



## Dilated cardiomyopathy

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Dilated cardiomyopathy is defined by the presence of left ventricular **dilatation** and **contractile** dysfunction. **Genetic mutations** involving genes that encode cytoskeletal, sarcomere, and nuclear envelope proteins, among others, account for up to **35% of cases**. **Acquired** causes include **myocarditis** and exposure to **alcohol**, **drugs** and **toxins**, and **metabolic** and **endocrine** disturbances. The most common presenting symptoms relate to congestive heart failure, but can also include **circulatory collapse**, **arrhythmias**, and **thromboembolic** events. **Secondary neurohormonal** changes contribute to **reverse remodelling** and ongoing **myocyte damage**. The **prognosis is worst** for individuals with the **lowest ejection fractions** or **severe diastolic dysfunction**. **Treatment** of chronic heart failure comprises medications that improve survival and reduce hospital admission—namely, **angiotensin converting enzyme inhibitors** and **β blockers**. Other interventions include enrolment in a multidisciplinary heart failure service, and **device** therapy for arrhythmia management and sudden death prevention. Patients who are refractory to medical therapy might benefit from **mechanical circulatory** support and heart **transplantation**. Treatment of preclinical disease and the potential role of **stem-cell** therapy are being investigated.

### Introduction

**Cardiomyopathies** are a heterogeneous group of myocardial diseases associated with **mechanical** or **electrical dysfunction** that usually exhibit inappropriate ventricular hypertrophy or dilatation.<sup>1</sup> **Primary** cardiomyopathies are predominantly confined to heart **muscle**, whereas **secondary** cardiomyopathies are generally caused by **systemic conditions** with associated cardiac dysfunction. In the American Heart Association classification, cardiomyopathies are classified according to cause (figure 1),<sup>1</sup> whereas the European Society of Cardiology classification is based on a combination of morphology and haemodynamics.<sup>2</sup>

**Dilated** cardiomyopathy is defined by the presence of **left ventricular dilatation** and **contractile dysfunction**, in the **absence** of abnormal loading conditions and **severe coronary artery disease**.<sup>3,4</sup>

### Epidemiology

**Dilated** cardiomyopathy is **one of the most common causes** of heart **failure** and the **most common indication** for heart **transplantation** worldwide,<sup>1</sup> with an estimated prevalence of 40 cases per 100 000 individuals and an annual incidence of 7 cases per 100 000 individuals.<sup>1,5,6</sup> Racial differences exist,<sup>3,5</sup> whereas sex-related differences are less consistent.<sup>3</sup> This disorder accounts for

around 60% of childhood cardiomyopathies,<sup>7,8</sup> with infants younger than 12 months having the highest incidence.<sup>8,9</sup>

### Causes

Tables 1 and 2 summarise the causes of dilated cardiomyopathy. **Genetic** causes are important at **all ages**. Clinical and echocardiographic **screening** in **families** of affected individuals show evidence of **familial transmission** in **20–35%** of cases.<sup>6,10,11</sup> **Acquired** causes of cardiomyopathy include **infectious** agents, **drugs** and **toxins**, and **endocrine** disturbances.<sup>1</sup> In children, common causes of dilated cardiomyopathy are genetic mutations, myocarditis, and inborn errors of metabolism.<sup>9,12</sup>

**Peripartum** cardiomyopathy is defined by otherwise unexplained dilated cardiomyopathy, with **onset** in the **last month of pregnancy** or **within 5 months of delivery**.<sup>13</sup> Disease progression occurs in up to a half of cases and **recovery** occurs in **less than a quarter**. The fundamental **cause** is **unknown** and the **highest** incidence has been reported in **sub-Saharan** Africa.<sup>14</sup> In some cases, familial peripartum cardiomyopathy or familial dilated cardiomyopathy is present.<sup>15</sup> **If** heart function **returns** to normal, the risk of **recurrence** is **low**.<sup>16</sup>

### Drugs and toxins

Table 2 lists the causes of secondary cardiomyopathy.<sup>14,17</sup> **Alcohol** abuse accounts for **21–36%** of dilated cardiomyopathy cases in high-income countries.<sup>18</sup> The relationship between alcohol intake and clinical heart failure is influenced by various genetic, racial, and behavioural susceptibility factors.<sup>19</sup> The diagnosis is based on a history of **heavy alcohol intake (>80–100 g/day for >10 years)**,<sup>18,19</sup> in combination with otherwise unexplained cardiomyopathy.<sup>20</sup>

**Cocaine** and **methamphetamines** are potent sympathomimetic drugs that induce heightened inotropic and chronotropic effects. Mechanisms of cardiac toxicity include myocardial ischaemia from increased oxygen consumption, prothrombotic effects, coronary vasospasm,

#### Search strategy and selection criteria

We searched the Cochrane Library, MEDLINE, and Embase from Jan 1, 1981, to Jan 1, 2016, with the search terms “dilated cardiomyopathy” or “congestive heart failure” for articles published in English. We largely selected publications from the past 5 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 selected those we deemed relevant. Review articles are cited to provide readers with more details and more references than this Seminar has room for.

and accelerated coronary atherosclerosis.<sup>21,22</sup> The prevalence of methamphetamine abuse is high among young adult patients with newly diagnosed dilated cardiomyopathy.<sup>23</sup>

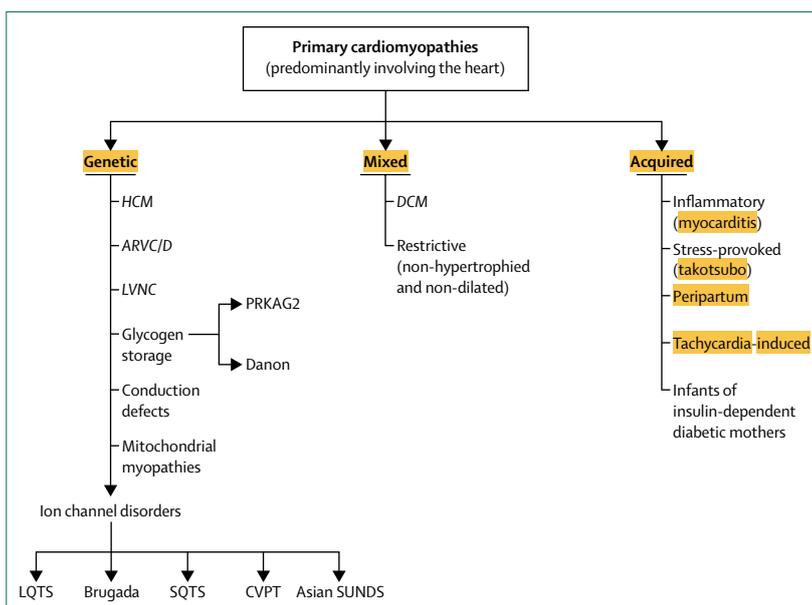
**Anthracycline-induced** cardiotoxicity can occur **during** treatment or many **years afterward**. The mechanisms of anthracycline-induced cardiotoxicity include oxidative stress, changes in **mitochondrial** membrane permeability, and **suppression** of **respiratory chain** activity.<sup>24</sup> Echocardiographic abnormalities are detected in between **25% and 50%** of **childhood cancer survivors** within **20 years** of treatment.<sup>25–27</sup> The **cumulative risk** of congestive heart failure 30 years after diagnosis is **8%** in childhood cancer survivors who received a cumulative anthracycline dose of more than 250 mg/m<sup>2</sup>.<sup>28</sup> Treatment with **dexrazoxane, a free-radical scavenger**, prior to anthracycline administration has been shown to **diminish** markers of acute myocardial **damage**.<sup>29</sup>

### Myocarditis

The traditional histological criteria for **myocarditis** are based on an inflammatory cellular infiltrate, with or without myocyte necrosis (figure 2).<sup>30,31</sup> However, the clinical utility of these criteria is limited by both interobserver variability and low sensitivity,<sup>32–34</sup> alternative criteria that rely on immunoperoxidase staining for various anti-CD surface antigens and antihuman leucocyte antigen might have greater sensitivity and improved prognostic value.<sup>30,35</sup> **Cardiac MRI** can detect specific features of **myocarditis** without the sampling error associated with **endomyocardial biopsy**.<sup>36,37</sup> The sequence of events leading to myocarditis typically starts with cardiac damage from **viral** infection (**acute phase**) resulting in **exposure** of intracellular **antigens**, leading to a **T-lymphocyte-mediated inflammatory response** (**subacute phase**). In some patients the inflammatory response can persist because of a misdirected immune response against endogenous heart antigens.<sup>30</sup>

**Myocarditis** is an **important cause** of sudden death in adults **younger than 35 years** of age<sup>38</sup> and around **20%** of patients with **myocarditis** develop a **chronic dilated cardiomyopathy**.<sup>39</sup> The typical **manifestations** of **myocarditis** are similar to those of **dilated cardiomyopathy**, but can vary from **subclinical** disease to arrhythmias, heart block, and **sudden death**, and can **mimic** myocardial **infarction**.<sup>30</sup> In adults, fulminant lymphocytic myocarditis generally has a good prognosis.<sup>40</sup> **Lymphocytic myocarditis** accounts for around **10%** of newly diagnosed adult-onset **dilated cardiomyopathy**, and is more common in children than adults.<sup>8</sup>

Myocarditis is most commonly caused by **viral** infection, although other infections can produce a similar clinical scenario (table 2).<sup>34,41</sup> **Coxsackievirus B**, adenovirus, parvovirus B19, and human herpes virus 6 are common causes of myocarditis;<sup>34,42</sup> **many other viruses** have also been implicated. Other forms of myocarditis are caused by **drug-induced hypersensitivity**



**Figure 1: Classification of cardiomyopathies**

Reproduced from reference 1 by permission of Wolters Kluwer. ARVC/D=arrhythmogenic right ventricular cardiomyopathy/dysplasia. CVPT=catecholamine-induced polymorphic ventricular tachycardia. DCM=dilated cardiomyopathy. HCM=hypertrophic cardiomyopathy. LQTS=long QT syndrome. LVNC=left ventricular non-compaction. SQTs=short QT syndrome. SUNDs=sudden unexpected nocturnal death syndrome.

| Genetic causes                                | Features  |
|---|---|
| <b>Predominant cardiac phenotype</b>          |   |
| Titin ( <i>TTN</i> )                          | 20–25% of familial DCM; autosomal dominant mode                             |
| Lamin A/C ( <i>LMNA</i> )                     | ~5% of familial DCM; autosomal dominant mode                                |
| Myosin heavy chain 7 ( <i>MYH7</i> )          | ~4% of familial DCM; autosomal dominant mode                                |
| Troponin T ( <i>TNNT2</i> )                   | ~2% of familial DCM; autosomal dominant mode                                |
| Myosin-binding protein C ( <i>MYBPC3</i> )    | ~2% of familial DCM; autosomal dominant mode                                |
| Myopalladin ( <i>MYPN</i> )                   | ~2% of familial DCM; autosomal dominant mode                                |
| Sodium channel $\alpha$ unit ( <i>SCN5A</i> ) | ~2% of familial DCM; autosomal dominant mode                                |
| Phospholamban ( <i>PLN</i> )                  | ~1% of familial DCM; autosomal dominant mode                                |
| <b>Neuromuscular disorders</b>                |   |
| Duchenne muscular dystrophy ( <i>DMD</i> )    | X-linked mode; creatine kinase elevation                                    |
| Becker muscular dystrophy ( <i>BMD</i> )      | X-linked mode; creatine kinase elevation                                    |
| <b>Syndromic diseases</b>                     |   |
| <b>Mitochondrial diseases</b>                 |   |
|   | Mitochondrial inheritance; syndromic expression including skeletal myopathy |
| Tafazzin ( <i>TAZ/G4.5</i> )                  | X-linked mode; Barth syndrome   |
| DCM=dilated cardiomyopathy.                   |   |

**Table 1: Genetic causes of DCM<sup>a</sup>**

| Comments   |  |
|--|--|
| <b>Infection (myocarditis)</b>                     |  |
| <b>Viral</b> (including parvovirus B19, HPV6, HIV) | ..   |
| <b>Bacterial</b> (including Lyme disease)          | Atrioventricular block in Lyme disease   |
| Fungal   | ..   |
| Parasitic  | ..   |
| Rickettsial  | ..   |
| Protozoal  | ..   |
| <b>Autoimmune diseases</b>                         |  |
| Organ specific                                     |  |
| Giant cell myocarditis                             | Multinucleated giant cells; frequent AV block and ventricular arrhythmias              |
| Non-organ specific                                 |  |
| Non-infectious myocarditis                         | ..   |
| <b>Polymyositis/dermatomyositis</b>                | ..   |
| Churg-Strauss syndrome                             | ..   |
| <b>Wegener's granulomatosis</b>                    | ..   |
| <b>Systemic lupus erythematosus</b>                | ..   |
| <b>Sarcoidosis</b>                                 | Granulomatous myocarditis  |
| <b>Peripartum</b>                                  |  |
| ..   | Risk factors include multiparity, African descent, familial DCM, autoimmunity          |
| <b>Toxicity and overload</b>                       |  |
| <b>Ethanol</b>                                     | Risk proportionate to extent and duration of alcohol intake                            |
| <b>Cocaine, amphetamines, ecstasy</b>              | Chronic users  |
| Other toxins                                       | Arsenic, cobalt, anabolic or androgenic steroids                                       |
| <b>Iron overload</b>                               | Transfusions, haemochromatosis   |
| <b>Nutritional deficiency</b>                      |  |
| Selenium deficiency                                | Rare, high frequency in some parts of China (Keshan disease)                           |
| <b>Thiamine deficiency (Beriberi)</b>              | High output heart failure, contributing factors include malnutrition and alcohol abuse |
| Zinc and copper deficiency                         | Possible contributors to DCM   |

(Table 2 continues in next column)

and systemic hypereosinophilic syndromes, whereas giant-cell myocarditis is primarily autoimmune in nature.

#### Left ventricular non-compaction

Left ventricular non-compaction is characterised by left ventricular trabeculations, deep intertrabecular recesses, and a thin layer of normal myocardium.<sup>43</sup> Previously regarded as uncommon, this cardiomyopathy accounts for 5–9% of childhood cardiomyopathies.<sup>8,44</sup> Traditionally considered to be due to an arrest in myocardial compaction late in fetal cardiac development, left ventricular non-compaction can in fact be acquired or become more prominent in adult life. In addition to familial and sporadic forms, left ventricular non-compaction has been noted in highly trained athletes,<sup>45</sup> sickle-cell disease,<sup>46</sup> and pregnancy.<sup>47</sup> In children, the dilated cardiomyopathy

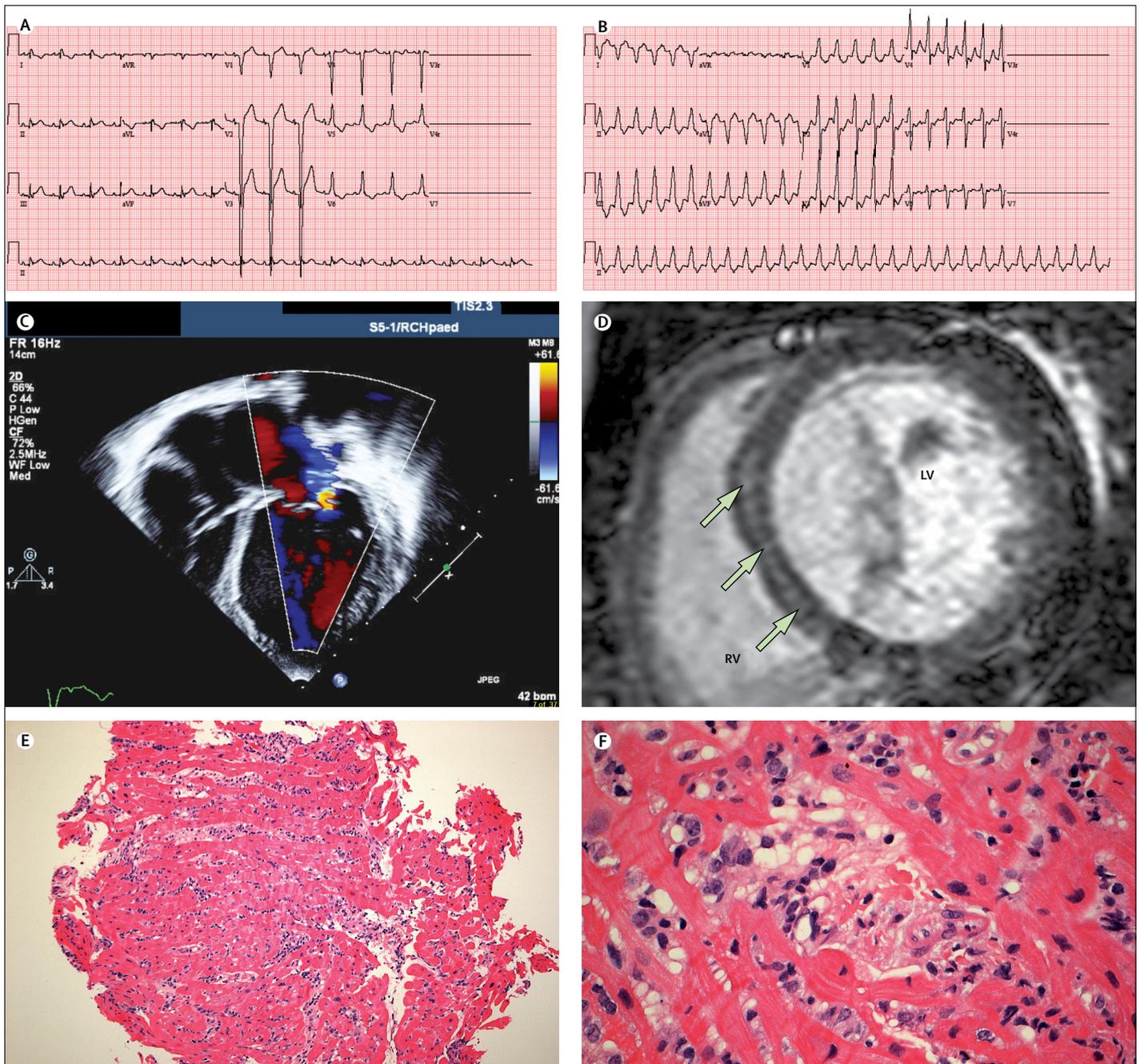
| Comments  |  |
|---|--|
| (Continued from previous column)                      |  |
| <b>Inborn errors of metabolism</b>                    |  |
| Fatty acid oxidation                                  | Many inborn errors of metabolism cause a mixed phenotype with varying degrees of hypertrophy and reduced systolic function   |
| Carnitine deficiency                                  | ..   |
| Glycogen storage diseases                             | ..   |
| Mucopolysaccharidoses                                 | ..   |
| Disorders of oxidative phosphorylation                | ..   |
| Organic acidurias                                     | ..   |
| <b>Drugs</b>  |  |
| <b>Antineoplastic drugs</b>                           | Anthracyclines, antimetabolites, alkylating agents, paclitaxel, hypomethylating agents, monoclonal antibodies, tyrosine kinase inhibitors, immunomodulating agents |
| <b>Psychiatric drugs</b>                              | Clozapine, olanzapine, chlorpromazine, risperidone, lithium, methylphenidate, tricyclic antidepressants, phenothiazines  |
| Others  | Chloroquine, all-trans retinoic acid, antiretroviral agents  |
| <b>Endocrinology</b>                                  |  |
| <b>Hypothyroidism</b>                                 | ..   |
| <b>Hyperthyroidism</b>                                | ..   |
| <b>Cushing's</b> and Addison disease                  | ..   |
| Pheochromocytoma                                      | ..   |
| <b>Takotsubo</b> cardiomyopathy                       | Stress-related   |
| Acromegaly  | ..   |
| Diabetes mellitus                                     | ..   |
| <b>Electrolyte disturbances</b>                       |  |
| <b>Hypocalcaemia</b>                                  | ..   |
| <b>Hypophosphataemia</b>                              | ..   |
| DCM=dilated cardiomyopathy. HPV=human papillomavirus. |  |

**Table 2: Other causes of DCM\* by subtype, disease, or agent**

phenotype is by far the most common, and in some cases no associated cardiac dysfunction is observed.

#### Clinical features

Initial symptoms of heart failure are present in 80% of patients with dilated cardiomyopathy.<sup>48</sup> These symptoms include excessive sweating, ankle oedema, orthopnoea, and fatigue after mild exertion. Abdominal discomfort, nausea, anorexia, and cachexia can be prominent in advanced cases. Circulatory collapse is the most severe manifestation of congestive heart failure. Some individuals have palpitations and syncope. Thromboembolic events and rarely, sudden death, might be the initial symptom, particularly in infants.<sup>8</sup> Physical symptoms can include peripheral and sacral oedema, tachycardia, an elevated jugular venous pressure, pulmonary crepitations, an inferolaterally displaced left



**Figure 2: Electrocardiographic, imaging, and light microscopy findings in dilated cardiomyopathy**

Electrocardiogram showing (A) left bundle branch block and (B) ventricular tachycardia of right bundle branch block morphology in a patient with a myopalladin mutation. (C) Echocardiogram showing a distended left atrium, a dilated and spherical left ventricle, and significant mitral regurgitation. (D) Basal short-axis image demonstrating mid-wall late gadolinium enhancement in the interventricular septum (arrows) in a patient with idiopathic dilated cardiomyopathy. (E) Diffuse lymphocytic infiltrate and (F) focal myocyte damage in a patient with myocarditis. LV=left ventricle. RV=right ventricle.

ventricular apex beat, a gallop rhythm, and a mitral regurgitant murmur.

### Pathophysiology

Left ventricular dilatation is accompanied by remodelling, in which the left ventricle assumes a spherical shape.

Pathophysiological changes include a decrease in stroke volume and cardiac output, impaired ventricular filling, and an increase in end-diastolic pressure. Compensatory changes in the vascular system include an increase in systemic vascular resistance, a decrease in arterial compliance, and an increase in venous pressure and

circulating blood volume. Both cardiac **preload** and **afterload** are **increased**, with increased afterload resulting in elevated **wall stress**.<sup>49,50</sup>

**Diastole** involves both **active** relaxation (**early** diastole) and **passive** compliance (**mid-to-late** diastole). In dilated cardiomyopathy, **diastolic dysfunction** that affects **both** components can accompany the reduction in systolic function. **Impaired** ventricular **relaxation** results in **reduced** rapid ventricular **filling**. **Reduction** in ventricular compliance due to **hypertrophy** or **fibrosis** causes **restrictive** pathophysiology, with reduced ventricular filling and elevated end-diastolic pressures.

**Secondary neurohormonal changes** include an **increase** in sympathetic adrenergic activity and a **reduction** in **vagal** activity to the heart. Neurohormonal changes include an increase in circulating catecholamines, an **increase** in **vasopressin** levels, and activation of the **renin-angiotensin-aldosterone system**. **Naturetic** peptide production is also **increased**. The combination of increased catecholamines, increased cardiac afterload, fluid retention, and tachycardia result in further elevation of wall stress and myocardial oxygen demand, as well as **direct cardiotoxicity**.<sup>51</sup> These secondary adaptations lead to ongoing myocyte damage with further reduction in myocardial performance. **Compensatory hypertrophy** allows more muscle fibres to share in **wall tension** for any given ventricular pressure and radius.

### Risk factors and clinical outcomes

Historic survival data from tertiary referral centres in adult patients with dilated cardiomyopathy,<sup>48</sup> indicated a **1 year mortality** of **25–30%** and a **50% survival at 5 years**. The prognosis is **worst** for patients with a left ventricular ejection fraction of **less than 25%**,<sup>48</sup> a **right ventricular** involvement,<sup>52</sup> a poor New York Heart Association functional class,<sup>53</sup> and a poor haemodynamic status at cardiac catheterisation.<sup>48</sup> Increasing **severity** of **diastolic dysfunction** on echocardiography is related to both symptoms and exercise intolerance,<sup>54</sup> and the **development** of **pulmonary hypertension** and mortality.<sup>55,56</sup>

**Sudden death** in dilated cardiomyopathy can be caused by electromechanical **dissociation** or ventricular **arrhythmias**. **Sudden death** occurs in up to **12%** of patients with this disorder and accounts for **25–30% of all deaths**.<sup>48</sup>

Mortality in children with dilated cardiomyopathy tends to be higher than in adults. Risk factors for death or transplantation include age at diagnosis (<4 weeks and >5 years), the presence of familial dilated cardiomyopathy, and severity of left ventricular systolic dysfunction at baseline.<sup>57</sup> Children with inborn errors of metabolism and those with malformation syndromes have the best transplant-free survival, whereas children with neuromuscular disorders have the worst outcomes.<sup>9</sup> Patients with dilated cardiomyopathy caused by myocarditis are more likely to have an improvement in left ventricular function and reverse remodelling than are those with idiopathic disease.<sup>57,58</sup> Sudden death in

children with dilated cardiomyopathy is relatively uncommon, with a 5 year incidence of between 3% and 5%.<sup>59,60</sup>

### Diagnostic investigations

The electrocardiogram (ECG) can only show **non-specific** repolarisation abnormalities. Left ventricular hypertrophy, pathological Q waves, or poor R wave progression in the lateral chest leads might be observed. Prolongation of the PR interval might be the first manifestation of cardiomyopathy due to lamin, emerin, and SCN5A mutations.<sup>61–63</sup> Other abnormalities of conduction can include atrioventricular block, left bundle branch block, and left anterior hemiblock (figures 2A, 2B).<sup>48</sup>

Chest **radiographs** usually show **cardiomegaly** and **pulmonary venous redistribution**, whereas pulmonary oedema is **less common**.<sup>48</sup>

Echocardiography typically shows **global** left ventricular **hypokinesis**; however, regional wall motion abnormalities might also exist. Left ventricular and atrial dilatation can be mild if the onset of the cardiomyopathy has been sudden. **Right ventricular** involvement is **variable**. Intracardiac thrombi and functional mitral regurgitation due to annular dilatation might also be noted (figure 2C). Doppler parameters can assist in quantifying the severity of diastolic dysfunction.<sup>54</sup>

**Cardiac MRI** provides accurate assessment of ventricular volumes, wall thickness, and contractile function, as well as tissue characterisation (figure 2D). **Delayed gadolinium** enhancement can indicate myocardial **necrosis** or scarring. Myocardial **inflammation** is considered likely when necrosis or scarring (**late gadolinium enhancement**) is detected in conjunction with oedema (**high signal T2** intensity) and hyperaemia (early gadolinium enhancement).<sup>37,64,65</sup> The presence of a **pericardial effusion** supports the diagnosis of **myocarditis**.<sup>37</sup>

Electrocardiography,<sup>66</sup> tissue Doppler imaging,<sup>67</sup> and cardiac MRI<sup>68</sup> can facilitate early detection of myocardial dysfunction in children with genetically determined cardiomyopathies, such as Duchenne muscular dystrophy, before the development of a typical dilated cardiomyopathy phenotype.

**Histological** findings include irregular myocyte hypertrophy, with or without areas of fibrosis and myocyte damage. A lymphocytic infiltrate indicates the presence of inflammation that could be post-viral or immune-mediated (figure 2E, figure 2F). Because of possible sampling error and variability in mechanisms of viral damage, the absence of these histological changes does not exclude the diagnosis of myocarditis. **PCR** can identify **viral genome within** the **myocardium**, even when inflammatory changes have resolved.<sup>34</sup> Cardiac histological examination can also help to identify specific disorders, such as sarcoidosis and haemochromatosis, and abnormal mitochondria, lysosomes, or myocardial inclusions, can indicate the presence of specific metabolic and storage disorders. **Endomyocardial biopsy** can be **useful** when a

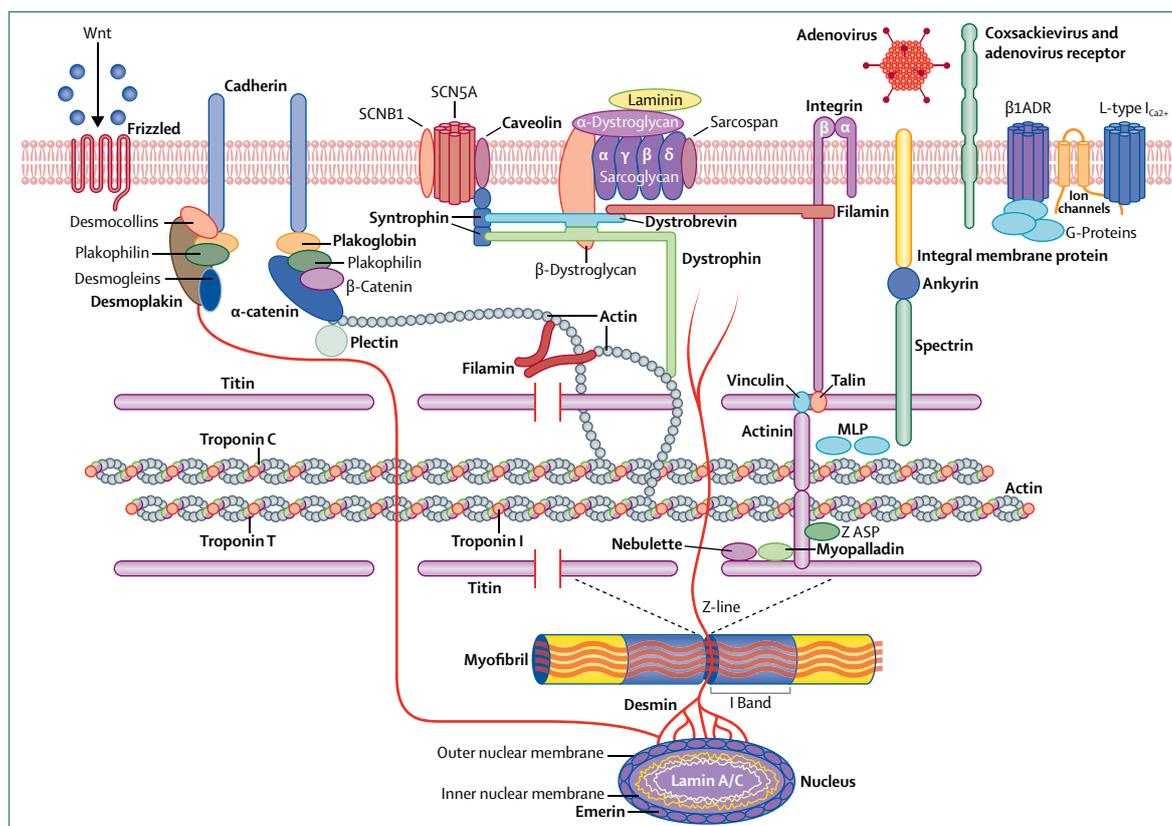


Figure 3: Genetic causes of dilated cardiomyopathy

Adapted from reference 76, by permission of Elsevier.  $\beta$ 1ADR= $\beta$ 1ADR adrenergic receptor. MLP=muscle LIM protein.

specific diagnosis is suspected that would influence therapy<sup>3,69,70</sup> and is most helpful in patients with dilated cardiomyopathy who have recent onset of heart failure, ventricular arrhythmias, or Mobitz type II second or third degree atrioventricular heart block.<sup>69</sup>

**Biomarkers**, most commonly B-type natriuretic peptide (BNP) and N-terminal-BNP, are **elevated in proportion** to the **severity** of heart failure,<sup>71</sup> leading to guidelines for their clinical use.<sup>72</sup> In children with dilated cardiomyopathy, a BNP concentration greater than 300 pg/mL has been strongly associated with death, transplantation, or hospital admission due to heart failure.<sup>73</sup>

## Genetics

Familial patterns of dilated cardiomyopathy and genetic causes have been identified in up to 35% of cases of idiopathic disease.<sup>11,74</sup> Most commonly, familial dilated cardiomyopathy is inherited as an autosomal dominant trait, with 50% of offspring at risk of inheriting the disease-causing gene mutation. Autosomal recessive, X-linked, and mitochondrial inheritance patterns are less common.<sup>74,75</sup> The genetic causes of dilated cardiomyopathy are diverse, and mechanistically involve genes that encode the sarcomere, cytoskeleton, nuclear envelope,

transcriptional pathways, and mitochondrial proteins (figure 3). Clinically and functionally, the genetic causes can be classified as those with a predominant cardiac phenotype, those associated with neuromuscular disease, and dilated cardiomyopathy presenting as part of a syndrome (table 1).

The main genes associated with a predominant cardiac phenotype include *TTN* and *LMNA*, which account for up to 25% and 5% of all cases of autosomal dominant dilated cardiomyopathy, respectively.<sup>77-79</sup> Titin is a component of the sarcomere structure and represents the largest known protein in humans. Pathogenic variants in the *TTN* gene are mainly truncation mutations;<sup>80</sup> however, the precise pathogenic role of missense mutations in *TTN* are not fully elucidated. Mutations in the nuclear envelope intermediate filament protein, *LMNA*, classically cause both dilated cardiomyopathy and progressive conduction disease, including atrioventricular block, atrial fibrillation, and ventricular arrhythmias.<sup>78,79,81</sup> *LMNA* mutations also cause Emery-Dreifuss muscular dystrophy and Dunnigan partial lipodystrophy, with the X-linked *EMD* encoding a nuclear lamin protein.<sup>82</sup>

Mutations in sarcomere genes have likewise been implicated in autosomal dominant dilated cardiomyopathy, and encode primarily the same thick and thin filament

contractile sarcomere proteins observed in hypertrophic cardiomyopathy, including *MYH7*, *MYBPC3*, *ACTC1*, and *TNNT2*.<sup>83</sup> Collectively, sarcomere gene mutations account for up to 5% of all cases of dilated cardiomyopathy. Other genetic causes of a predominant cardiac dilated cardiomyopathy phenotype include mutations in the Z-disc protein-encoding genes, such as muscle LIM protein (*CSRP3*), *ACTN2*, *MYPN*, and cypher/*ZASP* genes; other genes encoding desmosomal proteins, such as *DES*; and genes associated with ion channel function, including *PLN* (calcium handling) and the *SCN5A* gene.<sup>84–88</sup>

The cardiac dilated cardiomyopathy phenotype associated with neuromuscular disease is caused by mutations in various genes. By contrast to the pure cardiac dilated cardiomyopathy mutations, mutations in patients with dilated cardiomyopathy who have a neuromuscular phenotype commonly have X-linked or autosomal recessive inheritance. In addition to Emery-Dreifuss muscular dystrophy, Duchenne muscular dystrophy and Becker muscular dystrophy commonly present in childhood, with a predominant musculoskeletal phenotype, in the setting of coexistent dilated cardiomyopathy. These two dystrophies are caused by mutations in the *DMD* gene.<sup>89,90</sup>

Among the syndromic diseases in which dilated cardiomyopathy is part of the phenotype, the mitochondrial diseases predominate, with early clinical presentation of disease. Mutations in mitochondrial DNA or in nuclear genes that code for mitochondrial components have also been implicated in dilated cardiomyopathy. Patients with mitochondrial gene mutations often present in early childhood, and have a range of multisystem disorders including skeletal myopathies, neurological, and developmental symptoms, in conjunction with dilated cardiomyopathy of variable severity. Other syndromic disorders that can present with dilated cardiomyopathy include Barth syndrome—an X-linked disorder that often presents in childhood with cardiomyopathy, cyclic neutropenia, and skeletal myopathy, and that is caused by mutations in the *TAZ/G4.5* gene.<sup>91,92</sup>

Left ventricular non-compaction is most commonly inherited in an X-linked recessive or autosomal dominant pattern, with recessive and mitochondrial inheritance also described.<sup>93–95</sup> X-linked left ventricular non-compaction is usually caused by mutations in the *TAZ/G4.5* gene resulting in Barth syndrome. Sarcomere-encoding gene mutations, most commonly in *MYH7* and *MYBPC3*, account for up to 25% of cases of left ventricular non-compaction.<sup>96</sup> Mutations in the *SCN5A* and *DMD* genes have also been associated with left ventricular non-compaction.<sup>97,98</sup>

### Mechanisms of disease pathogenesis

Mutations in over 50 genes, which include missense changes, deletions, insertions, and variants that alter splicing, have been associated with dilated cardio-

myopathy.<sup>75</sup> These mutations can lead to either abnormal proteins of normal size, leading to a dominant negative effect, or abnormal truncated proteins, leading to a haploinsufficiency mechanism. The diversity of genes identified, including sarcomere, Z-disc-related, cytoskeletal, nuclear envelope, and ion channel genes, suggests great complexity in the mechanisms underpinning dilated cardiomyopathy (figure 1). Furthermore, consideration of dilated cardiomyopathy as a single gene disorder is probably too simplistic, with variants in several genes likely to also support an oligogenic basis of dilated cardiomyopathy.

To date, several mechanistic insights have been reported, including alterations in force generation and transmission, altered metabolic profiles, disruption of energy production and consumption, abnormal nuclear integrity, transcriptional dysregulation, altered protein degradation, and ion channel abnormalities—mainly, calcium homeostasis and abnormal calcium handling.<sup>75,99,100</sup> These diverse mechanisms in dilated cardiomyopathy have also been suggested to lead to a final common pathway, with the outcome of altered force generation and transmission, and cell death, leading to left ventricular systolic dysfunction and heart failure.<sup>101</sup> These mechanistic insights, based on studies in various different experimental models and in a range of dilated cardiomyopathy genes, collectively underscore the genetic complexity of dilated cardiomyopathy and the pathways from gene mutation to human disease.

### Clinical and genetic testing in families

The genetic basis of dilated cardiomyopathy highlights the importance of screening at-risk family members.<sup>1,102,103</sup> Dependent on the mode of inheritance, up to 50% of relatives might carry a pathogenic gene mutation, which provides a basis for possible early intervention, prevention of disease progression, and improving clinical outcomes in patients with dilated cardiomyopathy. Genetic testing is now commercially available for dilated cardiomyopathy in a cardiomyopathy panel consisting of 20–50 genes. Other next generation sequencing methods, such as whole exome or genome sequencing, are emerging approaches for more extensive genetic analysis, with both research and clinical implications.<sup>104</sup> The pick-up rate of genetic testing in dilated cardiomyopathy ranges from 15% to 40% depending on patient selection and family history.<sup>104–06</sup>

The basic evaluation of a family in which dilated cardiomyopathy is present should include a detailed family history spanning a minimum of three generations, and initial clinical screening of first-degree relatives. Clinical screening should include an ECG and 2D transthoracic echocardiogram as first-line investigations. Additional investigations, such as exercise testing, 24 h ambulatory ECG monitoring, and cardiac MRI should be considered on an individual basis. In families in which pathogenic gene mutation has been

identified, cascade genetic testing in at-risk relatives can be offered with comprehensive pretest and post-test genetic counselling.<sup>107</sup> Tested individuals who do not carry the pathogenic gene mutation can be released from lifelong clinical surveillance, whereas those who are identified as gene mutation carriers are monitored at regular intervals and any available prevention strategies initiated. In the absence of an identified pathogenic mutation, first-degree relatives should have periodic ECG and echocardiography. The frequency of review should be individualised depending on the family history and age of onset of disease in affected family

members. As a general rule, clinical screening of family relatives should occur every 1–2 years up to age 20 years, every 2–3 years from 20 years to 40 years, then every 3–5 years thereafter.

Findings from longitudinal studies<sup>108,109</sup> have shown that about 10% of individuals with mild echocardiographic abnormalities at initial screening will develop cardiomyopathy within 5 years. Additional investigations, including cardiac MRI and measurement of biomarkers such as BNP, might help to distinguish early disease from normal variants (eg, cardiac adaptation to athletic training).

|   | Number of patients | Population   | Design   | Active drug or device  | Outcome  |
|---|--------------------|--|--|--|--|
| <b>ACEIs</b>  |                    |  |  |  |  |
| Consensus <sup>117</sup><br><i>N Engl J Med</i> 1987        | 253                | NYHA IV; 38 (15%) with non-ischaemic cardiomyopathy  | Double-blind, placebo-controlled, parallel group | Enalapril (target 20 mg twice a day)                               | Improved survival and NYHA class; mean dose 18.4 mg/day                                      |
| SOLVD drug <sup>118</sup><br><i>N Engl J Med</i> 1991       | 2569               | NYHA II–III; 469 (18%) with non-ischaemic cardiomyopathy   | Double-blind, placebo-controlled, parallel group | Enalapril (target 10 mg twice a day)                               | Improved survival and fewer hospital admissions; mean dose 11 mg/day                         |
| SOLVD Prevention <sup>119</sup><br><i>N Engl J Med</i> 1992 | 4228               | NYHA I; 396 (10%) with non-ischaemic cardiomyopathy  | Double-blind, placebo-controlled, parallel group | Enalapril (target 10 mg twice a day)                               | Improved survival, fewer hospital admissions, and less HF progression; mean dose 12.7 mg/day |
| <b>Angiotensin receptor antagonists</b>                     |                    |  |  |  |  |
| ELITE II <sup>120</sup><br><i>Lancet</i> 2000               | 3152               | NYHA II–IV; ≥60 years; 1292 (41%) with non-ischaemic cardiomyopathy  | Double-blind, active-controlled                  | Losartan (50 mg once a day) vs captopril (50 mg three times a day) | No difference in survival or hospital admissions   |
| CHARM-alternative <sup>121</sup><br><i>Lancet</i> 2003      | 2028               | NYHA II–IV; β blocker; 396 (20%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor intolerant   | Double-blind, placebo-controlled                 | Candesartan Cilexetil (32 mg once a day)                           | Reduced mortality and hospital admissions  |
| <b>β blockers</b>   |                    |  |  |  |  |
| US Heart Failure <sup>122</sup><br><i>N Engl J Med</i> 1996 | 1094               | NYHA II–IV; 570 (52%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor or angiotensin receptor blocker   | Double-blind, placebo-controlled                 | Carvedilol (variable dosing)                                       | Reduced mortality and hospital admissions  |
| Cibis II <sup>123</sup><br><i>Lancet</i> 1999               | 2647               | NYHA class III–IV; 317 (12%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor or angiotensin receptor blocker  | Double-blind, placebo-controlled                 | Bisoprolol (10 mg once a day)                                      | Reduced mortality and hospital admissions  |
| MERIT HF <sup>124</sup><br><i>Lancet</i> 1999               | 3991               | NYHA II–IV; 1385 (35%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor or angiotensin receptor blocker  | Double-blind, placebo-controlled                 | Metoprolol controlled release (200 mg once a day)                  | Reduced mortality and hospital admissions  |
| Copernicus <sup>125</sup><br><i>N Engl J Med</i> 2001       | 2289               | NYHA III–IV; 755 (33%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor or angiotensin receptor blocker  | Double-blind, placebo-controlled                 | Carvedilol (25 mg twice a day)                                     | Reduced mortality and hospital admissions  |
| <b>Mineralocorticoid antagonists</b>                        |                    |  |  |  |  |
| Rales <sup>126</sup><br><i>N Engl J Med</i> 1999            | 1663               | NYHA III–IV; 765 (46%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor or angiotensin receptor blocker  | Double-blind, placebo-controlled                 | Spirolactone (25 mg once a day)                                    | Reduced mortality and hospital admissions  |
| Emphasis <sup>127</sup><br><i>N Engl J Med</i> 2011         | 2737               | NYHA II; 846 (31%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor or angiotensin receptor blocker + β blocker  | Double-blind, placebo-controlled                 | Eplerenone (25–50 mg once a day)                                   | Reduced mortality and hospital admissions  |
| <b>Ivabradine</b>   |                    |  |  |  |  |
| Shift <sup>128</sup><br><i>Lancet</i> 2010                  | 6558               | NYHA II–IV; sinus rhythm with heart rate of >70 beats per min; 2087 (33%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor or angiotensin receptor blocker + β blocker | DB, PC   | Ivabradine (5–7.5 mg twice a day)                                  | Reduced hospital admissions  |
| <b>Angiotensin receptor-neprilysin inhibitors</b>           |                    |  |  |  |  |
| Paradigm <sup>129</sup><br><i>N Engl J Med</i> 2014         | 8442               | NYHA II–IV; 3363 (40%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor or angiotensin receptor blocker; β blocker   | Double-blind, active-controlled with enalapril   | Sacubitril valsartan (200 mg twice a day)                          | Reduced mortality and hospital admissions  |

(Table 3 continued on next page)

|  | Number of patients | Population   | Design  | Active drug or device  | Outcome   |
|--|--------------------|--|---|--|---|
| (Continued from previous page)   |                    |  |   |  |   |
| <b>Devices</b>   |                    |  |   |  |   |
| SCD-Heft <sup>129</sup><br><i>N Engl J Med</i> 2005  | 2521               | NYHA II-III; 1211 (48%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor or angiotensin receptor blocker + $\beta$ blocker                   | Placebo vs amiodarone vs implantable cardioverter defibrillator   | Single lead implantable cardioverter defibrillator                         | Reduced mortality with ICD; Amiodarone had no effect  |
| COMPANION <sup>130</sup><br><i>N Engl J Med</i> 2004   | 1520               | NYHA III-IV; QRS $\geq$ 120 ms; 678 (44%) with non-ischaemic cardiomyopathy; angiotensin converting enzyme inhibitor or angiotensin receptor blocker + $\beta$ blocker | Randomised optimal medical therapy vs cardiac resynchronisation therapy vs cardiac resynchronisation therapy + implantable cardioverter defibrillator | Cardiac resynchronisation therapy + implantable cardioverter defibrillator | Reduced mortality and hospital admissions with cardiac resynchronisation therapy and cardiac resynchronisation therapy + implantable cardioverter defibrillator |
| CARE HF <sup>131</sup><br><i>N Engl J Med</i> 2005   | 813                | NYHA III-IV; QRS $\geq$ 120 ms; 370 (46%) with non-ischaemic cardiomyopathy  | Randomised optimal medical therapy vs cardiac resynchronisation therapy   | Cardiac resynchronisation therapy  | Reduced mortality and improved quality of life with cardiac resynchronisation therapy   |
| RAFT <sup>132</sup><br><i>N Engl J Med</i> 2010  | 1798               | NYHA II-III; QRS $\geq$ 120 ms; 597 (33%) with non-ischaemic cardiomyopathy; optimal medical therapy   | ICD vs CRT-ICD  | CRT-ICD  | Reduced mortality and hospital admissions with CRT-ICD  |
| DANISH <sup>133</sup><br><i>N Engl J Med</i> 2016  | 1116               | NYHA II-IV; 1116 (100%) with non-ischaemic cardiomyopathy; optimal medical therapy including cardiac resynchronisation pacemaker if indicated                          | Randomised optimal medical therapy vs optimal medical therapy + implantable cardioverter defibrillator  | Lead implantable cardioverter defibrillator                                | Reduced sudden cardiac death, but no difference in all-cause mortality  |
| <b>Mechanical circulatory support</b>  |                    |  |   |  |   |
| Rematch <sup>134</sup><br><i>N Engl J Med</i> 2001   | 129                | End-stage heart failure; 35 (27%) with non-ischaemic cardiomyopathy  | Optimal medical therapy vs left ventricular assist device   | Heartmate I left ventricular assist device                                 | Reduced mortality with left ventricular assist device   |
| Rematch 2 <sup>135</sup><br><i>N Engl J Med</i> 2009   | 200                | End-stage heart failure; 67 (33%) with non-ischaemic cardiomyopathy  | Pulsatile left ventricular assist device vs continuous flow left ventricular assist device  | Heartmate II vs Heartmate I  | Improved survival and less device failure with Heartmate II   |
| CRT-ICD=cardiac resynchronisation therapy-implantable cardioverter defibrillator. DCM=dilated cardiomyopathy. ICD=implantable cardioverter defibrillator. NYHA=New York Heart Association. |                    |  |   |  |   |
| Table 3: Pivotal treatment trials of patients with DCM   |                    |  |   |  |   |

## Management

### Established disease

For patients with established dilated cardiomyopathy, treatment is directed at the major clinical manifestations of heart failure and arrhythmias. Prevention and treatment of thromboembolism might also be required, particularly in the context of sustained or recurrent atrial fibrillation or flutter.

The pharmacological treatment of symptomatic heart failure with reduced ejection fraction has been extensively reviewed in heart failure guidelines.<sup>3,110,111</sup>

Management of acute (decompensated) heart failure remains an area of unmet need because no drug therapy has been shown to improve survival. The most frequently administered drug is intravenous furosemide, but the optimal dose and form of administration remains uncertain.<sup>112</sup> If patients do not respond, additional therapies include sublingual or intravenous glyceryl trinitrate to relieve pulmonary congestion. For patients who are hypotensive positive inotropic or pressor agents can also be used to stabilise blood pressure. Multiple drugs with vasodilator, natriuretic, or inotropic properties have been investigated in clinical trials; however, in most cases, results have proved disappointing.<sup>113</sup> Three novel drugs that show promise are relaxin, ularitide, and omecantiv mecarbil.<sup>114</sup> The future of these drugs will be determined by the outcome of ongoing phase 3 clinical trials.<sup>115,116</sup>

### Pharmacological treatment

First-line drugs are those that have been shown in large-scale clinical trials to improve survival and reduce hospital admissions (table 3). Angiotensin converting enzyme (ACE) inhibitors (or angiotensin receptor antagonists in patients who are intolerant of ACE inhibitors because of cough) and  $\beta$  blockers are now regarded as basic building blocks of drug therapy for chronic heart failure. Mineralocorticoid antagonists and the I<sub>1</sub> channel inhibitor, ivabradine, have been shown to provide incremental benefits in survival or hospital admission when combined with ACE inhibitors and  $\beta$  blockers.<sup>126–28</sup> The combined angiotensin receptor-neprilysin inhibitor, sacubitril—valsartan, has been shown to reduce total mortality and hospital admissions compared with the ACE inhibitor enalapril,<sup>116</sup> and could replace ACE inhibitors as one of the cornerstones of drug therapy in chronic heart failure. Loop diuretics are commonly used to control symptoms, but have not been shown to affect survival. Digoxin is recommended for patients with sustained atrial fibrillation or refractory heart failure symptoms; however, a post-hoc analysis of the DIG study suggested that the benefit of digoxin in patients with symptomatic heart failure and sinus rhythm was similar to that observed with ivabradine in the SHIFT trial.<sup>136</sup>

Although the information regarding drug therapy in the previous paragraph applies to all patients with chronic

heart failure and reduced ejection fraction, the additional information provided by a specific genetic diagnosis in patients with familial dilated cardiomyopathy might indicate additional or alternative drug therapies. Striking examples of specific genetic diagnoses include mutations in the *SCN5A* gene, which encodes the  $\alpha$  subunit of the cardiac sodium channel.<sup>137–39</sup> Gain-of-function mutations of the *SCN5A* gene are associated with a clinical phenotype of frequent Purkinje fibre premature ventricular ectopics in association with dilated cardiomyopathy.<sup>137–39</sup> These patients might respond poorly to conventional drug therapy, but their phenotype can be reversed by drugs that inhibit the sodium channel, such as amiodarone or flecainide.<sup>137–39</sup> By contrast, in children, little evidence exists that conventional heart failure therapy changes outcomes in the presence of established cardiomyopathy.<sup>140</sup> These findings might reflect differences in heart failure cause and the difficulty of undertaking adequately powered studies.

The management of lymphocytic myocarditis revolves around supportive therapy for heart failure and arrhythmias. Early randomised trials have shown no survival or functional benefit of immunosuppressive therapy consisting of prednisolone alone,<sup>141</sup> or in combination with either azathioprine or ciclosporin, in patients with lymphocytic myocarditis from any cause.<sup>142</sup> Patients with circulating cardiac autoantibodies and no detectable viral genome in myocardium might represent a subgroup with a more favourable response to immunosuppressive therapy,<sup>143</sup> as do patients with HLA upregulation on endomyocardial biopsy.<sup>144</sup> Intravenous immunoglobulin administered to patients with recent-onset dilated cardiomyopathy was not shown to be of benefit,<sup>145</sup> but is widely used in paediatric patients with myocarditis.<sup>146</sup>

### Non-pharmacological treatment

Non-pharmacological treatments include salt and fluid restriction. Although widely recommended, the evidence base to support these interventions is small.<sup>3,110,111</sup> Exercise training has been shown to improve quality of life with little effect on overall survival.<sup>147</sup> Sleep-disordered breathing affects up to 50% of patients with heart failure; however, treatment remains uncertain. Adaptive servoventilation, a type of non-invasive ventilatory support, has been found to worsen outcome in patients with central sleep apnoea;<sup>148</sup> however, other trials of non-invasive ventilation in obstructive sleep apnoea are ongoing (registered with ClinicalTrials.gov, numbers NCT01953874 and NCT01128816).

Arguably the most important non-pharmacological intervention for chronic heart failure is enrolment of the patient in a multidisciplinary heart failure service. Evidence has shown reduced hospital admissions and mortality in patients receiving multidisciplinary care.<sup>149,150</sup> Essential elements include education of patients and carers about dietary and lifestyle measures; self-monitoring strategies; medication adherence, including

up-titration of evidence-based therapies; and avoidance of potentially harmful drugs. Evidence favours home-based models of multidisciplinary care.<sup>151</sup>

### Electrical device therapies

Indications for implantable electrical devices include prevention and treatment of ventricular tachyarrhythmias, treatment of symptomatic bradyarrhythmias, and cardiac resynchronisation (also known as biventricular pacing). Implantable cardioverter defibrillators (ICDs) are indicated for patients who have survived ventricular fibrillation or symptomatic ventricular tachycardia. Implantation of an ICD for primary prevention in patients with non-ischaemic dilated cardiomyopathy does not provide an overall survival benefit, despite a reduced risk of sudden cardiac death.<sup>133</sup> Modern imaging modalities such as cardiac MRI, could help to refine risk stratification of patients with non-ischaemic dilated cardiomyopathy so that implantation of ICDs can be limited to patients at highest risk.<sup>152,153</sup>

Patients with dilated cardiomyopathy might require pacing for symptomatic bradycardia. Traditional right ventricular pacing can induce left ventricular dyssynchrony and precipitate heart failure in patients with or at risk of dilated cardiomyopathy.<sup>154,155</sup> For this reason, biventricular pacing is recommended for patients with dilated cardiomyopathy and symptomatic bradycardia. The most common indication for biventricular pacing in patients with dilated cardiomyopathy is the presence of left ventricular dys-synchrony usually manifested as left bundle branch block on the surface ECG. Although early trials focused on patients with dilated cardiomyopathy with advanced symptomatic heart failure<sup>131,156</sup> more recent studies<sup>157</sup> have focused on patients with dilated cardiomyopathy with milder symptoms. In appropriately selected patients, cardiac resynchronisation therapy (with or without ICD) improves survival, reduces hospital admissions, improves quality of life, and induces reverse left ventricular remodelling when added to optimal medical therapy. Recommendations about electrical device therapies in children with dilated cardiomyopathy are broadly similar to those of adults, but based on considerably less evidence.<sup>70</sup>

### Surgery

The two major surgical options in patients with dilated cardiomyopathy are heart transplantation and implantation of long-term mechanical circulatory support, either as a bridge to transplantation or as destination therapy. Other surgical approaches include surgical correction of mitral regurgitation, left ventricular remodelling, use of restraints to prevent progressive ventricular dilatation, or a combination of these approaches.<sup>158</sup> None of these methods has been shown to improve survival when compared with appropriately matched controls. Whether less invasive approaches to mitral valve repair or replacement in the setting of dilated cardiomyopathy lead to more favourable outcomes remains to be seen.<sup>159</sup>

### Heart transplantation

Patients with dilated cardiomyopathy constitute the single largest group of patients undergoing heart transplantation. Compared with the broader population with chronic heart failure, patients with dilated cardiomyopathy are usually younger with fewer comorbidities. Patients with dilated cardiomyopathy eligible for heart transplantation are those with intractable advanced symptomatic heart failure (New York Heart Association class III–IV<sup>160</sup>) despite optimal medical and device therapy. Cardiopulmonary stress testing is often used to provide an objective measure of functional limitation and to risk-stratify referred patients.<sup>160</sup> Most patients with dilated cardiomyopathy assessed for heart transplantation have an expected survival of less than 2 years without transplantation or long-term mechanical support. These survival estimates contrast with a median survival of more than 10 years after transplantation for adults and more than 20 years for infants younger than 1 year.<sup>161,162</sup>

### Mechanical support

A range of acute and long-term mechanical circulatory support devices are available to treat patients with cardiogenic shock or intractable advanced chronic heart failure. The most commonly used device for acute circulatory support in both adults and children is extracorporeal membrane oxygenation (ECMO). Implanted patients are usually critically ill with imminent or established multiorgan failure. These patients are not immediate candidates for heart transplantation and ECMO implantation in such individuals is used as a bridge to decision or candidacy. Following improvement in other organ systems, these patients could be considered for transplantation or transitioned to long-term mechanical circulatory support devices.<sup>163</sup>

The remarkable evolution in long-term mechanical circulatory support devices over the past decade has seen the virtual replacement of large implantable pulsatile devices with smaller and more reliable continuous flow ventricular assist devices.<sup>135,164</sup> Improved reliability and outcomes of ventricular assist devices has led to more widespread and earlier use. Among the smallest paediatric patients, paracorporeal pulsatile devices remain an important form of long-term mechanical support.<sup>165</sup> Most patients with dilated cardiomyopathy can be supported with a left-sided ventricular assist device; however, about 20% of patients require biventricular support. With existing devices, 6 month survival rates following implantation of a left ventricular assist device have been reported to be in excess of 80% in children and 90% in adults.<sup>164,165</sup> survival rates after implantation of a biventricular assist device are substantially inferior.<sup>166</sup> The aim of long-term mechanical circulatory support devices in most patients is to bridge the patient to heart transplantation; however, for patients with dilated cardiomyopathy who have contraindications to heart

transplantation, implantation of a long-term mechanical circulatory support device could be considered as a destination treatment for advanced heart failure.<sup>167</sup>

### Controversies and research questions

Many interesting questions remain related to the genetic basis and clinical management of dilated cardiomyopathy, and numerous cases of idiopathic and familial disease are yet to be explained. The discovery of new causative gene mutations and, possibly, use of whole genome sequencing, should contribute to an increase in diagnostic rates in patients with dilated cardiomyopathy. Appropriate early management of increasing numbers of individuals with preclinical disease (genotype-positive, phenotype-negative) is unclear. Two short-term, randomised, placebo-controlled trials<sup>168,169</sup> in patients with early familial dilated cardiomyopathy and in patients with Duchenne muscular dystrophy with preserved ventricular function showed favourable echocardiographic changes in treated patients. Whether individuals with preclinical disease would benefit from early pharmacological (or any other) interventions to prevent or delay the onset of clinical cardiomyopathy remains unresolved.

The potential use of stem cells to improve outcomes in patients with congestive heart failure and reduced left ventricular ejection fraction is a topic of considerable interest.<sup>170</sup> Preclinical studies of stem-cell therapies in dilated cardiomyopathy have been limited by the small number of suitable experimental models. Furthermore, no clinical studies have shown that stem-cell therapy improves the clinical outcome of patients with dilated cardiomyopathy.<sup>171</sup> Many questions remain, including about how stem cells exert a beneficial effect in a chronically myopathic ventricle, which stem cells should be used, how many stem cells should be administered, and by what route.

#### Contributors

All authors contributed equally to the literature search and writing of this report.

#### Declaration of interests

RGW serves on an advisory board for Actelion pharmaceuticals. PM has received grant support from Novartis, served on the Heart Failure Advisory Board for Novartis, and received speaker fees from Servier. CS declares no competing interests.

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