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# Inherited cardiomyopathies—Novel therapies

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ABSTRACT

Cardiomyopathies arising due to a single gene defect represent various pathways that evoke adverse remodeling and cardiac dysfunction. While the gene therapy approach is slowly evolving and has not yet reached clinical "prime time" and gene correction approaches are applicable at the bench but not at the bedside, major advances are being made with molecular and drug therapies. This review summarizes the contemporary drugs introduced or being tested to help manage these unique disorders bearing a major impact on the quality of life and survival of the affected individuals.

The restoration of the RNA reading frame facilitates the expression of partly functional protein to salvage or alleviate the disease phenotype. Chaperones are used to prevent the degradation of abnormal but still functional proteins, while other molecules are given for pathogen silencing, to prevent aggregation or to enhance clearance of protein deposits. The absence of protein may be managed by viral gene delivery or protein therapy. Enzyme replacement therapy is already a clinical reality for a series of metabolic diseases. The progress in molecular biology, based on the knowledge of the gene defect, helps generate small molecules and pharmaceuticals targeting the key events occurring in the malfunctioning element of the sick organ.

Cumulatively, these tools augment the existing armamentarium of phenotype oriented symptomatic and evidence-based therapies for patients with inherited cardiomyopathies.



**Contents**



*Abbreviations:* ACM, arrhythmogenic cardiomyopathy; AON, antisense oligo-nucleotide; α-Gal A, α-galactosidase A; BMD, Becker muscular dystrophy; cMyBPC, myosin-binding protein C; DCM, dilated cardiomyopathy; DMD, Duchenne muscular dystrophy; ERT, enzyme replace therapy; GAA, lysosomal acid α-glucosidase; $Gb_3$, globotriaosylceramide; HCM, hypertrophic cardiomyopathy; HF, heart failure; LV, left ventricle; LVOT, LV outflow tract; LVEF, left ventricular ejection fraction; PLN, phospholamban; RCM, restrictive cardiomyopathy; SAP, serum amyloid P component; SCD, sudden cardiac death; SR, sarcoplasmic reticulum; TTR-FAP, familial amyloidotic polyneuropathy; WPW, Wolff–Parkinson–White.

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## 1. Introduction

Cardiomyopathies arising due to a single gene defect represent various pathways to evoke adverse remodeling and cardiac dysfunction. While the gene therapy approach is slowly evolving and has not yet reached clinical "prime time" and gene correction approaches are being developed at the bench but not at the bedside, progress is gradually being made with medical therapies. This review summarizes the contemporary drugs being tested and introduced into the clinical arena to help manage these diseases. We selected drugs soon to be used in the clinic, those being tested in clinical trials or having abundant experimental evidence in their favor and are about to start clinical experimentation in various cardiomyopathy groups (Table 1).

We hereby grouped the cardiomyopathies according to the principal subtypes as defined by the most recent cardiomyopathy classification (Elliott et al., 2008), while paying specific attention to unique subtypes characterized by *Red Flags* useful for disease diagnosis (Rapezzi et al., 2013). There are numerous diverse diseases caused by metabolic defects, substrate accumulation, and protein aggregates. Being unable to address every particular gene-variant, we describe the representative examples to demonstrate the status of current therapy and future directions (see Table 1).

## 2. Hypertrophic cardiomyopathy (HCM)

### 2.1. Clinical overview

HCM is the most common genetic cardiovascular disease with an estimated prevalence of 1 in 500. It is characterized by a thickened, but not dilated, left ventricle (LV) without a secondary cause for the hypertrophy (such as aortic stenosis). HCM is the most common cause of sudden cardiac death (SCD) in the young and in athletes. Adults may suffer from effort intolerance due to angina or heart failure while in the elderly atrial fibrillation, and strokes are common complications. Yet many individuals with the disease have a normal life expectancy and have little, if any, medical limitations (Maron & Maron, 2013; Maron et al., 2009).

#### 2.1.1. Genetics

HCM is the result of a mutation in one of 11 genes encoding components of the sarcomere or (sometimes) the Z-disc. Of the genetically

**Table 1**
Mechanisms and treatment strategies of main subtypes of inherited cardiomyopathies.

| Type | Genetics | Principal mechanisms | Current treatment | Novel interventions and future targets |
|---|---|---|---|---|
| Hypertrophic CM | Mostly autosomal dominant: Mutations in genes encoding components of the sarcomere or Z-disc. Significant phenotypic heterogeneity. | Increased $Ca^{2+}$ sensitivity, energy deficit | Symptomatic, ICD implantation, stroke prevention, myectomy/septal reduction for persistent symptoms. | - $Ca^{2+}$ homeostasis: Blebbistatin, parvalbumin, adenoviral delivery of SERCA2a, diltiazem<br>- Gene transfer: recombinant viral vectors of cMyBPC<br>- Diversion of myocardial substrate utilization: perhexiline, trimetazidine, ranolazine<br>- Preventing fibrosis: aldosterone/ARB blockade: spironolactone, eplerenone, losartan, candesartan |
| Dilated CM | Mostly autosomal dominant: results from defects in multiple cellular components with a final common pathway of deranged cardiomyocytes contraction | Variable: decreased $Ca^{2+}$ sensitivity: disruption of sarcolemmal integrity and ion function; impaired force transmission due to cytoskeletal damage; altered gene expression; apoptosis | Early diagnosis is crucial. Treatment as in other forms of systolic dysfunction. | - Immune system modulation: immunoabsorption, COR-1 cyclopeptide<br>- N-3 polyunsaturated fatty acids (nPUFA)<br>- Gene therapy: SERCA2 gene<br>- Intracoronary stem cells transplantation ($CD34^+$ cells)<br>- Tissue repair and regeneration: lxmyelocel-T<br>- $Ca^{2+}$ sensitization: levosimendan, pimobendan, EMD 53998, MCI-154<br>- Cardiac myosin activators: omecamtiv mecarbil |
| Duchenne/Becker muscular dystrophy (DMD) | X-linked inheritance: dystrophin gene mutations | Disruption of sarcolemmal and cytoskeletal structure and function | Symptomatic; corticosteroids, ACE inhibitors/β-blockers to prevent systolic dysfunction, noninvasive ventilation and removing secretions | - Gene therapy: dystrophin or utrophin, SERCA2a<br>- Reading frame restoration: antisense oligo-nucleotide (AON)<br>- "Read through" therapy: ataluren<br>- Proteasome inhibitors |
| Arrhythmogenic CM | Mutations in the genes that encode for the desmosomal proteins which are responsible for cell to cell adhesion | Impaired adhesion and electrical conductance between adjacent cardiomyocytes | Antiarrhythmics, banning of intense physical activity, ICD implantation | - Wall stress reduction: combining afterload reduction and diuretics<br>- Mineralocorticoid therapy<br>- Wnt/β-catenin signaling pathway<br>- PPAR-γ |
| Restrictive CM | Mutations in sarcomere genes causing severe fibrosis or gene defects that cause intracellular or extracellular accumulation of various substances (e.g., desmin, glycolipid, iron, amyloid protein) | Wall stiffening due to intracellular or extracellular substrate accumulation, or myocardial fibrosis | Symptomatic treatment for heart failure, arrhythmias and hypotension | - Fibrosis attenuation<br>- Small interference RNA<br>- Prevention of TTR fibril formation: tafamidis meglumine, diflunisal<br>- Removal of TTR amyloid deposits: doxycycline plus TUDCA<br>Clearance of serum amyloid protein (SAP): CPHAP |
| Metabolic CM | Autosomal recessive, X-linked or maternal (in mitochondrial diseases). Caused by enzyme deficiency or defects in oxidative phosphorylation | Cardiomyocyte dysfunction and death due to storage, arrested autophagy, energetic deficit, and ROS damage | Substrate modification, substrate supplementation, enzyme replacement therapy, antioxidants | - Novel enzyme replacement therapy: PRX-102<br>- Pharmacological chaperone: Migalastat HCl<br>- Enhancers of pharmacological chaperones: ambroxol, rosiglitazone<br>- Mitochondrial protectors |