Heart Failure 1

In search of new therapeutic targets and strategies for heart failure: recent advances in basic science

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This is the first in a **Series** of four papers about heart failure

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Chronic heart failure continues to impose a substantial health-care burden, despite recent treatment advances. The key pathophysiological process that ultimately leads to chronic heart failure is cardiac remodelling in response to chronic disease stresses. Here, we review recent advances in our understanding of molecular and cellular mechanisms that play a part in the complex remodelling process, with a focus on key molecules and pathways that might be suitable targets for therapeutic manipulation. Such pathways include those that regulate cardiac myocyte hypertrophy, calcium homoeostasis, energetics, and cell survival, and processes that take place outside the cardiac myocyte—eg, in the myocardial vasculature and extracellular matrix. We also discuss major gaps in our current understanding, take a critical look at conventional approaches to target discovery that have been used to date, and consider new investigational avenues that might accelerate clinically relevant discovery.

Introduction

Chronic heart failure is a complex clinical syndrome that arises secondary to inherited or acquired abnormalities of cardiac structure, function, or both that impair the ability of the heart to fill or eject blood. Common causes include disorders that chronically increase cardiac workload, such as loss of muscle due to myocardial infarction or pressure overload due to hypertension. The cardiac response to such stresses entails complex remodelling of cardiomyocytes and the non-myocyte compartment, which could initially be adaptive but eventually might progress to contractile dysfunction, ventricular dilatation, and arrhythmias. Here, we review recent advances to decipher the molecular mechanisms underlying cardiac remodelling, focusing on chronic heart failure with depressed systolic function rather than the less-defined condition of heart failure with preserved ejection fraction. We do not discuss myocardial regeneration, which has been reviewed elsewhere.[1]

The remodelling phenotype

A prominent feature of the remodelling heart is cardiomyocyte hypertrophy, but substantial changes also take place in myocyte electrical properties, calcium (Ca^{2+}) handling, energy metabolism, contractile function, and cell viability.[2] Extracellular matrix remodelling includes both fibrosis and activation of collagenolytic enzymes (matrix metalloproteinases) that lead to chamber dilatation and important changes in myocardial vasculature. Although this broad phenotype is common to diverse causes of chronic heart failure, findings of studies in gene-modified mouse models show that different phenotypic components can be regulated independently. For example, hypertrophy without contractile dysfunction, fibrosis, or dilatation—mimicking so-called physiological hypertrophy in athletes—is noted in some models, suggesting that specific pathways could drive adaptive versus maladaptive remodelling.[3,4]

Search strategy and selection criteria

We searched PubMed (2000–10) and ClinicalTrials.gov with the terms "heart failure", "cardiac hypertrophy", "mechanisms", "remodeling", "remodelling", "network biology", "necrosis", "apoptosis", "microRNAs", "systems biology", "gene networks", and "animal models". We mainly selected articles published within the past 5 years, but we did not exclude classic citations in this area. Relevant review articles are cited to provide readers with an in-depth understanding of the areas reviewed herein. Our reference list was modified based on comments received at peer-review.

Hypertrophic signalling

Figure 1 shows that many pathways can regulate cardiomyocyte hypertrophy, acting through a complex network of intracellular signalling cascades. The insulin-like growth factor (IGF), phosphatidylinositol 3 kinase alpha (PI3Kα), protein kinase B (AKT) pathway is strongly implicated in physiological hypertrophy.[4] By contrast, pathological remodelling entails many overlapping steps.[5–7] Cell-membrane receptors, including G-protein coupled receptors, receptor tyrosine kinases, and natriuretic peptide receptors, are activated by agonists such as catecholamines, angiotensin II, and endothelin. Mechanosensitive signalling pathways activated at sarcolemmal and sarcomeric levels could also play a part.[8] The net effects of intracellular signalling ascertain the final myocyte phenotype.

Activation of G-protein coupled receptors leads to signalling via different G proteins (Gαs, Gαq, $G\alpha_{11}$, Gβγ) and couples to phospholipase C, mitogen-activated protein kinases (MAPKs), or, in the case of β-adrenergic receptors, to adenyl cyclase and protein kinase A, thereby switching on pro-hypertrophic programmes. Triggering of phospholipase C leads to generation of both inositol triphosphate (which causes release of Ca^{2+} from intracellular stores) and diacylglycerol (which activates protein kinase C). A rise in

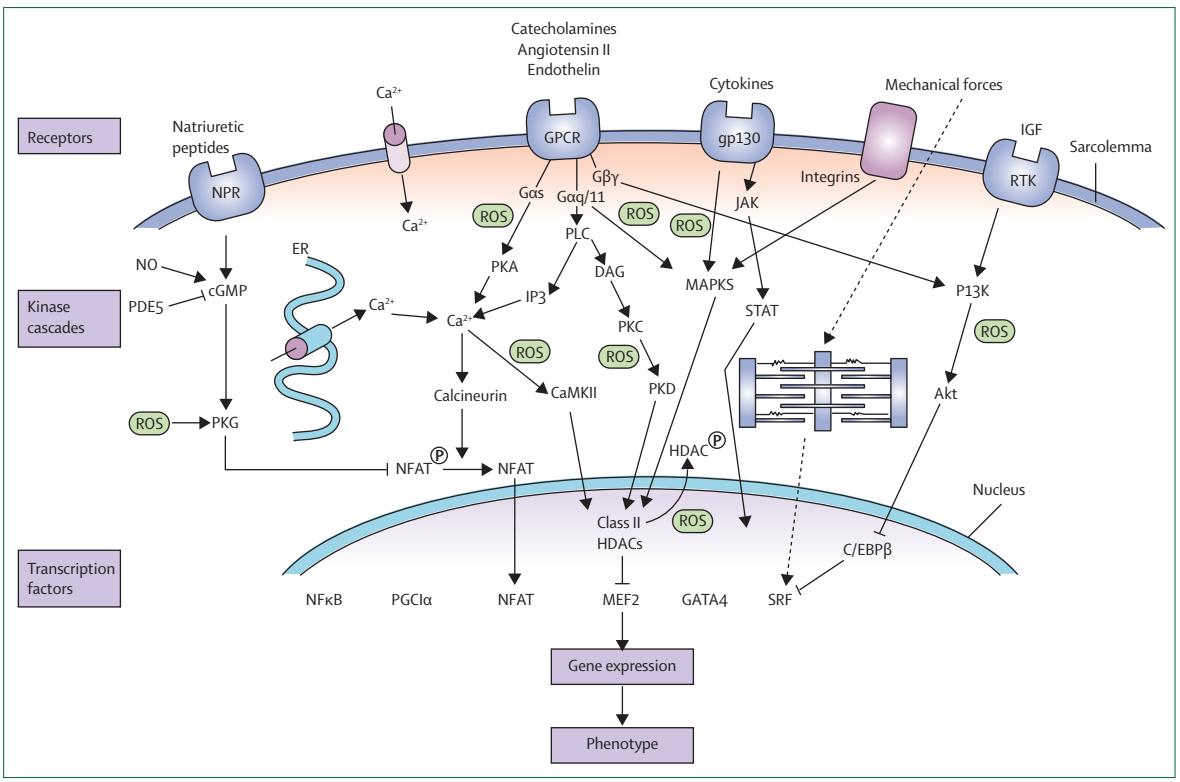

Figure 1: **Cellular signalling pathways in cardiomyocyte hypertrophy**
Akt=protein kinase B. CaMKII=calcium-calmodulin-dependent kinase. C/EBPβ=CCAAT/enhancer binding protein beta. DAG=diacylglycerol. ER=endoplasmic reticulum. GATA4=GATA binding protein 4. gp130=glycoprotein 130. GPCR=G-protein coupled receptor. HDAC=histone deacetylases. IGF=insulin-like growth factor. IP3=inositol triphosphate. JAK=Janus kinase. MAPKs=mitogen-activated protein kinases. MEF2=myocyte enhancer factor 2. NFAT=nuclear factor of activated T cells. NFκB=nuclear factor kappa light polypeptide gene enhancer in B cells. NO=nitric oxide. NPR=natriuretic peptide receptor. P=phosphorylation. P13K=phosphatidylinositol 3 kinase. PDE5=phosphodiesterase type 5. PGC1α=peroxisome proliferator-activated receptor gamma, coactivator 1 alpha. PKA=protein kinase A. PKC=protein kinase C. PKD=protein kinase D. PKG=protein kinase G. PLC=phospholipase C. ROS=reactive oxygen species. RTK=receptor tyrosine kinase. STAT=signal transducer and activator of transcription. SRF=serum response factor.

the amount of intracellular Ca^{2+}, by either influx from outside the cell or release from intracellular stores, elicits activation of calcineurin (a phosphatase that activates nuclear factor of activated T cells [NFAT]) and calcium-calmodulin-dependent kinase (CaMKII). Activation of natriuretic peptide receptors and release of nitric oxide (NO) both stimulate a protein kinase G-mediated anti-hypertrophic pathway that is modulated by activity of phosphodiesterase type 5 (PDE5). Local release of reactive oxygen species (generated by specific enzymes) amplifies activation of several pathways.[9]

These cascades do not operate in parallel but show substantial cross-talk, and key points of convergence could be especially amenable to therapeutic targeting (figure 1). Major targets are transcription factors such as NFAT, myocyte enhancer factor 2 (MEF2), GATA binding protein 4 (GATA4), and serum response factor (SRF), which drive hypertrophic gene programmes, and those that affect metabolic remodelling (eg, peroxisome proliferator-activated receptor gamma, coactivator 1 alpha [PGC1α]) and viability (eg, nuclear factor kappa light polypeptide gene enhancer in B cells [NFκB]). Regulation of these transcription factors includes positive control and removal of negative effects (eg, class II histone deacetylases that inhibit MEF2 signalling). Elimination of the inhibitory effect of the transcription factor CCAAT/enhancer binding protein beta (C/EBPβ) on SRF and GATA4 could be important.[10] Enhancement of this so-called adaptive pathway, either with IGF or growth hormone therapy, could be a promising strategy, which is being addressed in current clinical trials (ClinicalTrials.gov identifiers NCT00791843 and NCT01235273).

The calcineurin-NFAT pathway is regulated not only by Ca^{2+} but also by kinases that inhibit NFAT activity and interactions with sarcomeric proteins. Pharmacological inhibitors of calcineurin (eg, ciclosporin) are used clinically as immunosuppressants but are unsuitable for use in chronic heart failure because of their side-effects. However, agents targeting other components of this pathway (eg, regulators of calcineurin) might prove useful. Another important signalling convergence point is activity of histone deacetylases, which inhibit access of transcription factors to DNA.[11] Phosphorylation of class II histone deacetylases by kinases such as protein kinase D and CaMKII relieves this inhibition and de-represses the transcriptional activity of MEF2 (figure 1). Histone

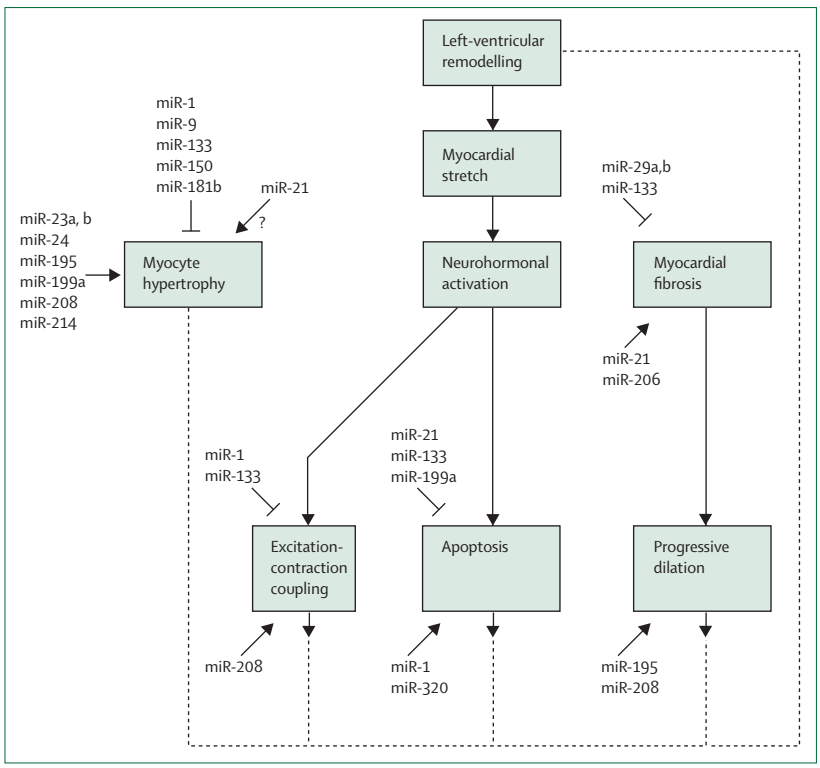

Figure 2: **Candidate miRs with suggested roles in cardiac remodelling process**
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deacetylases are regulated by receptor-activated pathways and Ca^{2+} and by reactive oxygen species, and these different inputs could be integrated to fine-tune the hypertrophic response. Class I histone deacetylases seem to have opposite effects to class II enzymes,[12] so any therapeutic targeting of this pathway would need to be selective. Other pathways can also act as a brake to pro-hypertrophic signalling. For example, activation of cGMP-dependent protein kinase G by NO and natriuretic peptides inhibits hypertrophic signalling pathways at many levels.[2] Indeed, cGMP phosphodiesterase inhibitors (eg, sildenafil) that amplify cGMP and enhance protein kinase G signalling are beneficial in animal models of chronic heart failure and are in current clinical trials.[13,14]

MicroRNAs (miRs) are short, highly conserved, non-coding RNAs that regulate gene expression at the post-transcriptional level by inhibition of translation or promotion of degradation of target mRNAs. Extant published work suggests that miRs are regulated differentially in the failing heart and have a key role in pathogenesis of heart failure through their ability to negatively regulate expression levels of networks of genes that govern adaptive and maladaptive cardiac remodelling (figure 2).[15,16] Data from gain-of-function and loss-of-function experiments in mice show that miRs modulate various aspects of the chronic heart failure phenotype, including cardiac myocyte hypertrophy, excitation-contraction coupling, apoptotic cell death, and myocardial fibrosis.[15,17–19] Technologies based on RNA interference are in development as clinical treatments to antagonise specific miRs that have been associated with expansion of a heart failure phenotype in small and large animal models of cardiac injury.[20] Moreover, use of either miRs in plasma or miR signatures as disease biomarkers is of great interest.[21,22]

Calcium dysregulation

Excitation-contraction coupling includes Ca^{2+} influx through sarcolemmal L-type channels, Ca^{2+}-induced Ca^{2+} release from the sarcoplasmic reticulum through ryanodine receptor channels, and binding of Ca^{2+} to myofilaments to initiate contraction (figure 3). The process is reversed by Ca^{2+} reuptake into the sarcoplasmic reticulum via a Ca^{2+}-ATPase pump (SERCA2a [also known as ATP2A2]) and cellular efflux via the sodium (Na^{2+})-Ca^{2+} exchanger. The failing myocyte has reduced transient amplitude of Ca^{2+} and raised diastolic Ca^{2+} concentration due to several abnormalities, including impaired SERCA2a function and increased Ca^{2+} leak through ryanodine receptor channels (figure 3).[23] The decrease in Ca^{2+} transient amplitude contributes to reduced contractile force, whereas increased leak from the sarcoplasmic reticulum and raised diastolic Ca^{2+} could cause arrhythmia and diastolic dysfunction. Defective SERCA2a function is related to diminished amounts of this protein and altered phosphorylation of phospholamban (the regulator of SERCA activity), which can include perturbations in phosphatase activity.[24,25] Increased leak of Ca^{2+} from the sarcoplasmic reticulum has been attributed variably to hyperphosphorylation of ryanodine receptor channels (by protein kinase A, CaMKII, or both; figure 3) or defects in stabilisation of these channels.[26,27] Intracellular concentrations of Na^{2+} might also be increased in failing myocytes, thereby promoting arrhythmia and causing a reduction in amounts of mitochondrial Ca^{2+}, which compromise antioxidant capacity and enhance mitochondrial production of reactive oxygen species.[28] Impaired β-adrenergic signalling is an important contributor to abnormal excitation-contraction coupling and associated remodelling and is corrected by long-term treatment with β blockers. Recent work has enhanced substantially our understanding of the mechanisms underlying β-adrenergic dysregulation, such as isoform-specific roles of adenyl cyclase 5 and 6, the effects of G-protein coupled receptor kinases (which desensitise β receptors), and transactivation of protective epidermal growth factor receptor signalling by β_1 agonists.[29,30] These advances suggest promising therapeutic targets, such as inhibition of adenyl cyclase 5 or G-protein coupled receptor kinases.

Beyond contractile dysfunction and propensity to arrhythmia, myocyte Ca^{2+} dysregulation has an effect on pro-hypertrophic and cell-survival signalling pathways and on mitochondrial function and energy production. Ca^{2+} concentrations in specific subcellular microdomains of the failing myocyte—eg, plasmalemmal or perinuclear compartments—might be

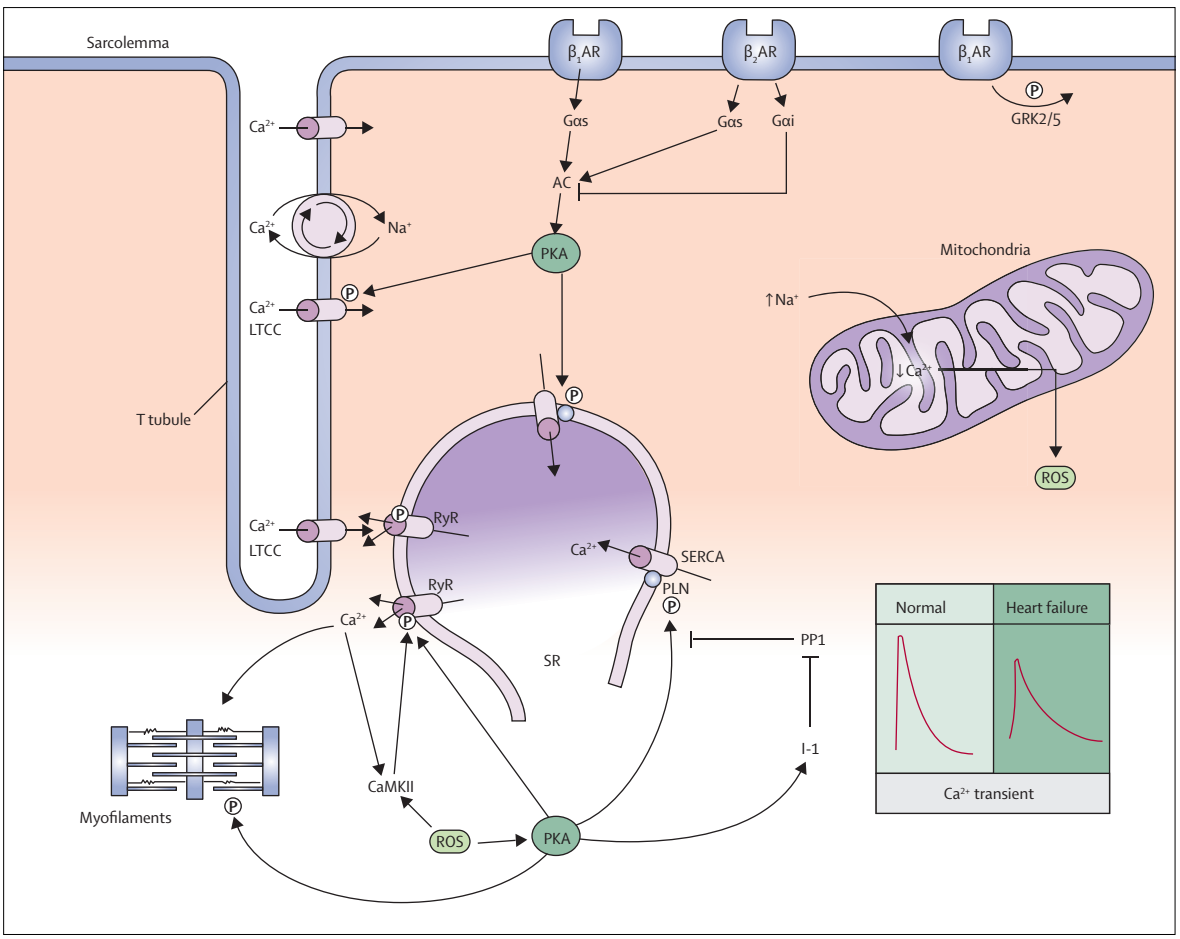

Figure 3: **Major contributors to abnormal excitation-contraction coupling in the failing heart**
AC=adenyl cyclase. βAR=β-adrenoceptor. CaMKII=calcium-calmodulin-dependent kinase. GRK=G-protein coupled receptor kinase. I-1=phosphatase inhibitor 1. LTCC=sarcolemmal L-type channel. P=phosphorylation. PKA=protein kinase A. PLN=phospholamban. PPI=protein phosphatase. ROS=reactive oxygen species. RyR=ryanodine receptor channel. SERCA=calcium ATPase pump. SR=sarcoplasmic reticulum.

regulated differentially and could affect distinct processes, such as contraction and transcription, respectively.[31–33] Approaches to correct abnormal excitation-contraction coupling in experimental models can prevent maladaptive remodelling, suggesting an important role for abnormal excitation-contraction coupling in the pathogenesis of chronic heart failure.

Several potential treatments to target abnormal excitation-contraction coupling are being developed and hold much promise.[34] Enhancement of SERCA2a activity by gene transfer of *ATP2A2* to increase the amount of protein has been tested in a small phase 1 study.[35] Although larger trials of this technique are needed, a more readily applicable approach might be to inhibit Ca^{2+} leak from ryanodine receptor channels (eg, with CaMKII inhibitors or agents that stabilise the channel); this strategy could be especially effective for reduction of arrhythmias. Increased intracellular Na^{2+} due to augmented late Na^{2+} currents might be treatable with the drug ranolazine, which is already available for use in patients with angina, although it might also have other actions. A positively inotropic small molecule—omecamtiv mecarbil (Cytokinetics, San Francisco, CA, USA)—activates cardiac myosin directly (ie, without altering amounts of Ca^{2+}); it does not increase energy demand or arrhythmia, unlike β-adrenergic agonists.[36] This agent seems promising but its long-term effects in chronic heart failure need to be tested.

Myocyte survival or death

Low-level but progressive loss of myocytes in the chronically overloaded heart is believed to contribute to cardiac remodelling and contractile failure.[37] Apoptosis can be triggered by activation of G-protein coupled receptors and cytokines and by increased production of reactive oxygen species. Apoptotic cell death induced by G-protein coupled receptors entails kinases such as apoptosis signal-regulating kinase 1 (ASK1), p38MAPK, c-Jun N-terminal kinase (JNK), and CaMKII; it also includes protein kinase C-dependent transcriptional upregulation of the pro-apoptotic protein NIX (also known as BNIP3L), which

targets mitochondria.[38] CaMKII might be a point of convergence of pro-apoptotic signalling because it is activated by both Ca^{2+} and regulated production of NADPH oxidase (NOX)-derived reactive oxygen species, downstream of angiotensin II-induced stimulation of G-protein coupled receptors.[39] Apoptotic cell death is counteracted by pro-survival pathways, such as activation of AKT and proto-oncogene serine-threonine protein kinase (PIM1) and inactivation of glycogen synthase kinase 3 beta (GSK3β).[40]

A different form of cell death, termed programmed necrosis, has recently been recognised as important in heart disease.[41] By contrast with apoptosis, necrosis is accompanied by early loss of plasma membrane and organelle integrity and striking inflammation. Inflammation can contribute to extracellular remodelling and development of contractile failure. The defining molecular feature of programmed necrosis is opening of the mitochondrial permeability transition pore in response to raised amounts of mitochondrial Ca^{2+} and perhaps oxidative stress. Opening of this channel causes collapse of mitochondrial membrane potential and ATP production and triggers necrosis. Findings of studies in gene-modified mice without cyclophilin D—a regulator of the mitochondrial permeability transition pore—suggest that this pathway is important in acute myocardial infarction.[42,43] Necrosis contributes to heart failure in a genetic model of myocardial Ca^{2+} overload[44] and in a model in which NIX is targeted to the endoplasmic reticulum instead of mitochondria,[45] but its contribution to chronic heart failure induced by increased workload remains to be defined.

A third process that could affect myocyte survival is autophagy (or self-digestion), an evolutionarily conserved mechanism for bulk degradation and recycling of long-lived proteins and organelles within cells during starvation. Autophagy is activated in the haemodynamically overloaded heart and after ischaemia or reperfusion.[46] Studies in gene-modified mice deficient in autophagy-related 5 homolog (ATG5) suggest that this process has an adaptive role, perhaps by removal of abnormal protein aggregates and increasing of cellular energy supply.[47] Indeed, protein quality control by other cellular pathways—such as the ubiquitin-proteosome system—might also be beneficial in the failing heart.[48] However, some reports of detrimental autophagy during haemodynamic overload[49] raise the possibility that excessive autophagy could be deleterious.

Myocardial perfusion and energetics

Maintenance of an oxygen supply-demand balance is vital for normal heart function, and recent findings show that myocardial capillary density is a key determinant of the remodelling response, even in non-ischaemic haemodynamically overloaded hearts.[50] Insufficient growth in capillary density relative to increasing muscle mass promotes pathological remodelling with fibrosis, dilatation, and contractile failure. Important stimuli for myocardial capillarisation in this setting are the transcription factors hypoxia-inducible factor 1 alpha (HIF1α) and GATA4, which induce production and release of vascular endothelial growth factor (VEGF) from cardiomyocytes to exert paracrine effects on myocardial vessels.[51,52] Tumour protein 53 (TP53; also known as p53) was found to antagonise HIF1α activation,[51] whereas an enzyme that generates reactive oxygen species (NOX4) was a positive driver of HIF1α activation during pressure overload.[53] These data are also of interest in that they identify a protective pathway mediated by reactive oxygen species, by contrast with detrimental effects initiated by these species, and suggest that therapeutic approaches could target specific sources of reactive oxygen species rather than non-specific antioxidants that have failed (to date) in clinical trials.

Energy production and metabolism within the cardiomyocyte are also of major importance in the failing heart. Mitochondria take centre stage in this process, and substantial remodelling of mitochondrial structure and function happens as the heart itself remodels. Substrate use (glucose *vs* fatty acids), ATP synthesis and handling, energy efficiency, and antioxidant reserve are all altered.[54] A byproduct of these changes is usually a substantial increase in mitochondrial reactive oxygen species, which has detrimental effects both within and outside mitochondria.[55] Mitochondrial remodelling is driven largely by a complex transcriptional programme in which PGC1α has a key role.[56] This protein induces and interacts with other transcription factors and drives an increase in mitochondrial number (biogenesis). To what extent are alterations in mitochondrial function a manifestation of the remodelled heart? Can these changes accelerate the process of remodelling? Irrespective of the answer to these questions, drugs that can modulate or return substrate use to normal (eg, perhexilene, glucagon-like peptide, metformin) are under investigation as treatments for heart failure.[57] Further discussion is beyond the scope of this report, but can be found elsewhere.[54,56,57]

Changes in the extracellular matrix

Alterations in the extramyocyte compartment—leading to fibrosis, dilatation, and shape change—are well-recognised as a major component of cardiac remodelling, and current treatments that reduce mortality in patients with chronic heart failure (eg, angiotensin-converting-enzyme inhibitors) have an important effect on these abnormalities. Enhanced matrix turnover due to activation of matrix metalloproteinases is an important part of the pathogenic mechanism implicated in ventricular dilatation, but initial clinical trials of inhibitors of matrix metalloproteinases in the post-myocardial infarction setting were unsuccessful.[58] The precise inter-relation between alterations that are ongoing in the extra-myocyte compartment and those happening within cardiomyocytes in the remodelling heart is not understood completely. The stressed or failing cardiomyocyte signals to fibroblasts and other cells within the matrix through release of factors such as connective

tissue growth factor (CTGF) and transforming growth factor β (TGFβ).[59] TGFβ can stimulate endothelial-mesenchymal transition to form new fibroblasts.[60] However, fibroblasts also signal to the myocyte in the reverse direction.[18] Paracrine secretion of IGF1 from fibroblasts to myocytes contributes to adaptive hypertrophy during haemodynamic overload in mice.[61] Likewise, signalling with mammalian sterile 20-like kinase 1 (MST1 [also known as STK4]) within fibroblasts inhibits release of tumour necrosis factor α (TNFα) and is protective through this mechanism.[62] Inflammatory cell influx within the myocardium also has a role in remodelling, not only after myocardial infarction or in myocarditis but also in the haemodynamically overloaded heart.[63] Attraction of inflammatory cells could be stimulated by programmed myocyte necrosis within the heart; during this process, damage-associated molecular patterns (DAMPs) are released from the cytosol that can provoke an inflammatory response by activation of the innate immune system.[64,65] Although trials of targeted anticytokine approaches in chronic heart failure have been unsuccessful,[66] deciphering the complexity of innate immune signalling,[67] and paracrine cross-talk among the different cell types within the myocardium, could yet lead to novel treatments that specifically target the fibroblast or inflammatory cell.

Gaps in understanding

Progress made in basic cardiovascular science over the past decade has strikingly increased the number of possible therapeutic targets for treatment of chronic heart failure. However, with the exception of the bradycardic agent ivabradine,[68] this proliferation of targets has not led to development of new drugs for heart failure with depressed ejection fraction. Moreover, no effective agents are available for acute decompensated heart failure and no treatments exist for patients with heart failure with preserved ejection fraction, despite extensive efforts in these areas. What issues should be considered so we can close the widening gap between target discovery and viable heart failure treatments?

Target identification

At present, treatments for chronic heart failure target cell-surface receptors or intracellular mineralocorticoid receptors. Although this reductionist approach has worked well to identify antagonists of the adrenergic and renin-angiotensin-aldosterone systems, it has not worked well for other systems (eg, endothelin, adenosine, tumour necrosis factor). New approaches designed to modulate gene networks (eg, antagonists of miRs) or specific intracellular signalling pathways (eg, kinase inhibitors) have the potential to expand on existing therapeutic strategies.

Classically, identification of new therapeutic targets was focused on prevention of chronic heart failure after cardiac injury rather than reversal of this phenotype. Although this approach is relevant to target development for treatments for acute myocardial infarction, it might work less well for effects on disease pathogenesis once chronic heart failure is fully established. Indeed, one of the many lessons gleaned from trials of chronic heart failure is that treatments that reverse the heart-failure phenotype (ie, myocardial recovery) are accompanied by improved outcomes in patients.[69] In view of how little we know about the biology of myocardial recovery at the gene, cell, and organ level, this opportunity is important for discovery and potential target development.

Methodological issues

The clinical syndrome of chronic heart failure includes changes in gene expression in the cardiac myocyte, quantitative and qualitative changes in cell types and composition of the extracellular matrix, and changes in geometry of the left ventricle that evolve over years. Therefore, development of experimental systems that model clinical chronic heart failure accurately has been challenging. Indeed, treatments such as β blockers were developed largely on the basis of observations from small clinical studies. We need to focus attention on methodological gaps in our approach to studying the pathobiology of heart failure. No model system has superiority over another, they are complementary.

Cardiomyocyte culture systems provide high-throughput means for identification and validation of potentially important signal transduction pathways. However, the limitations of extant neonatal and adult cell-culture models to identify relevant pathways in human chronic heart failure are well recognised. The ability to derive human cardiomyocytes from induced pluripotent stem cells (eg, from skin fibroblasts) could help to overcome some of these limitations and enable patient-specific studies.[70,71]

Mouse models to study left-ventricular structure and function in vivo after targeted genetic manipulation of various pathways have been important in advancing the area of research,[72] although findings of such studies can be ambiguous.[73] Moreover, aspects of physiology in mouse models (eg, Ca^{2+} handling) differ substantially from those in human beings.[72] Thus, targets that are identified in mouse models might not necessarily be germane to human physiology and will need to be validated in large animal models or patients. Furthermore, investigators typically use mouse strains and models of injury (eg, acute severe pressure overload) that develop the most overt heart-failure phenotype. How closely does this choice mimic the human remodelling response? Could this inherent experimental bias lead to false-positive target identification?

The physiology of large animal models more closely resembles that of human beings, and various injury models recapitulate the heart-failure phenotype.[74] However, although some models have high predictive accuracy in clinical trials,[75] no animal model predicts outcomes in phase 3 studies reliably. An obvious reason is that studies in large animal models undertaken over

several months focus largely on safety and potential efficacy with respect to outcomes such as prevention of remodelling, whereas human studies of chronic heart failure are done over many years and focus on hard endpoints such as death or admission for heart failure, which are difficult to study in large animal models. Renewed emphasis on integrative physiology in many universities could help to better inform the training of doctors who wish to engage in translational research and use several complementary models to this end.

New approaches to discovery

Research into the basic mechanisms of development and progression of heart failure has highlighted the great complexity of molecular and cellular interactions that govern the process of cardiac remodeling and reverse remodelling.[2,69] Unfortunately, clinical trial data have afforded only limited understanding of mechanisms that underlie myocardial recovery. Future therapeutic advances will require a more comprehensive understanding and analysis of the pathobiology of heart failure and the complex interactions that entail myocardial recovery. The emerging area of systems biology could allow investigators to accelerate the pace of novel target identification and potentially improve the likelihood of success in clinical trials (figure 4A). By contrast with reductionist experimental approaches, with which researchers aim to establish causal associations between distinct molecular or cellular entities and phenotypes, investigators use systems biology to attempt to understand how the interactions of several components of the cell (ie, genome, transcriptome, proteome, metabolome) govern its function. Systems biology uses so-called network theory to describe how inter-relations between genes, proteins, and metabolites lead to functional changes at the level of the cell, tissue, and organ. Networks are presented conceptually as a series of circles (termed nodes)—which represent a gene, protein, or metabolite—that are connected to each other by lines (termed edges); these edges represent the interaction (activation or suppression) between the nodes of interest (figure 4B). Although most nodes in a network have very few edges, some nodes (termed hubs) have many, suggesting that they potentially have a role in vital regulatory processes (figure 4C). Our understanding of how these networks and hubs are modulated in heart failure (eg, rewiring) and how they are affected by existing heart failure treatments is embryonic at present, but is beginning to be studied.[77–80] Such approaches have revealed specific cellular interactions that would not necessarily be obvious or predicted from extant published work (eg, ST2).[81] Moreover, network modelling allows for pathways to be identified that are not targeted by existing treatments but that might be synergistic with such pathways, which is potentially valuable since new therapeutic agents will probably have to be added to existing treatments in clinical trials. Furthermore, with network modelling, changes within the components of the network can be looked at in relation to alterations in cell phenotype (phenomics) or function after a given therapeutic intervention. Targeting of cellular function as a system, rather than as one target within the biological system, might increase the chances of progression from novel basic advances to viable treatments.

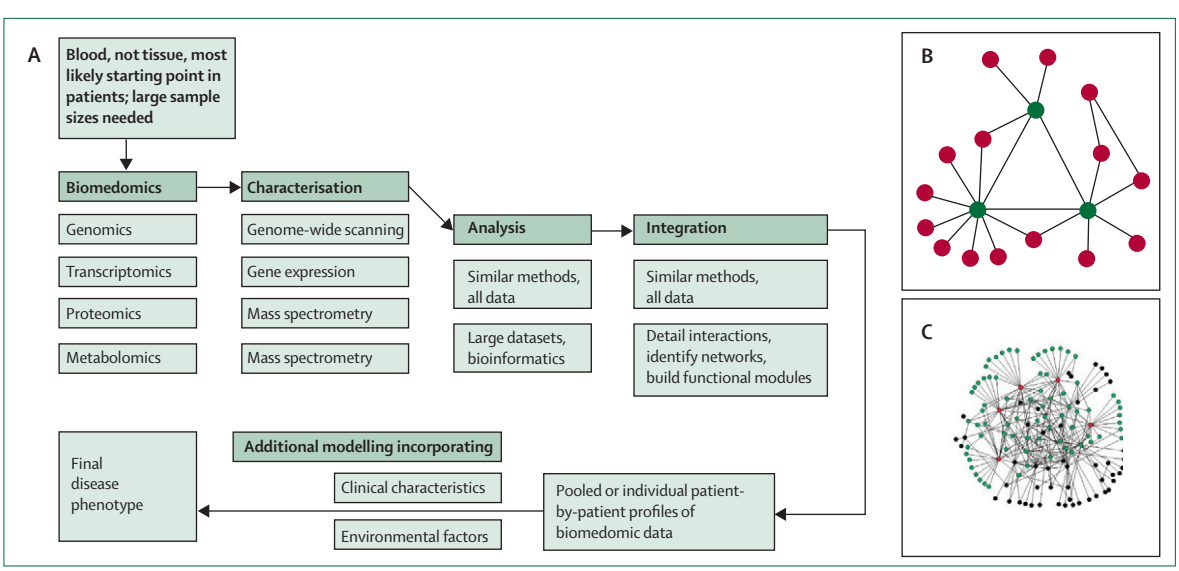

Figure 4: **Application of a systems biology approach**

(A) Systems biology entails a series of steps, beginning traditionally with advanced characterisation of genomic, transcriptomic, proteomic, and metabolomic datasets, which are then analysed by various bioinformatic approaches. Systems biology places emphasis on definition of interactions, delineating networks linking proteins, genes, or metabolites and describing functional units or sets to provide testable mechanistic models of clinical phenotypes. (B) A simple, scale-free, gene network, composed of nodes (depicted by circles) with many edges (depicted by lines) that represent the interaction between nodes. (C) A complex scale-free network, with most nodes having one or two edges and a few nodes (shown in red) having many (termed hubs). This high degree of connectivity guarantees that the system is fully connected. Adapted from reference 76, with permission of Springer Science+Business Media.

Although systems biology has not yet been applied broadly for development of new treatments for heart failure, the approach has been successful in oncology.[82,83] Further advances in systems biology for heart failure will need continued development of methods to obtain high-fidelity and comprehensive datasets (eg, new sequencing technologies), to analyse high-dimensional data sources, to annotate interactions, and to develop interactive platforms that facilitate layering of different types of datasets (eg, for transcriptomics and proteomics) or data obtained from alternative model systems. Indeed, analysis of combined transcriptomic and proteomic screens in animal models and samples of non-failing and failing human hearts has shown changes in gene transcription and mRNA stability that happen in concert with changes in post-translational modification of proteins (eg, nitrosylation, acetylation) and protein translocation.[84] By defining all biological components of the potential disease-causing pathway, systems biology approaches might allow investigators to focus on the most appropriate regions of the pathway to develop effective therapeutic agents, with fewer off-target effects. Implementation of a systems biology approach will probably be challenging both for economic reasons and with respect to the multidisciplinary skill sets that are needed, but it will prove ultimately to be priceless if these modern biological approaches facilitate new treatments for heart failure.

Contributors

AMS and DLM wrote the review and approved the final version.

Conflicts of interest

DLM is a member of the scientific advisory board of miRagen. AMS has no conflicts of interest.

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Heart Failure 2

Medical therapy for chronic heart failure

Henry Krum, John R Teerlink

Understanding of contemporary pharmacological therapy for chronic heart failure continues to evolve. In this Review, we discuss how findings from clinical trials have caused the roles of old therapies to be expanded and past treatment algorithms to be challenged. Several trials investigating preserved ejection fraction as a measure of heart failure had disappointing results, although important studies are in progress. Many novel therapeutic approaches for heart failure have emerged and are discussed in this review. The pharmacological treatments for heart failure continue to change, with many exciting possibilities for the future.

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This is the second in a **Series** of four papers about heart failure

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Introduction

In the past 40 years, pharmacological therapy for chronic heart failure has rapidly expanded beyond diuretics and digoxin with the serial addition of hydralazine and isosorbide dinitrate, angiotensin-converting enzyme (ACE) inhibitors, β blockers, mineralocorticoid-receptor antagonists, and angiotensin-receptor blockers. The role of early standard therapies, diuretics and digoxin, has changed as new approaches have developed; similarly, contemporary medical therapy for heart failure is evolving. We discuss the controversies that have been incited by emerging data and assess the development of drugs for both heart failure with reduced left ventricular ejection fraction and heart failure with preserved ejection fraction. Additionally, we briefly describe new therapies that extend or address new approaches.

Drug therapy of systolic heart failure

New data for existing agents

Neurohormonal antagonists are key to pharmacological management of patients with impaired ventricular systolic function and symptoms of heart failure. Agents that block the renin-angiotensin-aldosterone system and sympathetic nervous system have substantially improved morbidity and mortality rates in these patients.[1,2] This benefit has been established in adequately sized trials[2] that assess the effects of these drugs on major clinical outcomes. Nevertheless, rates of morbidity and mortality are still high in patients with heart failure. Additionally, some aspects of the use of these drugs for such patients are still controversial and data gaps remain. New studies have shown how to optimise treatment with existing therapies and have also supported the addition of novel drugs that might act independently of neurohormonal blocking systems.

Guidelines have long supported the use of mineralocorticoid-receptor antagonists in systolic heart failure. However, these recommendations have been restricted to the patient populations that have benefited in clinical trials—eg, patients with advanced New York Heart Association (NYHA) class III–IV heart failure in the RALES study with spironolactone[3] and those with left ventricular systolic dysfunction and heart failure symptoms after myocardial infarction (MI) in the EPHESUS study with eplerenone.[4] Therefore, no recommendations existed for patients with mild symptoms of heart failure (NYHA class II) and left ventricular systolic dysfunction remote from an MI. This gap has now been filled with findings from the EMPHASIS-HF study.[5] In this report, the selective mineralocorticoid-receptor antagonist eplerenone significantly reduced cardiovascular death and admission to hospital for heart failure (the study's primary endpoint) and all-cause mortality (a pre-specified secondary endpoint of the study) for patients with mild symptoms (figure 1). These findings are noteworthy because patients were also being well treated with conventional background neurohormonal blocking agents. However, eplerenone produced anticipated (but manageable) side-effects, such as hyperkalaemia, hypotension, and worsened renal function.

Accordingly, 2011 guideline updates[6,7] have recommended eplerenone for systolic heart failure patients who have NYHA class II symptoms despite receiving standard background therapy. Whether the mineralocorticoid-receptor antagonist spironolactone can also be recommended for such patients is uncertain, because it was not specifically studied in EMPHASIS-HF.[5] Spironolactone could be considered in this setting because it is less expensive and more widely available than eplerenone, and is effective across disease severities.

Novel strategies independent of and additional to neurohormonal blockade can provide clinical benefit. One such approach involves the use of marine-based

Search strategy and selection criteria

We searched the Cochrane Library, Medline, and Embase databases, with the search term "heart failure" in combination with the term "drug therapy", and limited the results to include only adult populations, when available. We largely selected publications in the past 3 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified by this search strategy, and presentations from major international cardiology and heart failure scientific sessions and selected those that we judged relevant. Review articles and book chapters are cited to provide readers with more details and references than this review has room for. Our reference list was modified on the basis of comments from peer reviewers.

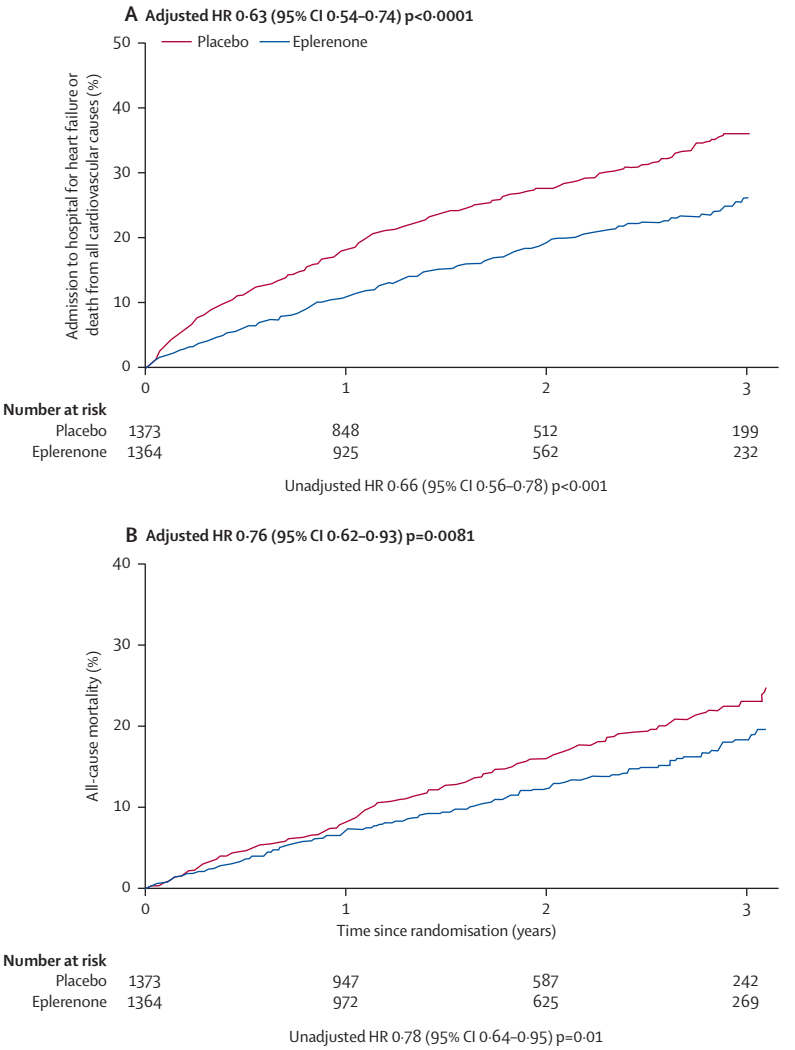

Figure 1: **Kaplan-Meier curves for time to admission to hospital for heart failure or death from all cardiovascular causes (A) and all-cause death (B)**

The primary outcome occurred in 18·3% patients in the eplerenone group compared with 25·9% in the placebo group. A total of 12·5% patients receiving eplerenone and 15·5% of those receiving placebo died; 10·8% given eplerenone and 13·5% given placebo died of cardiovascular causes (HR 0·76 [95% CI 0·61–0·94] p=0·01). HR was adjusted for confounding factors. HR=hazard ratio. Reproduced from Zannad and colleagues,[5] by permission of the Massachusetts Medical Society.

polyunsaturated fatty acids, which have several mechanistic effects (eg, potent anti-inflammatory actions) that seem to be favourable in chronic heart failure.[8] The GISSI-HF investigators[9] reported an improvement in clinical outcomes of borderline significance with n-3 polyunsaturated fatty acids versus placebo in patients with predominantly systolic heart failure, but noted no therapeutic benefit with a statin-based approach. No significant all-cause mortality benefit was recorded, but deaths and cardiovascular hospitalisations did decrease (figure 2), and patients had very few side-effects.

Iron deficiency is quite frequent in patients with systolic heart failure, usually (but not exclusively) associated with concomitant anaemia.[10] A study in such patients (FAIR-HF)[11] showed improvements in symptoms, exercise capacity, and quality of life with intravenous ferric carboxymaltose (figure 3). However, in view of the small size of this trial, its short duration, and its soft endpoints, further study—such as an adequately sized, definitive outcome trial—is necessary. Nevertheless, the symptomatic benefits recorded with intravenous ferric carboxymaltose in an iron-deficient population suggest that the use of iron replacement therapy could be rational and beneficial. A study of anaemia correction with an erythropoiesis-simulating agent (eg, darbepoetin-alpha) is also in progress (the RED-HF trial; NCT00358215), and the outcomes are eagerly awaited.

Doses

Which dosing strategies should be used to maximise the therapeutic benefit of existing agents remains somewhat controversial. Published data of ACE inhibitors in systolic heart failure suggest that the dose-response curve for benefit is not very steep, at least at the doses used in everyday clinical practice. Specifically, the ATLAS study[12] compared daily doses of 2·5–5·0 mg lisinopril with 32·5–35 mg and showed a borderline improvement in the combined morbidity and mortality endpoint, but no benefit for all-cause mortality (the primary endpoint) at the high dose despite the large difference in daily doses. Similarly, investigators of the NETWORK study[13] noted that doses of 2·5 mg, 5·0 mg, and 10·0 mg of enalapril twice a day had no substantial effect on major clinical outcomes over 24 weeks.

With regards to angiotensin-receptor blockers, investigators of the HEAAL study[14] noted a small but significant difference between daily doses of 150 mg versus 50 mg losartan in patients with systolic heart failure intolerant to ACE inhibitors. The disadvantage of high doses was an excess of expected adverse events. The population assessed in HEAAL[14] might differ from the general heart-failure population in many respects, so the study findings should not necessarily be extrapolated. Nevertheless, these data lend support to the general notion that patients should be uptitrated to the highest tolerated dose of angiotensin-receptor blockers, with the aim of target doses used in major trials. This recommendation also applies to ACE inhibitors.

A similar controversy concerns the optimum dose of β blockers to maximise clinical benefit. Generally, recommendations state that patients should be uptitrated to the target dose as used in the major clinical outcome trials and recommended by guidelines. However, many patients cannot reach these target doses because of hypotension, bradycardia, and other dose-limiting adverse events. Very few prospective dose-ranging studies have been done to formally test the hypothesis that high doses are better than low ones. Post-hoc analyses of high versus low achieved dose in studies in which patients were not prospectively randomised to different doses are

methodologically flawed and unable to adequately address this question. Findings from the MOCHA prospective study[15] did show a greater therapeutic benefit at high doses, but the absolute number of events was small.

However, heart rates recorded in patients given ivabradine, which blocks the channel involved in the hyperpolarisation-activated, cyclic-nucleotide-gated *funny* current (I_f-channel), suggest that heart rate might be a more effective guide to maximise therapeutic benefit than might titrations of all patients to identical target doses.[16,17] Several mechanistic explanations have been proposed for why use of β blockers guided by heart rate might provide large benefits. For example, β_1-adrenoceptor polymorphisms might lead to some patients being more sensitive than others to the blockade of the cardiac β_1-adrenoceptor.[18] In the BEST study,[19] a large difference in clinical outcomes was recorded with bucindolol according to the presence or absence of a specific β_1-adrenoceptor polymorphism (Arg-389 *vs* Gly-389). Further trials of heart-rate guided therapy are needed to address this issue, either to achieve a target reduction in heart rate or an absolute heart-rate target versus patients randomly assigned to a target dose. However, evidence from thousands of patients in randomised controlled trials currently supports the titration of β blockers to the highest tolerated dose.

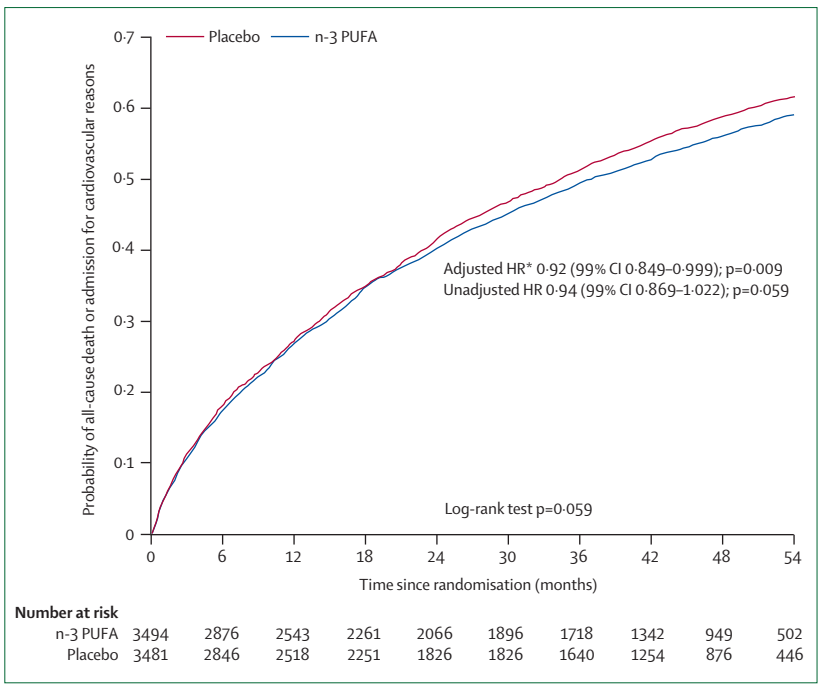

***Figure 2*: Kaplan-Meier curves for time to all-cause death or admission to hospital for cardiovascular reasons**
PUFA=polyunsaturated fatty acids. HR=hazard ratio. *Estimates were calculated with a Cox proportional hazards model, with adjustment for admission to hospital for heart failure in the previous year, previous pacemaker, and aortic stenosis. Reproduced from GISSI-HF investigators,[9] by permission of Elsevier.

Order of therapy

In what order should conventional agents be introduced in the management of patients with systolic chronic heart failure? It is not disputed that all new patients with systolic chronic heart failure should receive diuretics to achieve and maintain euvolaemia, and then ACE inhibitors (or angiotensin-receptor blockers if ACE-intolerant) and β blockers. Furthermore, these agents should be introduced as quickly and safely as possible to maximise clinical benefit. Because ACE inhibitors were established as a beneficial therapy for heart failure before the introduction of β blockers, the usual sequence has been to introduce an ACE inhibitor first and then a β blocker. Patients in the CIBIS III study[20] were initially given either class of agent as monotherapy and then both were given at 6 months to assess long-term outcomes with combined therapy. Overall, initial use of ACE inhibitors or β blockers made very little difference to major cardiovascular outcomes, although the study generated few endpoints in the initial 6 months. Nonetheless, the order of beneficial heart-failure drugs seems to have changed little even after CIBIS III.

Further controversy exists about what the next agent should be for patients with systolic left ventricular dysfunction who remain symptomatic after having been established on a regimen of diuretics, ACE inhibitors, and β blockers. From a pharmacological viewpoint, the options are mineralocorticoid-receptor antagonists, angiotensin-receptor blockers, hydralazine and nitrates, and digoxin. Investigators of the CHARM-Added[21] and Val-HeFT[22] studies reported a benefit in morbidity and mortality—but not mortality alone—with the angiotensin-receptor blockers candesartan and valsartan, respectively, in patients receiving background ACE inhibitors and β blockers (when tolerated). However the use of angiotensin-receptor blockers and ACE inhibitors together in everyday practice is not common, perhaps because of concerns that any clinical benefit might be outweighed by increases in adverse effects.[23] These concerns could be attributable to the anticipation of a higher adverse event profile, and because a stand-alone mortality benefit was not detected in the CHARM-Added[21] or Val-HeFT[22] studies. Conversely, data for mineralocorticoid-receptor antagonists (spironolactone in patients with NYHA class III–IV disease in RALES[3] and eplerenone in class II disease in EMPHASIS-HF[5]) show a mortality benefit with aldosterone blockade. Because the adverse-event profiles of mineralocorticoid-receptor antagonists and angiotensin-receptor blockers do not seem to differ substantially, mineralocorticoid-receptor antagonists should be the preferred option when another renin-angiotensin-aldosterone system blocker is added for patients who remain symptomatic despite ACE inhibitors and β blockers. Of the other established agents, the beneficial effects of hydralazine and nitrates have been largely confined to African-American patients who generally are in a low renin state generally and do not respond as well as do white patients to ACE inhibition or angiotensin-receptor blockade.[24] Digoxin is typically reserved for symptom relief and to reduce admission for patients with

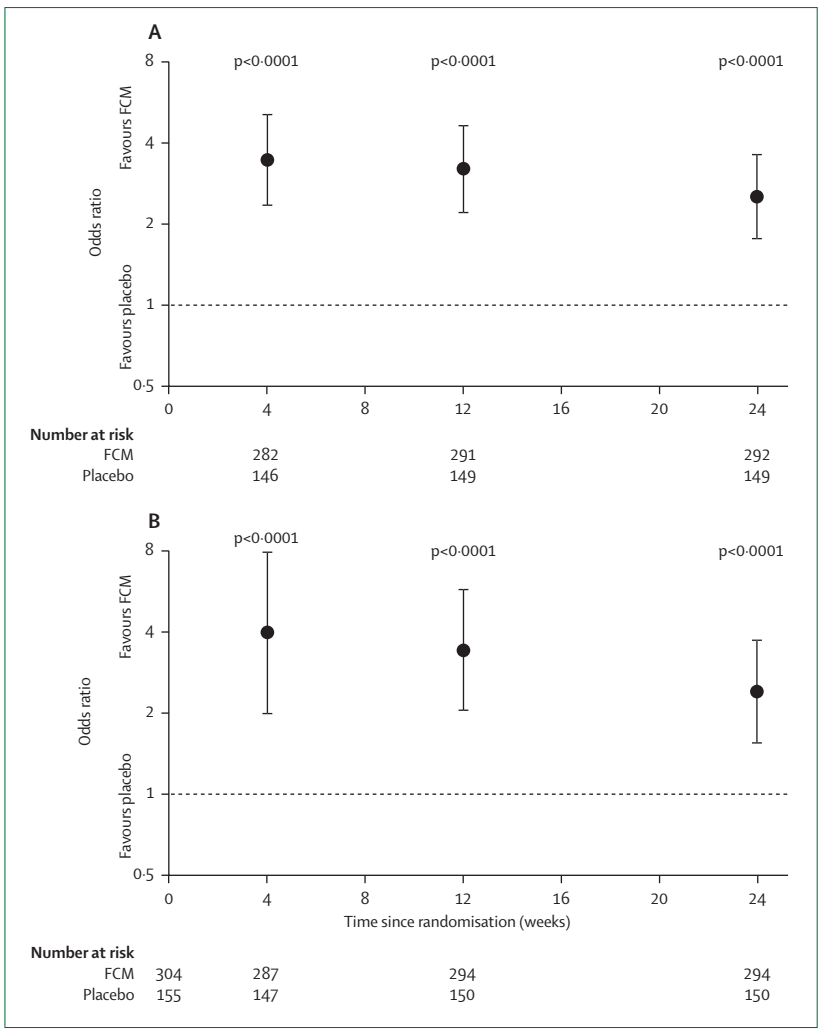

Figure 3: **Odds ratios for main secondary outcomes during the FAIR-HF study, according to assigned study treatment**

Odds ratios of a better Patient Global Assessment category (A) or NYHA functional class (B) for the FCM group compared with the placebo group. In both panels, the last available assessment was used for data on the self-reported Patient Global Assessment that were missing for patients known to be alive and not in the hospital at each timepoint. Patients who were admitted at each timepoint were given an assessment of much worse (in A) or an NYHA class of IV (in B). Patients who died before week 24 were categorised as dead (in B; NYHA class V). Data were not included for patients who were known to be alive at the timepoint but for whom no previous data was available. (A) Odds ratios at week 4 are 3·44 (95% CI 2·34–5·07) and at week 12 are 3·19 (2·20—4·63). (B) Odds ratios at week 4 are 3·96 (1·98–7·93) and at week 12 are 3·42 (2·04–5·72). FCM=ferric carboxymaltose treatment. NYHA=New York Heart Association. Reproduced from Anker and colleagues,[11] by permission of the Massachusetts Medical Society.

systolic heart failure and sinus rhythm.[25] The benefit of digoxin in ventricular-rate control in patients with systolic heart failure and atrial fibrillation is well established; however, their use has become less of a clinical issue over time with the introduction of β blockers.

Pharmacological treatment of heart failure with preserved ejection fraction

Whether heart failure with preserved ejection fraction represents a continuum of molecular, cellular, and histochemical derangements compared with heart failure with reduced ejection fraction has been debated. However, the condition is now accepted as a disease entity in its own right, and is affected by concomitant disorders such as hypertension, obesity, and diabetes.[26] Despite improved understanding of the pathophysiology of this disorder, pharmacological treatment (in addition to active management of comorbid factors) has thus far proven disappointing. Specifically, trials of agents that have seemed successful in heart failure with reduced ejection fraction have not been effective in heart failure with preserved ejection fraction, even though these drugs target neurohormonal systems that seem to be relevant to the disease processes of both disorders.[27–29]

ACE inhibitors and angiotensin-receptor blockers have been well studied in heart failure with preserved ejection fraction. The Perindopril Evaluation Program (PEP)[27] showed early beneficial effects of perindopril versus placebo on major clinical endpoints at 1 year. However, any treatment effect that might have existed was diluted by slow recruitment and high rates of drop in and drop out to active treatment, and the overall result was neutral. Two studies have comprehensively assessed the role of angiotensin-receptor blockers in the heart failure with preserved ejection fraction setting. First, the CHARM-Preserved study[28] reported that candesartan did not significantly reduce the primary endpoint of cardiovascular death or admission for heart failure compared with placebo. That trial has been criticised because of the rather loose definition of heart failure with preserved ejection fraction as an ejection fraction of more than 40% and minimal requirement to show impaired diastolic relaxation based on objective criteria, such as echocardiogram. This definition could have allowed inclusion of patients who had systolic heart failure but had improved their ejection fraction by use of ACE inhibitors and β blockers. The second major outcome study, I-PRESERVE,[29] showed a completely neutral result with irbesartan versus placebo. This study had a much tighter definition of preserved ejection fraction than did CHARM-Preserved. A meta-analysis[30] of these trials summarises the effect of blockade of the renin-angiotensin-aldosterone system in patients with heart failure with preserved ejection fraction (figure 4). Why a strategy to block the actions of angiotensin II would be unsuccessful in patients with heart failure with preserved ejection fraction is unclear, in view of the importance of chronic activation of the renin-angiotensin-aldosterone system in many of the underlying processes that characterise the disorder.

Blockade of the sympathetic nervous system has been assessed in patients with heart failure with preserved ejection fraction, but far less rigorously than for blockade of the renin-angiotensin-aldosterone system. The largest such investigation was the SENIORS study,[31] in which roughly a third of the patients enrolled were classified into a preserved ejection fraction category, but admission to hospital was necessary to meet entry criteria. In that study, the overall reduction in death and cardiovascular admission reported with the β blocker nebivolol versus

placebo was of similar magnitude to that noted for the true impaired systolic function population of that study. Nevertheless, preserved systolic function had no significant effect on the primary endpoint, which leaves the issue of β blockers in heart failure with preserved ejection fraction unresolved. Furthermore, patients with a left ventricular ejection fraction of 36% and above would certainly not represent a so-called pure population with heart failure with preserved ejection fraction. The remaining issues are being addressed in a large-scale (n=1200) trial[32] of patients with heart failure with preserved ejection fraction (left ventricular ejection fraction >50%) that compares metoprolol succinate with control.

Perhaps the most promising of the drug therapies for heart failure with preserved ejection fraction are mineralocorticoid-receptor antagonists. Aldosterone is a potent profibrotic factor, and fibrosis is a key pathophysiological feature of the disorder. A major outcome trial sponsored by the US National Institutes of Health (TOPCAT; NCT00094302) is assessing spironolactone versus placebo in a well delineated population with heart failure with preserved ejection fraction.

By contrast with heart failure with reduced ejection fraction for which statins have no benefit,[33,34] findings from a small observational study[35] have suggested a remodelling and symptomatic benefit in patients with heart failure with preserved ejection fraction given these agents. The underlying mechanism as to why statins would be beneficial for one form of heart failure and not another is unclear. Furthermore, a large-scale statin trial of heart failure with preserved ejection fraction is unlikely to be undertaken to definitively resolve this issue.

It is interesting to speculate why neurohormonal blocking agents, which have proved successful in heart failure with reduced ejection fraction, have been largely unsuccessful in patients with preserved ejection fraction. The most likely explanation is the heterogeneity of the patient populations being studied under the general descriptor of heart failure with preserved ejection fraction. Specifically, participants could be included who have hypertension and some degree of left ventricular hypertrophy and who might have symptoms that could overlap with that of heart failure but without a phenotype more amenable to blockade of the renin-angiotensin-aldosterone or sympathetic systems than can be achieved with lowering of blood pressure alone. However, this notion is somewhat speculative and the reasons for the poor success of drug therapies in heart failure with preserved ejection fraction are elusive.

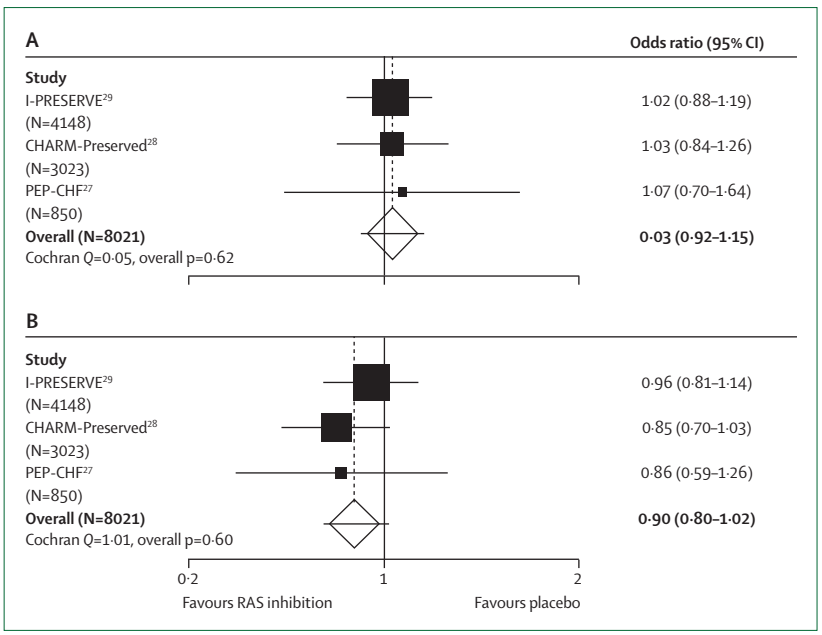

Figure 4: **All-cause mortality (A) and admission to hospital for heart failure (B) in randomised controlled trials of inhibition of the renin-angiotensin-aldosterone system in heart failure with preserved ejection fraction**
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New directions in heart-failure therapy

Neurohormonal blockade

The effect of neurohormonal blockade on the treatment of heart failure has been profound. Pharmacological challenges delayed the development of orally bioavailable renin inhibitors, despite renin's primary role in the renin-angiotensin-aldosterone system. The ALOFT study[36] investigated the effects of addition of an oral, direct renin inhibitor to an ACE inhibitor in 302 patients with chronic heart failure.[36] Aliskiren treatment significantly lowered concentrations of NT-proBNP compared with patients given placebo, and had further beneficial neurohormonal effects—eg, reduction of urinary aldosterone excretion, suggesting an additional benefit to ACE inhibition. However, investigators of ASPIRE[37] enrolled 820 patients within 2–8 weeks of myocardial infarction with left ventricular dysfunction, and reported no benefit of 26–36 weeks of aliskiren treatment on measures of left ventricular remodelling or clinical outcomes compared with standard therapy.

ASTRONAUT[38] is an event-driven trial with a planned enrolment of 1782 patients admitted to hospital with deteriorating chronic heart failure, a left ventricular ejection fraction less than or equal to 40%, and an estimated glomerular filtration rate greater than or equal to 40 mL/min per 1·73 m². After initial therapy for acute decompensated heart failure, patients were randomly assigned to receive either placebo or aliskiren in addition to standard therapy and will be followed up until at least 381 cardiovascular deaths or heart-failure admissions have occurred within 6 months. Researchers in the ATMOSPHERE study[39] are randomly assigning about 7000 patients to receive either aliskiren or enalapril, or the combination, and will assess the combined endpoint of cardiovascular death or admission for heart failure. Findings of the study will help to establish whether aliskiren should replace or be added to ACE inhibitors in patients with chronic heart failure.

Other development programmes have sought to augment antagonism of the renin-angiotensin-aldosterone system with inhibition of other pathways. This strategy was initially tested in a large clinical trial of omapatrilat—a vasopeptidase inhibitor that blocks three enzymes (ACE, aminopeptidase P, and neprilysin)—which suggested a possible clinical benefit in patients with heart failure compared with enalapril.[40] However, omapatrilat caused angio-oedema, probably because of reduced breakdown of bradykinin, which effectively ended the programme. LCZ696 is one of a new class of agents known as angiotensin receptor-neprilysin inhibitors (ARNI), which combines a moiety of valsartan (an angiotensin-receptor blocker) with the neutral endopeptidase inhibitor prodrug AHU377 into one molecule.[41] Neprilysin inhibitors decrease the degradation of natriuretic peptides and might increase their vasodilatory, natriuretic, and other beneficial effects, but do not seem to substantially affect bradykinin. A study[42] of LCZ696 in 1328 patients with hypertension reported no significant reductions in blood pressure compared with similar doses of valsartan, and no episodes of angio-oedema. This safety experience has provided the basis for the PARADIGM-HF trial (NCT01035255), which plans to assess the effect of LCZ696 compared with enalapril in nearly 8000 patients on the combined endpoint of cardiovascular death or admission for heart failure.

Another neurohormone that is closely related to the renin-angiotensin-aldosterone system is vasopressin. Early clinical trials with tolvaptan, a vasopressin V_2-receptor antagonist, noted encouraging early effects on volume loss and clinical outcomes.[43] The EVEREST study[44,45] enrolled more than 4000 patients admitted for heart failure; patients given tolvaptan for at least 60 days had decreased bodyweight and improvement in many signs and symptoms of heart failure compared with controls,[44] but there was no beneficial effect on death, cardiovascular mortality, or heart-failure admissions.[45]

Another unique approach to neurohormonal blockade is to develop therapies that extend the usefulness of available agents. Hyperkalaemia frequently limits the administration of antagonists of the renin-angiotensin-aldosterone system in patients with heart failure. Treatments for hyperkalaemia, such as sodium polystyrene sulfonate, are difficult to use chronically and can increase total body sodium concentrations. RLY5016—a non-absorbed, orally administered, potassium-binding polymer—seems to cause minimal gastric distress and does not exchange sodium for potassium. In the PEARL-HF study,[46] 105 patients with heart failure and a history of hyperkalaemia resulting in discontinuation of an inhibitor or blocker of the renin-angiotensin-aldosterone system, or a β-adrenergic blocking agent, or those with chronic kidney disease and an estimated glomerular filtration rate of less than 60 mL/min were randomly assigned to double-blind treatment with RLY5016 or placebo for 4 weeks. Patients given RLY5016 had lower serum potassium and a lower incidence of hyperkalaemia than did those given placebo, and a higher proportion were receiving the target spironolactone dose. However, these benefits were at the expense of an increased rate of hypokalaemia and hypomagnesaemia, both of which can promote arrhythmias and sudden death, which suggests that the net effect of this therapy on clinical outcomes should be assessed in larger trials.

Heart rate reduction

The success of β blockers in substantially reducing admissions to hospital and improving survival has led to many discussions about their potential mechanism. Some have postulated that at least part of this benefit is the direct result of heart rate reduction. Ivabradine is a selective inhibitor of the I_f-current that is involved in pacemaking-generation and responsiveness of the sinoatrial node, and results in heart rate reduction with no other apparent direct cardiovascular effects.[47] The SHIFT investigators[16] studied the effects of ivabradine in patients with chronic heart failure, NYHA class II–III symptoms despite optimum and stable medical therapy, an admission for heart failure in the previous 12 months, and sinus rhythm with a heart rate of at least 70 beats per min. Ivabradine treatment significantly reduced the primary endpoint of cardiovascular death or hospital admission for worsening heart failure, mainly driven by decreased heart-failure admissions. The investigators noted no significant reductions in all-cause or cardiovascular mortality, although a reduction in deaths related to heart failure was suggested. There was a diminishing benefit of ivabradine in patients with lower baseline heart rates (<77 beats per min) and higher β-blocker doses, but the data for the effect of the drug in the 26% of patients who were receiving full-dose β blockers in SHIFT have yet to be presented. An accompanying analysis[17] suggested that most of the beneficial effect of ivabradine in SHIFT was accounted for by heart-rate reduction. The absence of evidence that shows ivabradine improves mortality is a concern in view of consistent reductions in mortality in the β-blocker trials (figure 5), including one that compared two β blockers.[54] Whether this novel strategy to slow heart rates truly provides additional benefit to full-dose β blockers is unknown.[55]

Positive inotropes: can we develop safe chronic oral agents?

An increase in the performance of the heart should attenuate the underlying cause, subsequent neurohormonal activation, and adverse ventricular remodelling that result in progressive heart failure. However, multiple oral formulations of β-adrenergic receptor agonists (eg, xamoterol[56]) and phosphodiesterase inhibitors (eg milrinone,[57] enoximone[58,59]) have had poor clinical outcomes or no meaningful clinical benefit in trials. Almost all these agents have depended on mechanisms that increased myocardial intracellular

calcium, potentially causing increased ischaemia, arrhythmias, and death. However, several new, oral approaches to inotropy in chronic heart failure are in clinical development.[60]

Levosimendan, an inodilating agent with many mechanisms of action (such as calcium sensitisation, K^+-ATP channel activation, and possibly phosphodiesterase inhibition) has been studied in several acute-heart-failure trials as an intravenous formulation.[61,62] These investigations showed favourable haemodynamic and clinical effects, although some noted an increased incidence of atrial and ventricular arrhythmias, and possibly early mortality.[61,62] Nieminen and co-workers[63] randomly assigned 307 patients with chronic NYHA class IIIB–IV heart failure to one of two doses of oral levosimendan or placebo and followed them up for at least 180 days of treatment. They noted improvements in NT-proBNP and some quality-of-life measures, but not for the exploratory primary endpoint of the patient journey, measured by repeated symptom assessments, worsening heart failure events, and mortality in 60 days. Additionally, the non-significant overall mortality of 11% in patients given levosimendan compared with 6% in those given placebo reinforces the imperative for large outcome trials if this agent is going to be considered for long-term oral therapy.

New non-glycoside agents that increase myocardial contractility via inhibition of the Na^+/K^+-ATPase, similar to the mechanism of digoxin, and stimulation of the sarcoplasmic reticulum calcium (SERCA2a) pump have emerged and are being investigated in clinical studies. The addition of SERCA2a pump activation can theoretically improve diastolic function and mitigate the potential adverse effects of increased intracellular calcium. Several trials have investigated intravenous istaroxime, including a study[64] of 120 patients admitted for acute heart failure that showed decreased pulmonary capillary wedge pressure and improved diastolic function with istaroxime treatment. The absence of hypotension and arrhythmias was reassuring. Development of oral agents with similar pharmacological properties is underway, and these luso-inotropic drugs could lead to a resurgence of interest in agents using this mechanism.

Cardiac myosin activators are a novel class of agents that directly modulate the actomyosin cross-bridge cycle.[65,66] The selective cardiac myosin activator, omecamtiv mecarbil, binds to the myosin catalytic domain, which increases the transition rate of myosin into the strongly actin-bound state that generates force, while inhibiting ATP turnover in the absence of actin. This mechanism results in more myosin heads generating force on actin with each beat. Studies of healthy volunteers[67] and of patients with chronic stable heart failure[68] have confirmed that omecamtiv mecarbil prolongs the duration of systole, which results in increased stroke volume and fractional shortening with decreased ventricular volumes.[69] Another study,[70] which combined intravenous and oral dosing in 94 patients with ischaemic cardiomyopathy and angina, showed no adverse effects of omecamtiv mecarbil. Further studies into intravenous omecamtiv mecarbil are underway, and the availability of highly bioavailable oral formulations suggests that this therapy could be suitable as a chronic oral therapy.

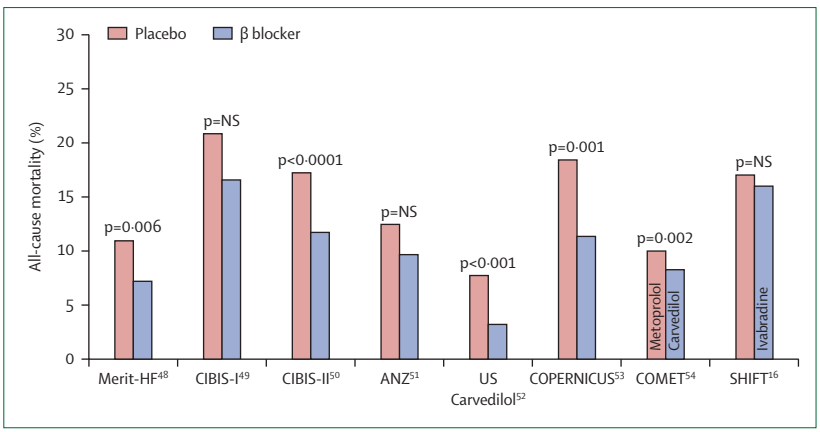

Figure 5: **All-cause mortality in selected chronic heart failure trials[16,48-54]**
Ivabradine is only drug without a demonstrated beneficial effect on mortality. NS=non-significant.

New vasodilators

Although related to phosphodiesterase-3 inhibitors (eg, milrinone, enoximone), phosphodiesterase-5A inhibitors (such as sildenafil) selectively decrease the hydrolysis of cGMP. cGMP has emerged as an important signalling molecule in heart failure, potentially having a role in myocardial dysfunction and pathological remodelling, as well as its more established role in pulmonary hypertension.[71] Findings from a series of small studies[72–74] showed that phosphodiesterase-5A inhibition improved exercise capacity, haemodynamics, and measures of quality of life in patients with heart failure. A 1-year study[75] of 45 patients with heart failure and reduced left ventricular systolic function (≤40%) randomly assigned to sildenafil or placebo confirmed the improved functional capacity in patients given sildenafil compared with placebo, but also suggested beneficial effects on left ventricular remodelling and diastolic function. These findings are encouraging for the future development of phosphodiesterase-5A inhibitors for heart failure caused by systolic dysfunction.[76] A trial in patients with diastolic dysfunction is currently enrolling (RELAX; NCT00763867).

Conclusions

Clinical trials have provided important guidance for how to maximise the benefits of established therapies in the treatment of patients with systolic chronic heart failure. Yet effective therapies for patients with heart failure with preserved ejection fraction are elusive. The emergence of several new treatment approaches provides encouragement that effective, clinically important therapies will be

added in the near future. However, advances in clinical trial design will need to accompany these developments. The era of the large trial enrolling all patients is most likely near its end, and future trials will need to more specifically target groups believed to derive the most benefit from novel therapeutics. Bayesian designs[77] and other newer methods[78] to make information available to guide the trial process and interpretation of results will need to be applied to better select patient populations, targeted either on the basis of their demographics, comorbidities, pathophysiology, genetics, or other factors.

Contributors

HK and JRT searched the available work; selected and designed figures; interpreted the results; and wrote, corrected, and modified the report.

Conflicts of interest

HK has received research grants from Amgen, Vifor, Novartis and Servier; and consulting fees from Novartis, Bayer and Amgen. JRT has received research grants from Amgen and Cytokinetics, Bristol-Myers Squibb, National Institutes of Health, and Novartis; and consulting fees from Amgen and Cytokinetics, and Novartis.

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Heart Failure 3

Implantable cardioverter defibrillators and cardiac resynchronisation therapy

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Implantable cardioverter defibrillators and cardiac resynchronisation therapy (CRT) have become standard of care in modern treatment for heart failure. Results from trials have provided ample evidence that CRT, in addition to its proven benefits in patients with symptomatic heart failure (New York Heart Association [NYHA] class III), might also reduce morbidity and mortality in those with mildly symptomatic heart failure (NYHA class II). As a result, the 2010 European Society of Cardiology guidelines now recommend CRT for both patient populations. In this review we summarise and critically assess the landmark randomised clinical trials REVERSE, MADIT-CRT, and RAFT. Furthermore, we discuss the rationale and available evidence for other emerging indications of CRT, including its use in patients with a mildly reduced left ventricular ejection fraction (>35%), in those with a narrow QRS complex (≤120 ms), and in those with concomitant bradyarrhythmic pacemaker indications. We also focus on patients who do not respond to CRT, and on CRT optimisation.

Introduction

Cardiac implantable electronic devices have revolutionised the treatment of patients with chronic heart failure. Implantable cardioverter defibrillators (ICDs) were introduced in the 1980s for patients at very high risk for sudden cardiac death as an experimental therapy in secondary prevention,[1] and are now regarded as standard therapy for patients at risk for sudden cardiac death for both secondary and primary prevention. Although ICDs reduce the risk for life-threatening arrhythmias, they have no effect on ventricular structure and function, and the underlying cardiomyopathy hence remains unchanged. By contrast, atrioventricular synchronised biventricular pacing, also referred to as cardiac resynchronisation therapy (CRT), was introduced in the early 1990s, and has since become standard of care for patients with heart failure in addition to optimum medical heart failure therapy (table 1).[2,3]

The rationale of CRT was originally based on the abnormal electrical activation frequently detected in patients with advanced heart failure.[4] These electrical abnormalities mainly consist of a lengthy PR interval and an increase in QRS duration, which in most cases is attributable to a left bundle branch block. Such conduction disturbances can induce important modifications of the heart at different levels, with regional alteration in protein expression, myocyte hypertrophy, apoptosis, and fibrosis, and alteration in the ventricular conduction system, eventually resulting in the process referred to as ventricular remodelling.[5,6] Electrical disturbances enhance mechanical dyssynchrony at different levels—ie, interatrial, atrioventricular, interventricular, and intraventricular dyssynchrony (figure).[4] The results of mechanical dyssynchrony on the cardiac cycle are prolonged isovolumic contraction and relaxation times, a slight increase in systole duration, a substantial decrease in ventricular filling time, and the occurrence or an increase in mitral regurgitation cumulating in an impaired efficiency of the heart as a pump.[4] In CRT, a left ventricular lead is placed in a tributary of the coronary sinus (in addition to a right ventricular and atrial lead), enabling biventricular pacing and subsequent resynchronisation of the impaired mechanical contraction patterns (figure).

In this review we summarise the role of ICDs in chronic heart failure, and critically assess the available studies of CRT in patients with symptomatic and oligosymptomatic heart failure. Furthermore, we discuss the rationale and available evidence for other emerging indications of CRT, including its use in patients with a mildly reduced left ventricular ejection fraction ([LVEF] >35%), in those with a narrow QRS complex (≤120 ms), and in those with concomitant bradyarrhythmic pacemaker indications. We focus on the issue of patients who do not respond to CRT, and on CRT optimisation.

Search strategy and selection criteria

We searched the Cochrane library, Medline, and Embase with the search terms "cardiac resynchronization therapy" and "implantable cardioverter defibrillator". We largely selected publications from the past 10 years but did not exclude earlier reports that might have been of relevance. We also searched guideline documents, governmental reports, and chapters of specialised books. This report is an update of a Review of heart failure, which was published in *The Lancet* in 2009. We focused in detail on data and references reported since that time in the specialty of devices in heart failure.

ICDs in patients with heart failure

Sudden cardiac death accounts for up to 50% of the mortality in patients with left ventricular dysfunction.[7,8] Findings from randomised clinical trials[9–15] have shown

that ICDs are the most efficient therapy available to prevent sudden cardiac death in these patients. Therefore, ICD treatment has become standard therapy for primary and secondary prevention of sudden cardiac death in addition to optimised medical heart failure therapy in patients with left ventricular dysfunction, as indicated by the guideline recommendations from the European Society of Cardiology (ESC; table 2). Patients with both ischaemic and non-ischaemic cardiomyopathy seem to benefit from an ICD.[16]

However, some limitations of the ICD stand-alone therapy have become apparent, particularly because older patients (>75 years) and those with some comorbidities seem to benefit less than do others.[17,18] New ICD systems, which have not been studied in large outcome trials, were associated with some morbidity because of technical failure and complications.[19] Hence, because of differences in ICD designs and materials particularly related to safety issues, whether there is a class effect of ICDs is unknown.

	Aim
Class IA	
NYHA III/IV, QRS ≥120 ms, SR, LVEF ≤35%	Reduce morbidity and mortality
NYHA II, QRS ≥150 ms, SR, LVEF ≤35%	Reduce morbidity or prevent disease progression
Class IB	
NYHA III/IV, QRS ≥ 120 ms, LVEF≤ 35%, class I PM indication	Reduce morbidity
Class IIA	
NYHA III/IV, LVEF ≤35%, QRS ≥130ms, AF+AVN ablation	Reduce morbidity
NYHA III/IV, LVEF ≤35%, QRS ≥130 ms, AF with slow ventricular rate	Reduce morbidity
NYHA III/IV, LVEF ≤35%, QRS <120 ms, class I PM indication	Reduce morbidity
Class IIB	
NYHA II, LVEF ≤35%, QRS <120 ms, class I PM indication	Reduce morbidity

CRT=cardiac resynchronisation therapy. NYHA=New York Heart Association. SR=sinus rhythm. LVEF=left ventricular ejection fraction. PM=cardiac pacemaker. AF=atrial fibrillation. AVN=atrioventricualr node.

Table 1: **Focused update of European Society of Cardiology guidelines on device therapy in heart failure with respect to CRT, by indication**

CRT

Patients with New York Heart Association (NYHA) class III and IV heart failure

Patients included in the first trials of CRT had NYHA class III or IV heart failure despite optimum drug treatment, LVEF less than 35%, a dilated left ventricle, and evidence of electrical dyssynchrony defined by a wide QRS. The cutoff value for the QRS duration in the early MUSTIC trial[20] was 150 ms, and this cutoff progressively decreased to 130–120 ms in the MIRACLE,[21] COMPANION,[22] and CARE-HF trials.[23] The MUSTIC trial,[20] with a crossover design including 67 patients, showed that CRT improved symptoms, exercise tolerance (assessed by the 6-min walk test), and quality of life. The parallel-designed MIRACLE trial,[21] including 453 patients with a QRS of 130 ms or greater, confirmed these findings. The functional improvements in patients given CRT were accompanied by left ventricular reverse remodelling and a significant 40% reduction in admissions for heart failure. The COMPANION trial[22] included 1520 patients with NYHA class III and IV heart failure, LVEF less than 35%, and QRS width greater than 120 ms. Patients were randomly assigned to one of three groups: optimal medical therapy (OPT) alone, CRT with biventricular pacing and OPT, or CRT with defibrillator. Although both CRT groups decreased the combined risk of death from any cause or first admission compared with OPT alone, only the CRT defibrillator group was associated with a significant reduction in the secondary endpoint of all-cause mortality. However, the COMPANION trial was not designed or powered to compare the two CRT strategies.

The CARE-HF trial[23] included 813 patients with NYHA class III or IV heart failure and LVEF greater than 35%. Patients with QRS duration between 120 and 150 ms had to have evidence of mechanical dyssynchrony on echocardiogram, whereas those with QRS greater than 150 ms were included without such evidence. Unfortunately, only 9% of patients included in the CARE-HF trial had a QRS duration between 120 and 150 ms. Patients were randomly assigned to OPT or to CRT with biventricular pacing and OPT, and the mean follow-up time was 29 months. CRT was associated with a 37% relative risk reduction of the composite primary endpoint—time to death from any cause or an unplanned admission for a major cardiovascular event. CRT with biventricular pacing significantly decreased all-cause mortality by 36%, which was confirmed at 36 months.[24] Moreover, this trial showed that CRT provided a sustained effect on left ventricular reverse remodelling, which increased over time.[24] After publication of the CARE-HF trial, the European and North American Guidelines implemented CRT in the treatment for patients with chronic heart failure NYHA class III and IV, with LVEF less than 35%, and QRS greater than 120 ms to improve morbidity and mortality.[2,3]

Patients with mildly symptomatic heart failure

After the convincing results in patients with severe heart failure, the effect of CRT on morbidity and mortality was assessed in patients with mildly symptomatic or asymptomatic heart failure and a severely depressed LVEF.[25] Three of five randomised prospective trials focused on the effect on morbidity and mortality of CRT in this population (table 3).[26–30]

In the REVERSE trial,[28] 610 patients with NYHA class I–II heart failure, LVEF 40% or less, a QRS complex of 120 ms or more, and in sinus rhythm were implanted with a CRT device (with or without an ICD backup), and were randomly assigned to the active CRT group (n=419) or to the control group (n=191). After a follow-up of 12 months, no significant differences between groups could be detected for the clinical composite primary endpoint. However, the prospectively powered secondary

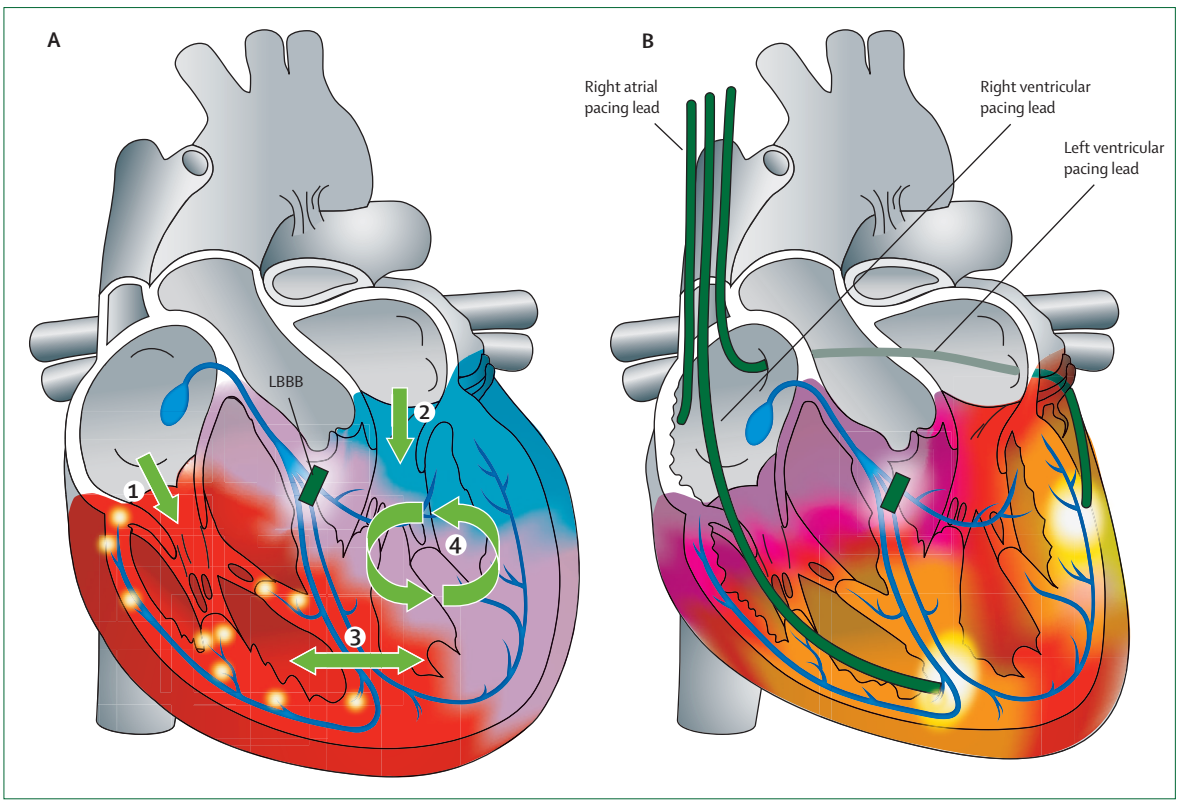

Figure: **Relation of the cardiac conduction system, mechanical dyssynchrony, and CRT**
(A) Electrical disturbances induce mechanical dyssynchrony at different levels: atrioventricular (1, 2), interventricular (3), and intra left ventricular dyssynchrony (4), resulting in an impaired mechanical efficiency of the cardiac cycle and decreased cardiac output. LBBB has been indentified to have an effect most on mechanical dyssynchrony. Early electrical activation is marked in red, whereas late electrical activation is marked in blue. (B) A standard CRT system consists of a right atrial lead, a right ventricular lead (in CRT pacemaker systems) or a right ventricular defibrillation lead (in CRT defibrillator systems), and a left ventricular lead. The left ventricular lead is placed in a tributary of the coronary sinus on the left lateral or posterolateral wall. CRT works by biventricular pacing and subsequent resynchronisation of the impaired mechanical contraction patterns. CRT=cardiac resynchronisation therapy. LBBB=left bundle branch block.

	Aim
Class IA	
NYHA II/III, LVEF≤35%, ischaemic cause, >40 days of MI, reasonable expectation of survival with good functional status for >1 year, optimum medical therapy	Reduce mortality
Survivor of VF	Reduce mortality
LVEF≤40%, haemodynamically unstable VT and/or VT with syncope, reasonable expectation of survival with good functional status for >1 year, optimum medical therapy	Reduce mortality
Class IB	
NYHA II/III, LVEF≤35%, non-ischaemic cause, reasonable expectation of survival with good functional status for >1 year, optimum medical therapy	Reduce mortality

ICD=implantable cardioverter defibrillator. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. MI=myocardial infarction. VF=ventricular fibrillation. VT=ventricular tachycardia.

Table 2: **Class I recommendations for ICDs in patients with chronic heart failure according to the European Society of Cardiology guidelines for the diagnosis and treatment of acute and chronic heart failure, 2008, by indication**

endpoint of left ventricular end-systolic volume index showed a significant decrease in the active group compared with the control group (mean –18·4 mL/m² [SD 29·5] *vs* –1·3 mL/m² [–23·4]; p<0·0001).[31] Furthermore, the time to first heart failure admission was substantially delayed in the active group (hazard ratio [HR] 0·47, p<0·03). By contrast, no effect on mortality rate was recorded at 12 months (2·2% *vs* 1·6%).[31] In the active treatment group, a significant three-fold reduction in left ventricular end-diastolic and end-systolic volume index, and a more than three-fold increase in LVEF, was recorded in patients with a non-ischaemic compared with an ischaemic cause of heart failure over 12 months.[32] Furthermore, a prespecified subgroup analysis showed that patients with a prolonged QRS complex (>150 ms) and those with pronounced interventricular dyssynchrony (as assessed by measurement of interventricular mechanical delay) seemed to benefit most from CRT.

REVERSE provided some evidence that patients with mild heart failure and a depressed LVEF might benefit from CRT. However, the trial design might not have been appropriate to show an effect on morbidity and mortality in this patient population, especially since follow-up was only 12 months. Analysis of the subgroup of 262 patients of the European cohort of REVERSE, who were followed up for 24 months, did show a significant clinical benefit with active treatment (n=180) compared with the control group (n=82), with 19% versus 34% of patients worsening

clinically over the study period (p=0·01).[31] Moreover, time to heart failure admission or death was delayed in the treatment group compared with the control group (HR 0·38, p=0·003).

In the MADIT-CRT trial,[29] 1820 patients with mildly symptomatic heart failure (NYHA I or II), LVEF 30% or less, and a QRS duration of 130 ms or more were randomly assigned to a CRT device with an ICD or to an ICD only.[29] After a mean follow-up of 2·4 years, the primary endpoint (death from any cause or non-fatal heart failure event) occurred in 187 of 1089 patients (17%) in the CRT-ICD group compared with 185 of 731 (25%) in the ICD group (HR 0·66, 95% CI 0·52–0·84; p=0·001). This difference was mainly attributable to a significantly reduced risk of having a non-fatal heart failure event in the ICD-CRT group (22·8% *vs* 13·9%; HR 0·59, 95% CI 0·47–0·74), whereas death at any time was similar between the two study groups (7·3% *vs* 6·8%; HR 1·00, 0·69–1·44; p=0·99). As in REVERSE, the prespecified subgroup of patients with a QRS greater than 150 ms seemed to benefit most.[29] 1 year after randomisation, CRT led to substantial left ventricular reverse remodelling, as shown by a greater reduction in left ventricular end-systolic (–28·7 mL/m² *vs* –9·1 mL/m²) and end-diastolic (–26·2 mL/m² *vs* –7·4 mL/m²) volume index, and a greater increase in LVEF (11% *vs* 3%) in the ICR-CRT group than in the ICD-only group.[33]

The RAFT trial[30] randomly assigned 1798 patients with NYHA II (n=1438) or III (n=360) heart failure, LVEF 30% or less, and QRS of 120 ms or more (or paced QRS ≥200 ms) to receive CRT plus ICD or ICD only.[30] After a follow-up of 40 months, the primary outcome (death from any cause or admission for heart failure) occurred in 297 of 894 patients (33%) in the ICD plus CRT group versus 364 of 904 (40%) in the ICD group (HR 0·75, 95% CI 0·64–0·87; p<0·001). By contrast with REVERSE and MADIT-CRT, investigators noted a reduction in all-cause mortality (26·1% *vs* 20·8%; HR 0·75, 95% CI 0·62–0·91; p=0·003) and death from cardiovascular cause (17·9% *vs* 14·5%; HR 0·68, 0·56–0·83; p=0·02) in the CRT plus ICD groups compared with the ICD-only group. These findings were consistent between patients with NYHA II and III heart failure. Again, subgroup analysis showed that patients with an intrinsic QRS width of 150 ms or more seemed to benefit the most (HR 0·59, 95% CI 0·48–0·73).

Thus data from REVERSE, MADIT-CRT, and RAFT provide strong evidence that CRT substantially reduces morbidity and mortality in patients with mildly symptomatic heart failure, especially in those with a QRS greater than 150 ms. Although convincing for mildly symptomatic (NYHA II) patients, data from REVERSE and MADIT-CRT do not adequately support the use of CRT in asymptomatic (NYHA class I) patients, mainly because the number of such patients enrolled in these trials was small. Additionally, symptomatic improvement is difficult, if not impossible, to measure in patients with NYHA class I heart failure, and the follow-up period to show a benefit in morbidity and mortality is probably even longer than in those with mildly symptomatic heart failure. In view of the risk of device-related complications and the associated costs, additional studies of CRT in patients with NYHA class I heart failure are necessary to establish the risk–benefit ratio.

Patients with LVEF greater than 35%

Several small studies[34,35] suggest a role for CRT in patients with mildly reduced LVEF (35–45%), which will need to be confirmed in randomised controlled clinical outcome trials. The present cutoff LVEF for CRT is more or less arbitrary and the result of findings from landmark ICD and CRT trials.[22,23,36] From a pathophysiological perspective, the decrease in left ventricular function is

	Patients	NYHA class	LVEF (%)	SR/AF	QRS (ms)	Endpoints	Outcome
CONTAK CD[26]	227	II, IV	≤35%	SR	≥120	All-cause mortality + HF admission, pVO_2, 6MWT, NYHA, QoL, LVEDD, LVEF	CRT-D improved pVO_2 and 6MWT, reduced LVEDD, and increased LVEF
MIRACLE ICD II[27]	186	II	≤35%	SR	≥130	VE/CO_2, pVO_2, NYHA, QoL, 6MWT, LV volumes, LVEF	CRT-D improved NYHA, VE/CO_2, LV volumes, and LVEF
REVERSE[28]	610	I, II	≤40%	SR	≥120	(a) Clinical composite endpoint, (b) LVESVi, (c) HF admission, (d) all-cause mortality	Primary endpoint (a) was NS; CRT-P/CRT-D reduced endpoints (b) and (c) but not (d)
MADIT CRT[29]	1820	I, II	≤30%	SR	≥130	(a) HF admission or all-cause mortality, (b) all-cause mortality, (c) LVESV	CRT-D reduced endpoints (a) and (c) but not (b)
RAFT[30]	1798	II, III	≤30%	SR/AF	≥130, ≥200*	(a) All-cause mortality or HF admission, (b) all-cause mortality, (c) CV mortality, (d) HF admission	CRT-D reduced all endpoints

CRT=cardiac resyncronisation therapy. NYHA=New York Heart Association. LVEF=left ventricular ejection fraction. SR=sinus rhythm. AF=atrial fibrillation. HF=heart failure. pVO_2=peak oxygen consumption. 6MWT=6-min walk test. QoL=quality of life. LVEDD=left ventricular end-diastolic diameter. CRT-D=CRT with defibrillator function. VE/CO_2=ventilation/carbon dioxide ratio. LV=left ventricular. LVESVi=left ventricular stroke volume index. NS=not significant. CRT-P=CRT with pacemaker function. LVESV=left ventricular end-systolic volume. CV=cardiovascular. *Patients with AF.

Table 3: **Inclusion criteria, endpoints, and outcome of randomised clinical trials evaluating CRT in mild and asymptomatic heart failure**

more appropriately viewed as a continuum; patients with heart failure and mildly and preserved LVEF are at substantial risk for adverse outcomes.[37]

Patients with a narrow QRS

Patients with heart failure with a QRS less than 120 ms (narrow QRS complex) are excluded from receiving CRT. However, most patients do have a narrow QRS complex, and the effect of CRT will need to be investigated thoroughly in this patient population.[38,39] So far only single centre observational studies have been done, showing reverse remodelling and symptomatic clinical benefit in this population.[40–42] One small (n=172) randomised clinical trial, RethinQ,[43] investigated the effect of CRT in patients with narrow QRS and signs of mechanical dyssynchrony, as assessed by tissue Doppler imaging (septal-to-lateral and anteroseptal-to-posterior wall delay) and M-mode echocardiogram (septal-to-posterior wall mechanical delay), in a multicentre environment.[43] The primary endpoint, an increase in peak oxygen consumption of 1 mL/kg or more during cardiopulmonary exercise testing, was similar in both groups (46% in the active group *vs* 41% in the control group). Several weaknesses are inherent to this trial, including the selection criteria chosen to assess mechanical dyssynchrony; thus an adequately powered and designed trial is needed to finally address this issue.[39] The EchoCRT trial (NCT00683696) is assessing the effects of CRT on morbidity and mortality in patients with heart failure, a narrow QRS width, and signs of ventricular dyssynchrony on echocardiogram in a large (>1250 patients) randomised, double-blind, event-driven design.

Patients with chronic right ventricular pacing

For many years, chronic right ventricular pacing was the standard treatment for patients with heart failure in need of cardiac pacing because of bradycardia caused by either severe sinus or atrioventricular nodal disease. However, this treatment results in a delayed activation of lateral left ventricular segments, and mechanical dyssynchrony.[44,45] Prospective randomised clinical outcome trials specifically addressing whether CRT is better than right ventricular pacing in pacing-dependent patients with heart failure are scarce, and only one small trial has shown promising results.[46] However, smaller observational studies have shown a clinical benefit and reverse remodelling in patients upgraded to CRT from chronic right ventricular pacing.[47–50] Taken together, there is evidence to avoid chronic right ventricular pacing in patients with heart failure, and guideline recommendations from the ESC have been changed accordingly (table 1 and table 2).[3] However, there is no convincing evidence at present to apply CRT to all patients who need chronic right ventricular pacing, especially those with preserved left ventricular function.

Non-response to CRT

Because up to 35% of patients do not respond to CRT clinically and 40–50% show no signs of reverse remodelling,[51] response to CRT needs to be maximised.[3] Optimisation of the response to CRT needs a multidimensional approach: patient selection, positioning of leads, and optimisation of CRT after implantation.

Patient selection

Present ESC guidelines considered the QRS duration as the marker of cardiac dyssynchrony to select candidates for CRT. However, the cutoff value of 120 ms seems questionable,[4] since the mean QRS of patients randomly assigned within the landmark trials establishing CRT for patients with symptomatic heart failure was 160 ms.[20–23] Furthermore, these trials showed that CRT was more effective in patients with a wide QRS (>150–160 ms) than in those with a narrow QRS. In the CARE-HF trial, patients with a QRS between 120 ms and 149 ms had to fulfil two of three echocardiogram dyssynchrony measurements to be enrolled, thus the trial did not represent a pure, unselected cohort. Moreover, data suggested that patients with left bundle branch block morphology benefit significantly from CRT compared with those with right bundle branch block or non-specific intraventricular conduction delay.[52,53] For patients with mild heart failure, the ESC guidelines considered a QRS duration of 150 ms rather than 120 ms, on the basis of results from trials in this population.[3]

Echocardiogram studies suggested weak correlation between the electrical dyssynchrony assessed by the QRS duration and mechanical dyssynchrony. These data showed that, by contrast with patients with narrow QRS, some patients with wide QRS might not exhibit mechanical dyssynchrony.[54] The PROSPECT trial, which included 426 patients implanted with a CRT device, assessed whether imaging techniques could predict non-responding patients.[51] In this trial, the response to CRT was assessed either clinically with a clinical composite score or by echocardiogram with decrease in left ventricular end-systolic volume as a marker of reverse remodelling. The results showed that simple criteria such as left ventricular pre-ejection delay, interventricular mechanical delay, or left ventricular filling time had a good intraobserver and interobserver reproducibility. By contrast, echocardiogram parameters with Doppler tissue imaging had poor intraobserver and interobserver reproducibility. In view of the modest sensitivity and specificity in this multicentre setting, and despite training and centralist analysis, no one echocardiogram measure of dyssynchrony can yet be recommended to improve patient selection for CRT beyond present guidelines. However, technical limitations and suboptimum patient selection could have confounded and limited the interpretation of this study.

Newer echocardiogram techniques with speckle tracking are evolving as improved predictors of response.[55–58] A substudy of 761 patients in the MADIT-CRT trial, using two-dimensional speckle-tracking echocardiogram to examine mechanical dyssychrony at

baseline and follow-up, has shown a greater improvement in dyssynchrony and contractile function at 1 year associated with reduced rates of the subsequent primary outcome of death or heart failure.[59] In the EchoCRT trial, which is recruiting patients, speckle tracking is one of the parameters used to select patients with a narrow QRS and mechanical dyssynchrony.

Real-time three-dimensional ultrasound technique or other techniques such as MRI or CT—which can provide information about scar, myocardial viability, or coronary venous anatomy—seem attractive options, but their use to predict response to CRT needs to be assessed.[60,61] Further predictors of response might be the underlying cardiac disease (ischaemic cardiomyopathy or non-ischaemic cardiomyopathy),[62,63] myocardial scar burden,[64] and a severe right ventricular dysfunction.[65,66]

Lead positioning and alternative pacing methods

The location of right and left pacing leads is crucial in CRT. A suboptimum positioning of leads could be a reason for non-optimum delivery of therapy. The right ventricular apex is most often the pacing site; however, the optimum lead location (apical or septal) is still debated. Traditionally, the left ventricle is paced via a pacing lead inserted in a tributary vein of the coronary sinus.[67] This transvenous approach provides epicardial pacing of the left ventricle. But the optimum left ventricular pacing site is controversial. In most cases, the lead is placed in the optimum anatomical location—ie, the lateral or posterolateral wall.[67] Other important constraints, such a pacing threshold or the presence of a phrenic nerve stimulation, could affect the implantation procedure and result in a less optimum position. Moreover, there is a complex interaction between the left and right ventricular activation pattern induced by right ventricular pacing. A retrospective subanalysis of the MADIT-CRT trial suggested that clinical outcome did not differ significantly in patients with a lateral left ventricular lead compared with in those with a non-lateral location; however, findings showed that the apical location of the left ventricular lead is associated with a worse outcome than are basal or midventricular locations.[68]

Some retrospective data have shown that pacing the left ventricle in a non-optimum site—ie, not at the site of the latest mechanical activation—might enhance remodelling of the heart and worsen clinical outcome.[69,70] CRT is an electrical treatment that attempts to target the site of the latest electrical activation.[71] New imaging techniques such as three-dimensional contact or non-contact mapping provide precise characterisation of the left ventricular activation sequence, but these techniques are not applicable in daily clinical practice.[72] Combination of data provided by different imaging and electrical techniques might assist in determining the optimum leads location, leading to a tailored CRT for each individual patient.

To further optimise pacing, multisite left ventricular pacing with two leads implanted in the coronary sinus has been proposed. The TRI-V study[73] providing dual site pacing has shown an improvement in left ventricular remodelling compared with conventional biventricular pacing. Furthermore, the development of a quadripolar lead allows a multipoint left ventricular pacing in the same coronary vein.[74] This new technology could substantially reduce the need of revision of left ventricular leads in cases of phrenic nerve stimulation; the haemodynamic improvement of multipoint pacing is being assessed.[74]

Alternative pacing methods to the coronary sinus route have been proposed. For failure of lead implantation—which can occur in around 5–10% of cases (eg, inability to cannulate the coronary sinus, absence of suitable veins, lead instability phrenic nerve stimulation)—an epicardial pacing with a mini-invasive thoracotomy or thoracoscopy can be done.[75] Another promising approach is the endocardial biventricular pacing, which provides a more physiological electrical activation via interatrial septum or transapical routes, since electrical activation originates in the endocardium and spreads towards the epicardium.[76] A study based on the measurement of rate of rise of left ventricular pressure (dp/dt) reported that there is much intervariability for the location of the best endocardial pacing site, suggesting a tailored, individualised approach for each patient.[77] However, safety issues need to be considered, such as thromboembolism or infection of the endocardial pacing lead or the effect of the functioning of the mitral valve.[76] Further studies are needed to assess the safety and superiority of these alternative strategies compared with conventional biventricular pacing.

CRT optimisation

The follow-up of patients implanted with a CRT device should focus on a multidimensional approach to maximise the clinical response to the therapy, including a systematically executed optimisation procedure of the device itself. Data suggest that a high percentage of biventricular pacing (>92%) is mandatory for the clinical success of the therapy.[78] Basic device parameters such as the basal pacing rate, the upper limit rate, and the need of rate responsive function have to be carefully assessed for each patient. The absence of optimisation of the atrioventricular intervals could be an important cause of non-response to CRT.[79] However, the FREEDOM[80] and SMART[81] atrioventricular trials, comparing intracardiac electrogram method (IEGM)-based algorithms or echo-based atrioventricular optimisation, have suggested that the default parameters ensuring biventricular pacing could be adequate. However, whether these studies have some limitations in their design, pre-study assumption, and power calculations is still debated. Present CRT devices provide the possibility to optimise the interventricular delay, allowing simultaneous biventricular pacing or sequential pacing with different degrees of interventricular delays (left or right ventricular first). Two studies have shown the absence of benefit for

symptomatic clinical outcome after systematic interventricular optimisation compared with default settings.[82,83] Whether an individual atrioventricular or interventricular optimisation protocol is necessary in every implanted CRT patient, or only for non-responding patients, is not known.

CRT patients can have supraventricular arrhythmias, which might reduce the percentage of biventricular pacing and increase the percentage of intrinsic conducted QRS. Some device-based algorithms, which are specifically designed to provide biventricular pacing for paroxysmal atrial arrhythmias, are available and can increase the percentage of biventricular pacing. In patients with persistent atrial fibrillation, radiofrequency ablation of the atrioventricular node might be necessary to maximise biventricular pacing and subsequent therapy delivery to improve outcome.[84] Similarly, ventricular arrhythmias can frequently be detected in the CRT patient population and sometimes can significantly reduce the rate of biventricular pacing. Some device-based algorithms, providing biventricular pacing for ventricular premature beat, are available but their efficacy is questionable. Antiarrhythmic medical therapy and ablation of ventricular arrhythmias might have to be done in some cases.

CRT with pacemaker versus CRT with defibrillator

The choice of the device—ie, CRT pacemaker or CRT defibrillator—is still debated. CRT with a defibrillator is now preferentially recommended for patients with NYHA class II heart failure, mainly because most patients included in randomised trials received this type of device.[3] For patients with heart failure of functional NYHA class III and IV, CRT with a defibrillator is recommended if the patient has a reasonable expectation of survival with good functional status for at least 1 year or a secondary prevention indication for an ICD.[3] The only way to address this issue appropriately would be a prospective randomised controlled trial comparing both devices. Since most patients have a concomitant class IA indication for an ICD, ethical concerns would probably prohibit the execution of such a trial. Thus the final decision of treatment and choice of device is made by the treating physician, with guidelines generally favouring implantation of CRT with a defibrillator rather than a pacemaker.

Conclusion

ICDs and CRT are both standard of care for patients with heart failure. Although ICDs protect only from arrhythmic events, CRTs have the advantage of improving left ventricular size and function and, hence, actively treat the underlying disease process. More than a decade after its invention, CRT remains the most successful heart failure therapy after the introduction of angiotensin-converting-enzyme inhibitors, β blockers, and spironolactone into the therapeutic regimen. The clinical indications for CRT have now been extended to patients with mildly symptomatic heart failure, and to those with heart failure in need of chronic pacing because of conduction diseases irrespective of their native QRS width. Thus the patient population will shift away from standalone simple ICD systems to more complex CRT systems. Still, research is needed to assess novel CRT indications, including patients with heart failure with a narrow QRS and those with mildly or persevered LVEF. Finally, efforts are necessary to tailor CRT to specific patients needs and characteristics, to reduce the number of non-responding patients.

Contributors

Both authors contributed equally to the literature search, figures, data interpretation, and writing of this report.

Conflicts of interest

JH has received consulting fees from St Jude Medical and Biotronik; has received research grants and speaker honoraria from Biotronik, St Jude Medical, Medtronic, and Boston Scientific; and is a co-principal investigator in EchoCRT. CL has received consulting fees from St Jude Medical, Sorin, Medtronic, and Biotronik; has received research grants and speaker honoraria from St Jude Medical, Sorin, Medtronic, Boston Scimed, and Biotronik; and was a principal investigator in Septal CRT, which was sponsored by Boston Scientific.

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