxidant paradox and support the notion that a singular view of oxidative stress as being universally deleterious is inadequate and does not emphasize the crucial role of reactive oxygen species (ROS), reactive nitrogen species and redox balance in regulating important physiological processes[53].

As one example of this complex interaction, pivotal studies have examined the relationship between

cardiomyocyte stretch, nitric oxide ($NO^{\bullet}$) generation, superoxide ($O_2^{\bullet-}$) generation and subsequent mechanotransduction–chemotransduction in the heart[56–59]. Stretching of cardiac muscle increases the amplitude of Ca^{2+} transients via Ca^{2+} release from RYR2s, secondary to $NO^{\bullet}$ (REF.[57]). Investigators have revealed that cardiomyocyte stretch results in increased $NO^{\bullet}$ generation via stretch-induced activation of PI3K, leading to phosphorylation of AKT and endothelial $NO^{\bullet}$ synthase (also known as NOS3), and that $NO^{\bullet}$ is responsible for increasing RYR2 activity[57]. This concept of RYR2 'tuning' was further characterized by the discovery that physiological cardiomyocyte stretch results in rapid activation of NADPH oxidase 2 (NOX2) to generate ROS[58]. This activation was found to be dependent on microtubules and was termed X-ROS signalling. X-ROS signalling occurs in the sarcolemma and transverse-tubule membranes and acts to sensitize RYR2s in the SR[58]. Importantly, a balance exists between physiological X-ROS signalling and hyperactive X-ROS signalling, which contributes to cardiomyopathy via dysregulated release of Ca^{2+} from the SR (FIG. 1). This relationship between $NO^{\bullet}$ generation, RYR2 sensitivity and mechanotransduction was further characterized when the increase in cardiac contractility by increased afterload (known as the Anrep effect) was discovered to be mediated by neuronal $NO^{\bullet}$ synthase (NOS1), NOX2 and CAMKII[56].

Oxidative stress and altered redox balance further impair multiple cellular processes via oxidative post-translational modifications of crucial enzymes. The complexity of these post-translational modifications is vast but one example has been demonstrated in a series of elegant studies on SERCA2 activity[60–63]. $NO^{\bullet}$ accelerates SERCA2 activity in a process mediated by the generation of peroxynitrite ($ONOO^-$), which together with reduced glutathione (GSH) induces *S*-glutathiolation of a key reactive cysteine residue (Cys674) on SERCA2 (REF.[60]). Glutathiolated SERCA2 (GSS–SERCA2) was found to have significantly higher Ca^{2+} uptake activity[60]. But importantly, Cys674 was found to be irreversibly oxidized by high levels of $ONOO^-$ or hydroxyl anion radical ($OH^{\bullet-}$), which can impair GSS–SERCA2 and can contribute to impaired cardiomyocyte relaxation and LV dysfunction[61–63].

The enormous complexity of redox state and the mechanisms by which oxidative stress influences myocardial performance is further emphasized by the unique energetic requirements of cardiomyocytes and the intricate interaction with Ca^{2+} handling for excitation–contraction coupling. Fundamentally, an inability to maintain redox homeostasis and meet the dynamic energy requirements of the heart is a crucial factor that leads to the development of cardiomyocyte dysfunction and HF.

Ventricular compliance

Although the exquisite interaction between myosin and actin can mediate powerful force generation during systole, the passive tension of cardiomyocytes and the maintenance of favourable ventricular compliance is also crucial to cardiac performance. As noted above, an altered end-diastolic pressure–volume relationship is an important characteristic of HFpEF with restrictive features, in which sarcomere strength and structure are primary components.

Titin. A substantial contribution to sarcomere compliance comes from titin. Titin is an elastic sarcomeric protein that spans from the Z-disc to the M-band and is encoded by the largest gene in terms of coding bases in the human genome (364 exons). Titin is the dominant regulator of passive myocardial tension and acts as a bidirectional elastic coil to form the molecular spring of the cardiomyocyte[64]. In an example of biological adaptation, alternative splicing can lead to shorter, less compliant forms or longer, more compliant forms of titin, thereby providing a splice-mediated dynamic regulation of cardiomyocyte compliance[65]. Similarly, altered titin isoform expression with an increased ratio of stiff to compliant titin isoforms has been observed in human hearts with DCM[66], prompting investigation into potential therapeutic strategies to treat restrictive cardiomyopathies by increasing the compliance of titin by altering splice variation[67].

Myocardial fibrosis. Myocardial interstitial fibrosis is the diffuse accumulation of fibrous tissue (type I and type III collagen fibres) within the interstitium that either is a reparative process in response to cardiomyocyte cell death (replacement fibrosis) or is secondary to a stimulatory process such as haemodynamic stress (caused by hypertension or aortic stenosis) or other profibrotic stimulatory molecules (reactive fibrosis)[29]. Replacement fibrosis forms in the region of cardiomyocyte dropout, leading to an increase in the thickness of the usually thin fibrous tissue layers in the intramural coronary perivascular arteries, perimysium and endomysium[29]. Increased myocardial fibrosis leads to worsened cardiac performance by impairing ventricular systolic function as well as increasing myocardial stiffness with restrictive physiology, thereby worsening clinical HF[68,69] (FIG. 1). Consequently, interest in treating HF by targeting myocardial fibrosis is growing[32]. Important mechanistic discoveries have led to the understanding that IL-11 is the downstream master regulator of transforming growth factor-β, which drives cardiac fibrosis[70], and therapeutic targeting of IL-11 to treat myocardial fibrosis and other fibrotic diseases is promising[71,72]. Additionally, a new approach has demonstrated a proof of principle that the use of immunotherapy with engineered T cells against myocardial fibrosis can result in reduced myocardial fibrosis and improved cardiac performance[73].

Microvascular rarefaction. Systemic factors occurring in response to HF cause further deleterious effects to the microvascular endothelium, leading to a decrease in microvascular density, a process termed microvascular rarefaction[74]. Experimental models of intermittent pressure overload as well as observations in human myocardial tissues have revealed that microvascular rarefaction occurs before the onset of myocardial hypertrophy, causes a depressed myocardial coronary flow reserve and correlates with increased myocardial fibrosis[30,31,75].

Therapeutics

The number of successful therapies for HFrEF has now increased to at least ten (FIG. 2), and several therapies for Mendelian diseases associated with cardiomyopathy have also been shown to be successful in pivotal clinical trials. Central therapies aimed at treating the maladaptive neurohormonal systemic response in HF, such as angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, β-blockers and mineralocorticoid-receptor antagonists have been the foundation of HF management for >20 years[76–82]. In this section, we briefly review novel therapies for HF, excluding classic neurohormonal blockers (which have been reviewed in detail previously[76,77,79,83]), emphasizing neprilysin inhibition, sodium–glucose cotransporter 2 (SGLT2) inhibition, NO• and cGMP signalling, myosin activation, 'funny' current (I_f; a slow, inwardly depolarizing, mixed Na^+–K^+ current) inhibition, and novel

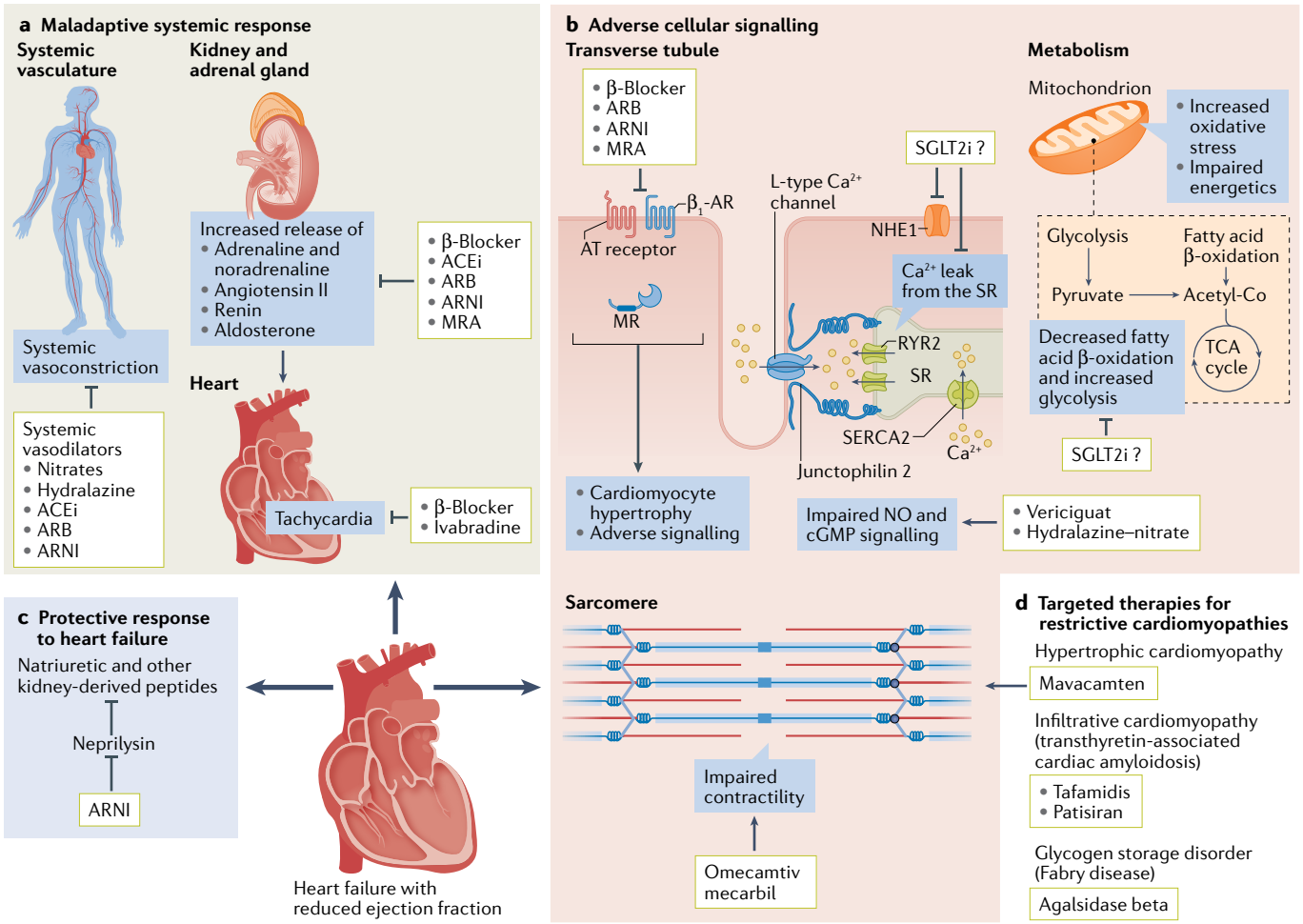

Fig. 2 | **Heart failure therapeutics and their mechanisms of effect.** **a** | In heart failure with reduced ejection fraction, therapies with proven benefit have largely focused on preventing the maladaptive systemic response that arises as a secondary process to the primary injury at the level of the cardiomyocyte and myocardium. With increased circulating levels of adrenaline, noradrenaline, angiotensin II, renin and aldosterone in heart failure, therapies such as a β-blocker, angiotensin-converting enzyme inhibitor (ACEi), angiotensin-receptor blocker (ARB), angiotensin-receptor blocker–neprilysin inhibitor (ARNI) or mineralocorticoid-receptor antagonist (MRA) work to inhibit the maladaptive effect. Maladaptive systemic responses lead to sinus tachycardia, which further increases the myocardial oxygen demand and impairs myocardial perfusion. β-Blocker or ivabradine therapy decreases myocardial oxygen demand and improves diastolic filling by reducing heart rate. Agents such as hydralazine–nitrates, ACEi, ARB and ARNI also work to promote systemic vasodilatation, which decreases cardiac afterload, thereby augmenting cardiac output and peripheral perfusion. **b** | Agents acting at the level of the myocardium can improve adverse cellular signalling through inhibition of the downstream effects of angiotensin (AT) receptor, β_1-adrenergic receptor (β_1-AR) and mineralocorticoid receptor (MR) agonism. Fewer therapies act directly to improve myocardial contractile function of the sarcomere, but omecamtiv mecarbil works as a myosin activator. Sodium–glucose cotransporter 2 inhibitor (SGLT2i) therapies have a direct effect on renal glucose excretion, but discoveries have highlighted additional mechanisms in mediating sodium–hydrogen exchanger 1 (NHE1) and sarcomere contractility as well as facilitating a more favourable energetic metabolism. Therapies that act on nitric oxide (NO) and cGMP signalling include vericiguat, which augments cGMP signalling, thereby enhancing the downstream cardioprotective effects of NO. Hydralazine–nitrates act by augmenting NO signalling via systemic effects on cardiac afterload as well as acting directly at the level of the myocardium. **c** | ARNI therapies work to increase the protective responses to heart failure via neprilysin inhibition, thereby augmenting natriuretic peptide and other kidney-derived peptide signalling. **d** | Targeted therapies for specific causes of restrictive cardiomyopathy include mavacamten for hypertrophic cardiomyopathy, tafamidis and patisiran for transthyretin-associated cardiac amyloidosis and agalsidase beta for Fabry disease. RYR2, ryanodine receptor 2; SERCA2, sarcoplasmic–endoplasmic reticulum Ca^{2+} ATPase 2; SR, sarcoplasmic reticulum; TCA, tricarboxylic acid.

therapies for transthyretin (TTR)-associated amyloidosis and HCM.

Neprilysin inhibition

In 2014, the PARADIGM-HF trial[84] in patients with HFrEF showed marked superiority of sacubitril–valsartan (the combination of a neprilysin inhibitor and an angiotensin-receptor blocker) over enalapril (an angiotensin-converting enzyme inhibitor). Although the trial design has received some criticism, such as the comparison with moderate-dose enalapril rather than a head-to-head comparison with valsartan only, the overall weight of evidence established the inhibition of neprilysin as a new molecular pathway in the treatment of HFrEF. Although the inhibition of neprilysin is hypothesized to provide its benefit primarily by augmenting the natriuretic peptide system, neprilysin is increasingly being recognized also to mediate the breakdown of various vasoactive peptides, such as adrenomedullin, endothelin 1 and substance P, as well as other hormones, such as glucagon-like peptide 1, highlighting that additional mechanisms are likely to be involved in mediating its effect[85–87] (FIG. 2).

SGLT2 inhibition

SGLT2 inhibitor therapies were hypothesized to provide benefit in patients with diabetes by reducing cardiovascular events through improved glycaemic control, but these therapies have been shown to provide a clear benefit in patients with HFrEF, irrespective of diabetes status[88,89]. Moreover, in patients with diabetes, SGLT2 inhibitors have a clear benefit in reducing cardiovascular events and improving renal outcomes that far exceeds the predicted benefit from glycaemic control only[90–93]. The mechanisms by which SGLT2 inhibitors provide benefit in patients with HF are broad and under active investigation (as reviewed previously[94]). With >180 g of glucose filtered by the renal glomeruli each day, reabsorption of glucose by the renal tubules is coupled to sodium, entering the cell through SGLT1 and SGLT2. Given that the expression of SGLT2 is predominantly in the kidney, inhibition of SGLT2 promotes osmotic diuresis and natriuresis, which overall reduces interstitial fluid and cardiac overload. Although this mechanism is hypothesized to provide benefit in patients with HFrEF by reducing the number of hospitalizations, the diuretic effect from SGLT2 inhibition attenuates over time and does not explain the entirety of the benefit in terms of reduction in HFrEF mortality.

SGLT2 inhibitor therapies might also have direct cardiac effects, whereby SGLT2 inhibitors block the cardiac sodium–hydrogen exchanger 1 (NHE1), directly improving myocardial contractility[95–97]. Improvement in cardiomyocyte contractility has also been shown to be due in part to SGLT2 inhibitor-induced reductions in both cardiomyocyte CAMKII activity and CAMKII-dependent Ca^{2+} leak from the SR[98]. These direct effects on cardiomyocytes seem to occur in tandem with systemic effects on metabolism, whereby SGLT2 inhibitors promote beneficial myocardial energetics with increased ketone body utilization[99–101] (FIG. 2). Other proposed mechanisms include the reduction in sympathetic nervous system activation, improved myocardial oxygen delivery through stimulation of renal erythropoietin secretion, and reductions in inflammation and oxidative stress[94].

NO–cGMP signalling augmentation

$NO^{\bullet}$ is a soluble, reactive, free radical gas that has fundamental roles in mediating vascular tone and cardiac performance via activation of soluble guanylate cyclase (sGC) and increasing cGMP-dependent signalling[56,57,102–104]. Nitrates are direct $NO^{\bullet}$ donors to the vasculature and myocardium and are combined with hydralazine therapy, which acts as an antioxidant and inhibits the conversion of $NO^{\bullet}$ to $ONOO^{-}$ via combination with $O_2^{\bullet-}$. Limitations of therapy with nitrates include nitrate tolerance and nitrate-induced oxidative and nitrosative stress[103,105,106]. The use of hydralazine plus isosorbide dinitrate (H-ISDN) in the treatment of HFrEF was studied in the first major randomized, placebo-controlled trial in cardiovascular medicine, V-HeFT I[107], followed by V-HeFT II[108], which indicated that H-ISDN has some benefit in patients with HFrEF but probably less than angiotensin-converting enzyme inhibitor therapy. A retrospective subgroup analysis of the V-HeFT I and II trials suggested that African American individuals might receive greater benefit from H-ISDN therapy than white individuals, and the subsequent prospective, randomized A-HeFT trial[109] involving self-identified Black individuals showed a clear reduction in mortality in those randomly assigned to H-ISDN therapy compared with those receiving placebo (10.2% versus 6.2%). This finding prompted deep discussion over the limitations of self-identified race as a surrogate for underlying biological variation, but clearly highlighted that individual mechanisms of disease can strongly influence response to therapy.

Given the biological complexity of $NO^{\bullet}$ donor therapies, interest has focused on bypassing direct $NO^{\bullet}$ donation and augmenting protective cGMP signalling via stimulation of sGC. In this way, sGC activation increases cGMP levels and beneficial cGMP signalling, which improves vascular function and cardiac performance[56,57,102–104]. Preclinical models of HF suggest that sGC stimulation provides a blood-pressure-independent effect to prevent myocardial fibrosis and HF progression[110,111]. In the large, phase III, randomized VICTORIA trial[112], the long-acting sGC stimulator vericiguat was shown to be beneficial in patients with HFrEF. The benefit of vericiguat was largely driven by a reduction in HF hospitalizations, without a significant change in blood pressure, and discussion about the role of this novel therapy in the treatment of HFrEF is ongoing (FIG. 2).

Myosin activation

Impaired contractility of the myocardium is a hallmark of HFrEF, and improving cardiomyocyte contractility is a reasonable strategy to reduce systemic neurohormonal activation and stabilize the decline in cardiac function. Unfortunately, therapies aimed at improving cardiac contractility via β-adrenergic receptor agonism or phosphodiesterase inhibition increase intracellular

Ca^{2+} concentrations, potentially leading to arrhythmias, increased heart rate, increased myocardial oxygen consumption and death[113]. Whether a therapy that improves cardiac contractility without triggering arrhythmia could improve outcomes was unknown. Omecamtiv mecarbil is a novel, selective, direct activator of myosin that improves myocardial contractility without increasing the amplitude of the Ca^{2+} transient. In phase I and phase II trials, treatment with omecamtiv mecarbil in patients with HFrEF increased LV ejection time, ejection fraction and stroke volume[114] (FIG. 2). The large, phase III, placebo-controlled GALACTIC-HF trial[115,116] demonstrated the efficacy of omecamtiv mecarbil in patients with HFrEF; the composite primary end point was met, driven by a reduction in HF hospitalizations, but without a clear reduction in mortality. Although the clinical benefit of this therapy is modest, this trial proves the overall concept that direct activation of myosin can safely improve the contractile function of cardiomyocytes and improve overall outcomes in patients with HFrEF.

Heart rate reduction

An elevated resting heart rate is a well-characterized risk factor for cardiovascular death[117] and is associated with increased myocardial oxygen demand and decreased myocardial perfusion. This maladaptive heart rate response in HF is partly mediated by the systemic activation of neurohormonal signals, such as adrenaline and noradrenaline. Cardiomyocytes in the sinoatrial node generate a cyclical change in their resting membrane potential, which leads to spontaneous depolarization by opening ion channels that conduct I_f[118,119]. Ivabradine is a selective inhibitor of the intracellular aspect of the I_f channel; it thereby blocks cation movement and works to slow heart rate, and, as a result, decreases myocardial oxygen demand, improves myocardial perfusion and improves diastolic filling. In the large, randomized SHIFT trial[120] evaluating the effect of ivabradine in patients with HFrEF (LV ejection fraction <35%) who were in sinus rhythm and had a heart rate of ≥70 bpm, the primary composite end point of cardiovascular death or hospitalization for worsening HF occurred less often in the ivabradine group than in the placebo group (24% versus 29%). Despite this randomized trial evidence of a benefit of ivabradine in patients with HFrEF, questions remain about whether this therapy provides a benefit beyond that obtained with additional β-blocker therapy, and the utility and prioritization of ivabradine in HFrEF management have been the subject of much debate[118,119].

Precision therapies for cardiac hypertrophy

Concentric cardiac hypertrophy remains a challenging diagnosis, with a broad differential informed by patient history, electrocardiography and advanced imaging techniques, such as MRI, ^{18}F-fluorodeoxyglucose PET and ^{99m}Tc-pyrophosphate scintigraphy. In many patients, a definitive molecular diagnosis for otherwise-unexplained concentric hypertrophy can be made using genetic sequencing combined with advanced imaging modalities, and molecular therapy can be targeted accordingly.

Amyloidosis. TTR-associated amyloidosis is a morbid disease that can present with cardiomyopathy secondary to the abnormal deposition of TTR monomeric protein in the interstitium of the myocardium[121]. Hereditary amyloidosis can be caused by >100 different *TTR* variants, leading to the expression of a variant form of TTR[121]. These variants are common in the general population. The autosomal dominant Val122Ile variant of TTR is present in 3.5% of African American individuals, in whom cardiomyopathy is the predominant clinical presentation of amyloidosis[121,122]. Amyloidosis associated with wild-type TTR is more common than hereditary amyloidosis and is defined by the abnormal deposition of TTR associated with age, usually presenting in individuals aged >70 years[121].

Although TTR-associated amyloidosis previously had no available therapies, in the past few years, two therapies have been approved by the FDA: tafamidis, a pharmacological chaperone agent designed to stabilize TTR in correctly folded tetramers, thereby preventing the deposition of the monomeric protein[123]; and patisiran, a small interfering RNA-based agent designed to silence *TTR* by inhibiting mRNA translation[123,124]. In the large ATTR-ACT trial[123], tafamidis therapy reduced mortality in patients with either hereditary or wild-type cardiac amyloidosis compared with placebo. So far, patisiran has been approved only for the treatment of polyneuropathy in patients with hereditary amyloidosis, but investigations into its potential benefit in treating cardiomyopathy in these patients are ongoing and promising[125]. Given these two new therapies, interest has been renewed in evaluating the frequency and degree of TTR-associated cardiac amyloidosis in patients with restrictive cardiomyopathy to identify those who would benefit from these treatments[126,127].

Hypertrophic cardiomyopathy. HCM is a Mendelian disease often caused by inherited variation in genes encoding sarcomeric proteins and is characterized by increased myosin–actin interactions, which facilitate a maladaptive hypertrophic response with substantial myofibrillar disarray and cardiac fibrosis. With the aim of treating the molecular mechanism of HCM, a small-molecule inhibitor of sarcomere contractility and myosin–actin crossbridge cycling was developed[128]. In the EXPLORER-HCM trial[129], mavacamten showed benefit in patients with obstructive HCM, and ongoing investigation suggests benefit in those with non-obstructive HCM[130].

Fabry disease. LV hypertrophy with restrictive cardiomyopathy can also present in patients with Fabry disease, an X-linked lysosomal storage disorder. Fabry disease is caused by genetic variants in *GLA*, which leads to an impairment in α-galactosidase A activity, resulting in the progressive accumulation of glycosphingolipid in the plasma and in cells throughout the body, including cardiomyocytes[131,132]. The 'classic' Fabry disease phenotype is characterized by a presentation in young boys with <1% of the normal level of α-galactosidase A activity, leading to severe multi-organ involvement, with an aggressive clinical course. Importantly, a larger group of

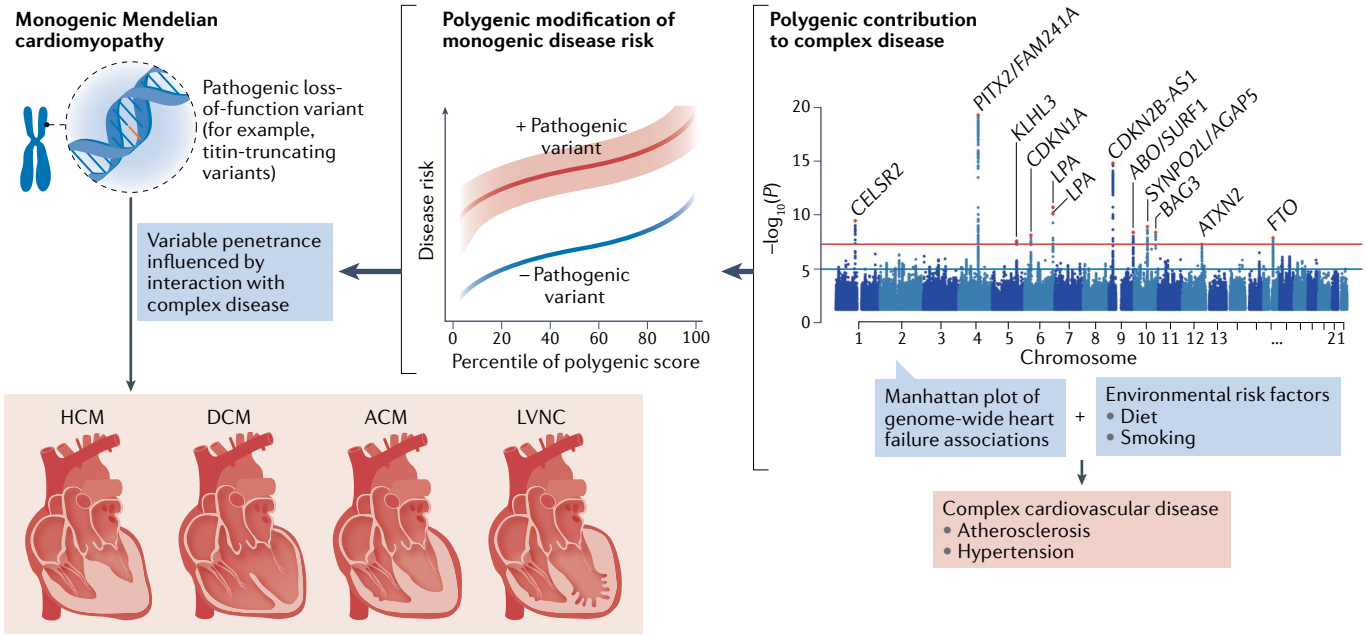

Fig. 3 | **From Mendelian to complex disease in heart failure.** Monogenic causes of cardiomyopathy in a Mendelian inheritance are caused by a pathogenic genetic variant that can result in various forms of cardiomyopathy, such as hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic cardiomyopathy (ACM) or left ventricular non-compaction cardiomyopathy (LVNC). Complex disease patterns of inheritance are influenced by millions of genetic variants, each with a small effect, in addition to environmental causes of disease. For example, the polygenic contribution to heart failure has been described by Shah and colleagues, who conducted a genome-wide association study using data from 47,309 patients with heart failure and 930,014 control individuals gathered from 26 studies and identified 11 genomic loci associated with heart failure (displayed on the Manhattan plot)[149]. This polygenic influence of disease modifies monogenic disease penetrance, thereby influencing the risk of disease in individuals with inherited pathogenic variants. Manhattan plot of genome-wide heart failure associations adapted from REF.[149], CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/).

patients have different levels of α-galactosidase A activity, resulting in delayed presentation and various clinical phenotypes[131,132]. Heterozygous female patients with Fabry disease have a spectrum of disease phenotypes[133]. Enzyme replacement therapy for Fabry disease with infusion of recombinant α-galactosidase A (agalsidase beta) has been shown to be effective in randomized clinical trials[134,135]. This approach can lead to multi-organ improvements, including the reversal of LV hypertrophy, with particular benefit in patients who start receiving the therapy early in their life, highlighting the importance of genetic screening and early detection[136].

HF: a complex and a Mendelian disease

HF exists as a result of both complex and Mendelian genetic disease mechanisms (complex versus Mendelian genetics in human disease have been reviewed previously[137]). In complex disease, up to millions of genetic variants with small effects combine to cause a genetic predisposition to diseases such as coronary artery disease (CAD), hypertension and diabetes, which then manifest in the context of a genetic predisposition to myocardial insufficiency. HF can also be caused by defined Mendelian diseases, such as HCM, familial DCM and other inherited cardiomyopathies, including LV non-compaction cardiomyopathy (FIG. 3). These diseases are increasingly well-characterized according to the genes involved. Importantly, a middle ground is emerging, in which variants in genes such as *TTN* provide a powerful, modifying, causal force that often requires another aetiological factor, either genetic or environmental, to result in the manifestation of HF (FIG. 3).

Conceptually, precision medicine offers an approach to the genetic and molecular underpinnings of disease to provide a deeper understanding of both healthy and disease states, further defining subgroups of patients and allowing more precise care[138,139]. With the development of computational tools to rapidly analyse genetic sequencing data — including the entirety of a human genome for clinical assessment[140] — genomic data are increasingly being used to guide clinical care in a precise way. HF is a heterogeneous clinical condition, and the benefit that an individual patient receives from a given therapy varies depending on the underlying causal biology of HF. Health-care systems are imprecise at delivering care at the level of the individual: in one analysis of the ten highest-grossing drugs in the USA, for every one person helped, between three and 24 individuals were estimated to receive no benefit[141]. Understanding HF at the individual patient level holds the promise to deliver more precise clinical care and improve outcomes for the majority.

HF as a complex phenotype

The genetic architecture of predisposing diseases such as CAD, hypertension and diabetes has been understood for a decade from large-scale, genome-wide association

studies (GWAS), but these studies have only just begun to influence our understanding of HF as a complex disease. Although many modifiable risk factors for HF have been identified, evidence also indicates that HF aggregates in families, suggesting that HF is at least partly heritable[142–144]. In the Framingham Offspring Study[142], if one parent had HF, the parent's offspring had an increased risk of LV systolic dysfunction (OR 2.37). In the Swedish Nationwide Adoptive Study[143], the researchers observed a significant increase in the risk of an offspring having HF if one biological parent had HF (OR 1.49), whereas the risk was not increased if an adoptive parent had HF. These findings support the notion that HF is a complex trait with non-Mendelian inheritance. The heritability has been estimated to be 20–30%[142,143].

Polygenic contribution to HF. GWAS have become an important method for evaluating causal genetic risk. Although >160 gene loci have been associated with CAD[145–147], fewer GWAS have been performed in HF populations, and very few loci have been identified[83]. In the past year, two large GWAS have successfully led to the discovery of 12 novel loci associated with the risk of HF[148,149]. In a meta-analysis GWAS involving 47,309 patients with HF and 930,014 control individuals, 12 independent genetic variants were identified at 11 loci across the genome[149]. Many of these variants are associated with upstream processes that lead to HF. For example, six loci were associated with CAD (such as 9p21–*CDKN2B-AS1* and *LPA*) and four were associated with atrial fibrillation (such as *PITX2–FAM241A*). To test for an independent association with HF, the researchers conditioned on known risk factors for HF and observed that when conditioning on atrial fibrillation, the risk effect was attenuated by >50% for the *PITX2–FAM241A* locus but not for other loci associated with atrial fibrillation, including *KLHL3* and *SYNPOL2–AGAP5*, suggesting that these loci might have an independent association with HF. The researchers identified two loci as being independently associated with LV systolic dysfunction: *BAG3* and *CDKN1A*. BAG3 family molecular chaperone protein 3 is a stress-activated anti-apoptotic protein and is associated with Mendelian DCM[150–152]. A subsequent meta-analysis GWAS was performed including 10,976 patients and 437,573 control individuals and identified a novel locus on chromosome 1 near to *ACTN2* (encoding α-actinin 2), which is associated with both ischaemic and non-ischaemic cardiomyopathies[148]. α-Actinin 2 is a structural protein that forms part of the sarcolemma, and rare variants in *ACTN2* have previously been reported to be associated with cardiomyopathy[153].

Linking genetics to cardiac structure. By combining GWAS and large databases of cardiac imaging data, several investigators have evaluated how genetic signatures correspond to cardiac structure, providing insights into the genetic underpinnings of cardiac function[154–157]. The UK Biobank is a large, long-term study designed to understand genetic and environmental contributions to disease[158]. A GWAS with cardiac MRI data from nearly 20,000 individuals was performed to evaluate genetic contributions to myocardial trabeculations by analysing cardiac MRI measures of fractal structure[155]. The researchers identified 16 genetic loci (such as *HAND1*, *PLN*, *TBX3*, *TNNT2* and *TTN*), ten of which were also associated with another component of heart function (such as heart rate, QRS duration, or LV structure or function) and some of which were associated with cardiac development (for example, *GOSR1* and *MTSS1*). By visualizing cardiac mechanics, the researchers demonstrated that increased trabeculation is associated with improved cardiac performance. In patients with DCM, trabecular fractal dimension was increased, particularly towards the base and apex of the left ventricle, compared with the value in control individuals. Importantly, a negative correlation was observed between trabeculation and HF (that is, decreased trabeculation was associated with increased likelihood of a clinical diagnosis of HF[155]), further supporting the concept that increased trabeculation is associated with improved cardiac performance in patients with DCM.

Polygenic modification of monogenic disease risk. Rare pathogenic variants causing monogenic familial forms of cardiomyopathy are an important cause of HF[159–161]. Pathogenic variants causing familial cardiomyopathies are inherited in a Mendelian pattern, but penetrance and disease manifestation can vary on the basis of additional environmental and genetic factors[160,162,163]. Additionally, rare pathogenic variants are likely to be under-recognized and might have a larger role in HF than is currently appreciated[164]. This understanding that polygenic background modifies the penetrance of monogenic variants was illustrated in an investigation of familial hypercholesterolaemia, hereditary breast and ovarian cancer, and Lynch syndrome[165] (FIG. 3). In this evaluation of familial hypercholesterolaemia, pathogenic variants in three disease-associated genes (*APOB*, *LDLR* and *PCSK9*) were found to confer a 3.21-fold increase in the risk of CAD[165]. Using a polygenic risk score for CAD, the researchers observed that the polygenic background had a dramatic influence on the risk of CAD conferred by the pathogenic variant, ranging from a 1.30-fold increased risk for those in the lowest quintile of polygenic risk score to a 12.6-fold increased risk for those in the highest quintile[165] (FIG. 3). Similarly, polygenic risk also strongly modified the monogenic risk of breast or ovarian cancer and Lynch syndrome[165].

Common genetic variants have been discovered to influence HCM susceptibility and expressivity[166,167]. A GWAS involving data from 2,780 patients with HCM and 47,486 controls identified 12 risk loci for HCM[166]. A polygenic risk score was found to predict the likelihood of developing HCM and the severity of the phenotype in carriers of a variant in a gene encoding a sarcomeric protein[166]. An additional GWAS meta-analysis involving data from 1,733 patients with HCM, 5,521 patients with DCM and 19,260 control individuals from the UK Biobank revealed that shared genetic pathways contribute to risk of HCM and DCM with opposing directions of effect[167]. A polygenic risk score for HCM that included an additional 16 single nucleotide polymorphisms

was found to stratify event-free survival in carriers of a variant in a gene encoding a sarcomeric protein[167]. Equivalent relationships have also been identified in Huntington disease[168], glaucoma[169] and in 11 rare genetic disorders[170]. Furthermore, the monogenic contribution of loss-of-function variants in *TTN* to the risk of atrial fibrillation has been shown to be modified by underlying polygenic risk[171].

Bridging from Mendelian to complex disease in precision care. Fundamentally, the model of precision treatment for Mendelian disease is focused on treating the underlying mechanism. Genetic therapy (for example, CRISPR-based therapies for Duchenne muscular dystrophy[172]) is increasingly in clinical development. Genetic variants can also act as strong modifiers of complex disease; for example, the contribution of titin-truncating variants (TTNtvs) to DCM (FIG. 3). TTNtvs are fairly common in general populations (reports range from 0.4% in the UK Biobank[173], 0.6% in Geisinger MyCode[174] to 1.2% in the Penn Biobank[174]), and these variants affect heart function[173–175]. Importantly, in an examination of patients with idiopathic non-ischaemic cardiomyopathy, TTNtvs were found to be present in 27% of patients, much higher than in a control population[176]. TTNtvs are the most commonly recognized genetic contributor to DCM, and clinical stratification of TTNtv-positive DCM compared with TTNtv-negative DCM suggests more severely impaired LV systolic function, lower stroke volume, thinner LV walls, an increased incidence of ventricular tachycardia, and more rapid progression to a composite end point of LV assist device implantation, listing for cardiac transplantation or all-cause mortality[177]. TTNtvs have also been found to be enriched in populations of patients with ischaemic cardiomyopathy, highlighting how TTNtvs can act to modify the incidence of HFrEF as a complex disease[178]. *TTN*-based therapies are under active investigation and have focused on exon skipping[179] as well as modification of *TTN* splice variation by targeting RNA-binding protein 20 (REF.[67]). Although TTNtvs were initially thought to be limited to individuals with rare Mendelian disease, our growing understanding of the prevalence of these variants suggests that a targeted model of precision therapy might be applicable to a large proportion of patients with DCM.

Precision approaches to HF

Pharmacogenomics

The application of pharmacogenomics in medicine has great promise that has so far been unfulfilled. Pharmacogenetics was originally focused on hypothesis-driven gene candidates. Data supporting the use of *CYP2C19* polymorphisms in clopidogrel prescribing, particularly in the setting of percutaneous intervention, coincided with the development of non-CYP2C19 therapeutics[180]. Although the use of pharmacogenetics for warfarin or β-blocker prescribing has been investigated in depth, the effect on mainstream prescribing has been minimal[181–183]. Nevertheless, huge variations in pharmacological response clearly exist between individuals, and pharmacological interventions need to be tailored to individual patients.

Variants in adrenergic receptors and G protein-coupled receptor kinases are common and have been found to influence the response to β-blocker therapy[181]. Although variants in nearly all adrenergic receptors and G protein-coupled receptor kinases have been shown to influence the response to β-blocker pharmacotherapy[181], the effect of these variants on clinical outcomes has been less clear. For example, *ADRB1* (which encodes the β_1-adrenergic receptor) has a common polymorphism resulting in either glycine or arginine at amino acid position 389 (REF.[184]). Pharmacological testing showed that receptors with the Arg389 variant have greater basal and agonist-stimulated activity than those with the Gly389 variant[184]. The hypothesis that individuals with the Arg389 variant would have a more pronounced response to β-blocker therapy was tested in several retrospective and prospective studies. Overall, the results suggested that patients with the Arg389 variant have greater improvement in LV ejection fraction in response to β-blocker therapy and a significant improvement in survival[185–189].

Pharmacogenomics, distinct from pharmacogenetics, is a field that moves away from a candidate-gene-driven, monogenic approach and instead uses gene array panels to evaluate multiple genes, with a new extension of these studies using an unbiased, polygenic approach with the use of GWAS[182,183]. Several candidate-gene pharmacogenetic studies have been validated by GWAS (including the roles of *VKORC1* and *CYP2C9* variants in the response to warfarin therapy), but the application of pharmacogenomics to HF is lacking[182,183,190]. The power of this approach was demonstrated by a GWAS in which patients with substantial improvement in LV ejection fraction in response to medical therapy were compared with those without improvement, resulting in the discovery of a minor allele (rs7767652) located 2,705 bp upstream of *HCRTR2* (which encodes the orexin receptor type 2)[191]. Functional validation revealed that this minor allele impairs β-catenin–TCF4-mediated transactivation in vitro, highlighting a potential novel mechanism for orexin (also known as hypocretin) in the pathogenesis of HFrEF[191]. In mice that had received an infusion of angiotensin II and isoprenaline to mimic HF, the infusion of orexin A, an agonist of the orexin receptor type 2, significantly improved cardiac function[191] (FIG. 4).

Defining HF subtypes

Proteomics. Plasma biomarkers have been important in testing and monitoring the response to HF therapies[27,28]. Novel investigations in HF have examined population cohorts with the use of commercially available proteomic platforms[192–201]. In these proteomic investigations, themes have emerged that highlight the underlying biology of HF, including inflammation[195–197,200], altered coagulation[200] and impaired redox balance[194], and that important proteomic changes occur in the plasma of patients whose heart recovers[198,200]. Of note, proteomic data can be combined with electronic health record data to improve the prediction of HF outcomes[199] (FIG. 4).

In an important study demonstrating the limitations of preselected proteomic panels to predict HF, proteomic

profiling was performed on the plasma or serum of 901 men aged 70 years, measuring the abundance of 92 proteins[197]. In this study, 18 proteins were found to be significantly associated with incident HF, which was confirmed in two independent cohorts; these proteins included several inflammatory factors, such as growth/differentiation factor 15, T cell immunoglobulin and mucin receptor 1 and tumour necrosis factor-related

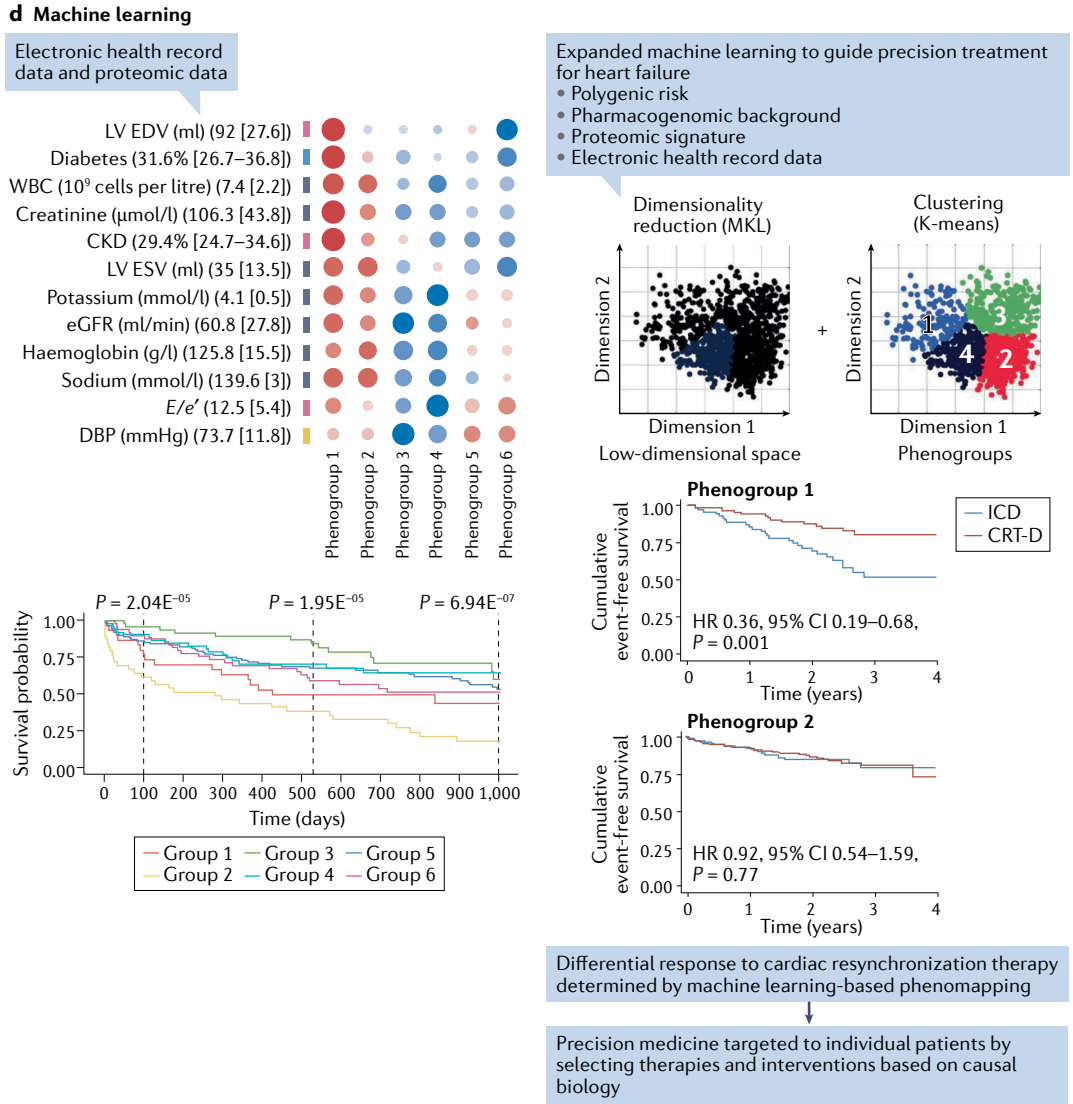

Fig. 4 | **Connecting biology with data to guide precision care for heart failure. a** | Novel genetic discoveries from genome-wide association studies (GWAS) have identified genes in which common variants contribute to the risk of heart failure[148,149,155]. **b** | Pharmacogenomic studies have identified genetic marks that influence the clinical response to heart failure therapies[181,184–188,191]. **c** | Proteomic studies have identified biological pathways that modulate the risk of heart failure and the response to therapies[193–200]. **d** | Characterizing an individual's heart failure biology from genetics, pharmacogenomics and proteomics can be combined with characterization derived from machine learning of clinical data to guide precision treatment of heart failure on the basis of the underlying causal biology. For example, Hedman and colleagues[204] developed a model clustering algorithm based on echocardiographic and clinical laboratory variables in 320 outpatients with heart failure with preserved ejection fraction and identified six distinct phenogroups that had differential clinical outcomes and plasma levels of proteomic markers. For each variable, the population mean and standard deviation or the percentage with 95% confidence intervals is shown. The circles are sized according to the absolute *Z*-score and coloured according to a priori knowledge on heart failure, with red (increase) representing more severe heart failure and/or worse prognosis and blue (decrease) representing less severe heart failure and/or better prognosis. The lower graph shows Kaplan–Meier curves during 1,000 days of follow-up for each of the six phenogroups. In another example, Cikes and colleagues[207] analysed differential responses to clinical therapy based on machine learning-derived phenogroups. An unsupervised machine learning algorithm was used to categorize participants in the MADIT-CRT trial on the basis of their clinical parameters, biomarkers and left ventricular (LV) volume, revealing four distinct phenogroups. Patients in phenogroups 1 and 3 had a beneficial response to cardiac resynchronization therapy–defibrillator (CRT-D) treatment compared with their response to implantable cardioverter–defibrillator (ICD) therapy only, and the response was much greater than in phenogroups 2 and 4 (Kaplan–Meier estimates of the probability of survival free from heart failure are shown for phenogroups 1 and 2 only)[207]. CKD, chronic kidney disease; DBP, diastolic blood pressure; EDV, end-diastolic volume; *E/e′*, ratio between early mitral inflow velocity and mitral annular early diastolic velocity; eGFR, estimated glomerular filtration rate; ESV, end-systolic volume; MKL, multiple kernel learning; WBC, white blood cell. Part **d** (left-hand graphs) adapted by permission from BMJ Publishing Group Limited from REF.[204], *Heart*, Hedman, A. K. et al. **106**, 342–349 (2020). Part **d** (right-hand graphs) adapted with permission from REF.[207], Wiley.

apoptosis-inducing ligand receptor 2. The researchers evaluated whether a preselected set of 24 or 11 proteins could predict incident HF as an addition to established risk factors (the ARIC score), but all the predictive power was driven by N-terminal pro-B-type natriuretic peptide (NT-proBNP), an established biomarker of HF.

Expanding beyond a preselected proteomic platform, a study involving deep proteomic profiling was performed in which 1,305 proteins were analysed in the plasma of patients in three different cohorts: those with incident HF in a prospective cohort, those with acute manifest HF and those with advanced HF from whom samples were collected before and after heart transplantation[200]. In the incident HF cohort, 16 proteins were significantly altered, including vascular messengers (NT-proBNP), proteins of matrix remodelling (thrombospondin 2), cytokines and immune mediators (C-reactive protein, CXC motif chemokine 13, IL-1 receptor antagonist protein and IL-18 receptor 1), elements of the complement system (C5a and C9), elements of the coagulation system (protein C and tissue plasminogen activator), and intracellular or membrane-bound proteins (carbonic anhydrase 13, contactin 1, gelsolin and cAMP-dependent protein kinase catalytic subunit-α). In the manifest HF cohort, markedly more proteins were observed to be significantly altered (421 proteins met correction of significance) and pathway analysis revealed that the PI3K–AKT–mTOR pathway, the complement system and the epithelial-to-mesenchymal transition involved in fibrosis were the most enriched[200]. The researchers also confirmed that many of the proteins that were altered in the incident and manifest HF cohorts had also changed in the predicted direction after the patients with advanced HF had undergone transplantation, supporting the hypothesis that altered plasma protein levels can partially revert to normal when the heart is no longer failing.

The researchers then performed a GWAS involving 1,421 individuals in a case–cohort subset for the 16 proteins identified in the incident HF analysis. Significant associations were observed at 11 loci for nine proteins. The researchers observed that the proportion of protein variability explained was modest for most single-nucleotide polymorphisms (1–6%) but was higher for three proteins — IL-18 receptor 1 (37%), thrombospondin 2 (13%) and protein C (15%) — prompting the suggestion that IL-18 in particular is involved in the onset of HF[200]. Although the researchers did not further subclassify HF cohorts on the basis of proteomic profiles, the insights gained into the biological underpinnings of an individual's presentation of HF suggest the potential to use proteomics to guide precision care.

Machine learning. Interest in subclassifying disease through the application of machine learning to the medical record is growing. Machine learning, defined as an algorithm that learns to perform a task or make a decision from data, exists on a spectrum between fully human-guided to fully machine-guided[202]. Deep learning models are complex networks of artificial neurons (weights) that are iteratively improved using prediction learning from raw data[202]. An algorithm-driven, unbiased subgrouping of a large, heterogeneous group of patients could provide insights into predicting clinical outcomes and potential response to therapies (FIG. 4). In one example, a clustering analysis of 45 clinical variables was performed in 1,619 patients with HFrEF[203]. The clusters were differentiated by exercise capacity (peak O_2 consumption) as well as biomarkers (such as NT-proBNP), and significant between-cluster differences were found in clinical outcomes such as all-cause mortality, cardiovascular mortality and HF hospitalizations[203].

These methods have been termed phenomapping and have also been performed in the evaluation of HFpEF[204–206]. In a prospective analysis, 420 patients with HFpEF were enrolled in a study in which the researchers defined clusters of individuals on the basis of multivariate normal distributions of phenotypic variables, defining three distinct clusters[206]. These three clusters of patients differed in phenotypes such as electrocardiographic findings (PR interval), echocardiography (E/e' ratio) and invasive haemodynamics. The clusters had clear differences in clinical outcomes (compared with phenogroup 1, phenogroups 2 and 3 had a hazard ratio of 4.0 and 6.5 for all-cause death, respectively)[206]. A similar machine learning approach was performed in a Swedish population but included additional plasma proteomic analysis, which resulted in six distinct clusters of patients with HFpEF, with differentially expressed plasma proteins[204]. These proteins included angiopoietin 1 receptor, BNP, endothelial cell-specific molecule 1, fibroblast growth factor 23, NF-κB essential modulator and renin, suggesting unique biological underpinnings[204].

Given the potential for machine learning-based phenomapping to categorize patients with HF, significant interest exists in whether different phenogroups might respond differently to clinical therapy. In an important proof-of-concept study, machine learning-guided phenomapping was used to evaluate the response to cardiac resynchronization therapy (CRT)[207]. The benefit of CRT in patients with HFrEF and intraventricular conduction delay with a QRS of >130 ms was demonstrated in the MADIT-CRT trial[208], in which 1,820 patients were randomly assigned in a 3:2 ratio to receive a CRT–defibrillator (CRT-D) or an implantable cardioverter–defibrillator (ICD). In a subsequent study, the MADIT-CRT data were retrospectively analysed. Machine learning-guided phenogrouping was performed on the baseline characteristics, resulting in four distinct phenogroups. Phenogroups 1 and 3 had a clear improvement in clinical outcomes after receiving CRT-D compared with ICD, whereas phenogroups 2 and 4 did not[207] (FIG. 4). This concept that clinical heterogeneity might influence the response to HF therapy has also been suggested in a machine learning-driven phenogrouping analysis of >40,000 patients in the Swedish HF Registry[209]. In this analysis, phenogrouping revealed a significant interaction between propensity-matched clusters and patient response to β-blocker therapy; clusters 3 and 4 derived the greatest benefit from therapy, whereas cluster 1 derived the least benefit. For angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker therapy, outcomes were similar among all the clusters despite

heterogeneity in patient risks, implying an interaction between therapy and cluster[209].

Although machine learning has tremendous power for retrospective learning and discovery, applying machine learning models so that they are prospectively clinically useful remains unsolved[210]. This objective could be achieved by combining causal inferences from biological experiments with clinical data to subclassify patients and prospectively evaluate their response to therapies (FIG. 4). An example of how proteomic data can be combined with machine learning to classify patients with HFpEF was provided by a study in which a multiplex assay of 49 plasma biomarkers was used to evaluate the response to spironolactone of participants in the TOPCAT trial[211]. Biomarker data were used to classify patients into six distinct groups, and some clusters had more prominent markers of fibrosis and tissue remodelling, inflammation, neurohormonal regulation or myocardial injury than others[211]. The researchers observed that particular biomarkers (fibroblast growth factor 23 and soluble tumour necrosis factor receptor 1) were strong predictors of hospital admission for decompensated HF. Modelling using machine learning and taking into account all the biomarkers strongly predicted the risk of hospital admission for HF and far outperformed a traditional statistical risk model (the MAGGIC risk calculator).

Precision therapeutics

Although targeted medications for Mendelian cardiomyopathy provide an obvious path to precision therapy, the challenge facing clinicians is choosing among the ten or more therapies with evidence from randomized, controlled trials of efficacy in the treatment of HFrEF as well as identifying potential roles for therapies in the treatment of HFpEF. For patients with HFrEF, a consensus has evolved towards initiating four therapies as rapidly as possible: a β-blocker, an angiotensin-receptor–neprilysin inhibitor, a mineralocorticoid-receptor antagonist and an SGLT2 inhibitor (known as 'quad therapy') (FIG. 5). This approach is based on the weight of evidence and the relative efficacy of these drugs in broad populations of patients with HFrEF.

In what order should patients receive this quad therapy? And how should we treat patients whose blood pressure does not allow them to tolerate maximal doses of these drugs? Should these patients receive lower doses of all four agents or higher doses of the less vasoactive medications? If patients have diabetes or kidney disease, should SGLT2 inhibitors be prioritized? If their

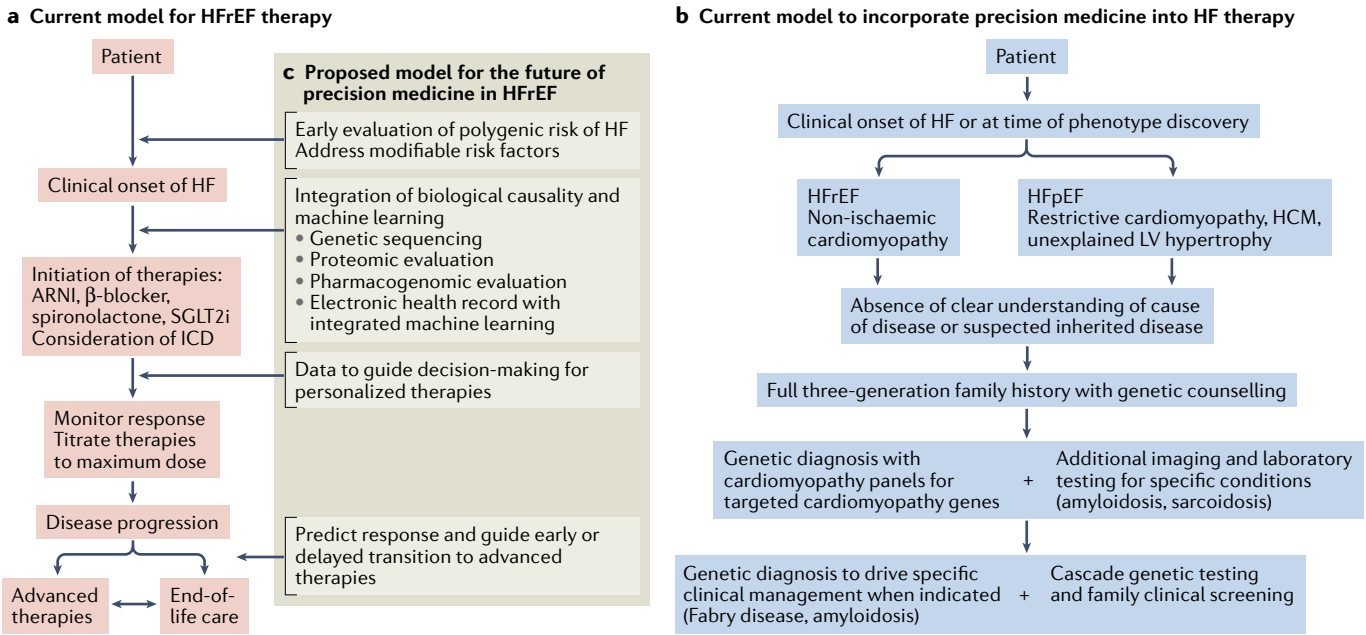

Fig. 5 | **Precision medicine in heart failure. a** | The current model for the management of heart failure (HF) with reduced ejection fraction (HFrEF) is focused on initiation of medical therapies at the time of clinical onset of HF, with an emphasis on the initiation of β-blockers, an angiotensin-receptor blocker–neprilysin inhibitor (ARNI) and spironolactone, and recently on the early initiation of a sodium–glucose cotransporter 2 inhibitor (SGLT2i). **b** | Precision medicine is beginning to be incorporated into HF therapy. In patients with suspected Mendelian cardiovascular disease, a full three-generation family history is taken and genetic evaluation with counselling and sequencing is performed, often based on a gene panel populated with genes known to be associated with cardiomyopathy. Genetic diagnoses can lead to clear changes in treatment plans for particular conditions (such as hypertrophic cardiomyopathy (HCM), Fabry disease, transthyretin-associated amyloidosis or sarcoidosis) and has important implications for families. **c** | We propose a model for the future of precision medicine in patients with HFrEF. The earlier evaluation of the polygenic risk of HF will inform a physician to address modifiable risk factors. At the clinical onset of HF, the integration of biological causality through genetics, pharmacogenomics and proteomics with electronic health record data through machine learning algorithms can guide HF therapies. The ongoing evaluation of biological and clinical data can be used to predict treatment response and guide transition to advanced therapies. The gap between our current model and idealized models of precision medicine in HF is large. Bridging this gap must be evidence-based and be built on the evaluation of massive genetic, proteomic and electronic health record data sets from patients with real-world outcomes and from randomized controlled trials. HFpEF, heart failure with preserved ejection fraction; ICD, implantable cardioverter–defibrillator; LV, left ventricular.

heart rate is high but their blood pressure is low, should patients receive a higher dose of the β-blocker and lower doses of vasodilators? These are daily, real-world decisions for HF practitioners that current clinical trial evidence and guidelines are ill equipped to answer.

A call has been made to prioritize β-blocker and SGLT2 inhibitor therapy, with angiotensin-receptor–neprilysin inhibitor and mineralocorticoid-receptor antagonist therapies added sequentially thereafter, allowing the rapid up-titration of therapies to target dosages[212]. However, this strategy does not fully account for the wide range of patient presentations and the diversity of therapeutic responses in real-world practice. Most patients with HFrEF in daily practice would not have qualified for many of the clinical trials that have been conducted because of the strict inclusion and exclusion criteria (often relating to comorbidities, which affect the majority of patients in the real world but a minority of patients in clinical trials).

Many other questions remain. When is there a role for therapies directed at the NO• pathway, such as hydralazine–nitrates or vericiguat? Each of these has clinical trial evidence of their benefit in patients with HFrEF. Is there an additional role for hydralazine–nitrates in patients who are already receiving quad therapy who lack adequate blood pressure control? In patients of African ancestry, should hydralazine–nitrates be prioritized over one of the quad agents? Currently, no guidelines or consensus exist on how these decisions should be made.

One approach might be to prioritize agents that primarily target the myocardium over those that prevent secondary neurohormonal effects. However, prioritizing omecamtiv mecarbil, which showed no reduction in mortality, would be difficult to justify when secondary neurohormonal blockers are associated with a significant reduction in mortality[79]. But what would have happened if omecamtiv mecarbil had been discovered first? Could a primary effector possibly make secondary neurohormonal agents obsolete? A clinical trial to address this question is unlikely to be performed.

Given that a massive, multi-group, multi-omic, randomized study of all the current HF medications is not feasible, what would an effort to obtain real-world evidence look like? A very large cohort (perhaps in the millions) would be required, and data gathering would take advantage of the natural experiment whereby some patients are given medications at different dosages in different orders by different physicians around the world. Evidence gathering would also take advantage of time series data and would have the substantial 'causal limitation' of ascertainment — that only naturally occurring variation in drug dosing and gene variants could be studied. Nevertheless, a study of this nature might begin to inform rational prescribing, or at least the rational design of follow-up randomized studies, in an age of precision medicine. Meanwhile, we can look to monogenic diseases to harness precision therapy for an increasingly broad array of presentations of myocardial disease, including those discussed above (HCM, Fabry disease and cardiac amyloidosis) and others, such as RASopathies (a family of disorders affecting growth caused by dysregulated intracellular RAS and mitogen-activated protein kinase, which can lead to HCM[213]) and primary neuromuscular conditions in which molecular testing is increasingly uncovering the underlying, targetable mechanism of disease.

Implementation and future directions

In this Review, we highlight the biology of HF and identify methods to guide the development of an idealized model of precision medicine by using individual myocardial biology to inform and rationalize clinical care. Our current model of precision medicine in HF is far from ideal, but important precision medicine approaches that are available today remain largely underutilized (FIG. 5). For patients with HFpEF and associated LV hypertrophy but without an identified underlying cause, precision-based approaches include genetic evaluation for HCM, Fabry disease, Noonan syndrome, RASopathy or other genetic causes of LV hypertrophy. Additionally, careful evaluation with the use of imaging modalities such as cardiac MRI and pyrophosphate nuclear scanning with accompanying laboratory evaluation is necessary to evaluate for possible cardiac amyloidosis. In this model, the diagnosis of a specific cause of HFpEF with LV hypertrophy can lead to the initiation of life-changing targeted therapies as well as crucial information for families. In patients with non-ischaemic cardiomyopathy and HFrEF, genetic evaluation for potential genetic aetiologies might be beneficial in terms of specific management (for example, *LMNA*-associated cardiomyopathies and an indication for an ICD for the primary prevention of sudden cardiac death) as well as crucial information for family members and clinical screening (FIG. 5).

Although a genetic diagnosis of a specific condition can result in clearly altered treatment plans, we have yet to incorporate biomarkers or provide guidance on how to start general therapies for HF, leaving a gap between our current vision of precision medicine in HF (FIG. 5) and an idealized version. A future model would incorporate broad protein biomarkers in conjunction with genomic assessment and an unbiased evaluation of electronic medical record data to guide clinical care at the level of individual patients. Bridging this gap must be achieved by an evidence-based approach built on the further collection of patient data combined with real-world clinical outcome data, leading to subsequent randomized controlled trials to determine how and when to use and prioritize HF therapies for each individual patient. Current clinical trial biobanks are also available and have been under-appreciated as a possible source of genomic and proteomic data to guide our understanding of individual responses to HF therapies. Finally, precision-based genetic therapies that are under development, such as those targeting TTNtvs, might make additional fundamental contributions to treating HF driven by personalized genomics. Finally, as the disease progresses, we see a role for precision medicine in predicting patient responses to therapies for advanced HF and providing important guidance to patients who will receive benefit from the most invasive and life-saving options: LV assist device implantation and heart transplantation.

Conclusions

We are on the verge of a new era in HF, in which our understanding of the basic biology of myocardial disease and the genetic predisposition in an individual patient can inform precision approaches to therapy. By reviewing the fundamental biology of HF and the causal relationships between genetic contributors, the mechanisms of action of traditional and novel therapeutics can be viewed in the context of precision medicine. Our understanding of both the Mendelian genetics of cardiomyopathies and the complex genetics of the clinical syndrome presenting as HF has advanced greatly. In addition, machine learning can be applied to subclassify patients with HF in ways that might inform rational prescribing. We have presented a vision to bridge the gap between the basic biology of the failing heart, its diverse clinical presentations and the range of medications that we can now use to treat it, laying out a roadmap for the future of precision medicine in HF.

Published online: 09 June 2021

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Author contributions
Both authors contributed substantially to all aspects of this article.

Competing interests
E.A.A. is a co-founder of Deepcell, Personalis and SVEXA; a board member of AstraZeneca; and an adviser to Apple, Foresite Labs, Nuevocor and Sequencebio. C.S.W. declares no competing interests.

Peer review information
Nature Reviews Cardiology thanks L. Stevenson, F. Zannad and the other, anonymous, reviewer(s) for their contribution to the peer review of this work.

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