Almanac 2014: cardiomyopathies*
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Abstract: Cardiomyopathies are myocardial disorders that are not explained by abnormal loading conditions and coronary artery disease. They are classified into a number of morphological and functional phenotypes that can be caused by genetic and non-genetic mechanisms. The dominant themes in papers published in 2012–2013 are similar to those reported in Almanac 2011, namely, the use (and interpretation) of genetic testing, development and application of novel non-invasive imaging techniques and use of serum biomarkers for diagnosis and prognosis. An important innovation since the last Almanac is the development of more sophisticated models for predicting adverse clinical events.

INTRODUCTION
Cardiomyopathies are myocardial disorders that are not explained by abnormal loading conditions and coronary artery disease. They are classified into a number of morphological and functional phenotypes that can be caused by genetic and non-genetic mechanisms. The dominant themes in papers published in 2012–2013 are similar to those reported in Almanac 2011, namely, the use (and interpretation) of genetic testing, development and application of novel non-invasive imaging techniques and use of serum biomarkers for diagnosis and prognosis. An important innovation since the last Almanac is the development of more sophisticated models for predicting adverse clinical events.

HYPERTROPHIC CARDIOMYOPATHY
Cardiac imaging and circulating biomarkers
Hypertrophic cardiomyopathy (HCM) occurs in one in every 500 adults and in most individuals is inherited as an autosomal dominant trait caused by mutations in cardiac sarcomere protein genes and is associated with an increased risk of sudden cardiac death (SCD), progressive ventricular dysfunction and stroke (Figure 1)1-3. Diagnostic tools such as ECG and echocardiography remain fundamental to diagnosis and treatment of HCM but cardiac MRI (CMR) improves diagnostic accuracy and provides additional phenotypic information in patients with established disease (Figure 2)4-7.

For example, in one study, CMR identified hypertrophy in about 10% of sarcomere mutation carriers thought to have normal wall thickness by echocardiography8. Novel CMR sequences, such as T1 mapping, provide quantitative estimates of the myocardial extracellular volume (ECV) (and therefore a surrogate measure of interstitial fibrosis)9 and, in one study, an increase in ECV was reported in individuals with sarcomere mutations but without LV hypertrophy9. These findings suggest that selective use of CMR may be helpful in family screening, particularly when they are other features consistent with HCM, such as ECG abnormalities.

The clinical relevance of myocardial scar inferred from abnormal gadolinium enhanced CMR is a recurring subject in the literature. Available data support a relation among late gadolinium enhancement (LGE), representing macroscopic focal myocardial scar, and cardiovascular mortality, heart failure death and all-cause mortality but show only a trend towards an increased risk of SCD10,11. ECV measured by CMR correlates with concentrations of both N-terminal pro-brain natriuretic peptide and serum biomarkers of collagen synthesis providing further evidence that myocardial fibrosis is important early in disease pathogenesis9.

Numerous papers have investigated biomarkers as a tool for diagnosis and prognosis and have shown predicting poor outcome in patients with heart failure12. In a study of 772 patients with HCM, brain natriuretic peptide (BNP) was an independent predictor of morbi-
obstruction (LVOTO), and palliation of limiting symptoms caused by systolic or diastolic dysfunction. There have been few developments in therapy since the last Almanac, but early prophylactic β-blocker therapy in physically active patients (NYHA 1 and 2) with provokable LVOTO has been shown to be effective in reducing outflow gradients during physiological exercise\textsuperscript{17}. Another study has confirmed the additive benefit of disopyramide in therapy of symptomatic patients with obstruction resistant to initial therapy with β-blocker or verapamil\textsuperscript{18}.

Invasive treatment of LVOTO is recommended for patients with drug-refractory symptoms. Several stu-

\begin{figure}[h]
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\caption{Prevalence of atrial fibrillation and thromboembolism. Guttmann et al\textsuperscript{3} investigated a population of 7381 patients with hypertrophic cardiomyopathy. A meta-analysis reveals an overall prevalence of atrial fibrillation of 22.45%. The forest plot from random effect meta-analysis shows study-specific prevalence and the pooled (overall) prevalence of AF. The heterogeneity between the study was estimated as $I^2=78.9\%$ (\(p<0.001\)). The overall prevalence of thromboembolism is 27.09%. The forest plot from random effect meta-analysis shows study-specific prevalence and the pooled (overall) prevalence of thromboembolism in patients with hypertrophic cardiomyopathy and atrial fibrillation. The heterogeneity between the studies was estimated as $I^2=61.4\%$ (\(p<0.01\)).}
\end{figure}
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Another study reports a cumulative incidence of HCM-related death of 3.3% at 5 years. Finally, in 699 patients where age and persistent atrial fibrillation were reported to be predictors of poorer outcome in patients undergoing surgical myectomy.

New data have re-examined the efficacy of dual chamber pacing for refractory symptomatic LVOTO. In a recent Cochrane review, it was noted that all data derive from small studies and that the few randomised trials concentrate on physiological outcome measures rather than hard clinical endpoints. As a result, they recommend large and high quality trials.

**Prevention of SCD**

A recent systematic review and meta-analysis of 27 studies reported an appropriate ICD intervention rate of 3.3% per year with an inappropriate shock rate of 4.8% per annum but in a single centre study of 334 patients with HCM, patients still had a significant cardiovascular mortality (predominantly heart failure) and experienced frequent inappropriate shocks and implant complications. These findings suggest that new strategies are required to improve patient selection for ICDs and prevent disease progression in those who receive a device.

Contemporary risk assessment relies on a small number of readily obtained clinical risk markers to predict SCD and is widely used to guide implantation of ICDs, but recent evidence suggests that this approach distinguishes high and low risk individuals with only limited predictive power. Additionally, several recently proposed prognostic factors (such as LVOTO and age) are not included in the assessment. Recent data have also reinforced the importance of age in risk stratification. In a study of 428 patients above the age of 60 years, 3.7% died secondary to HCM-related causes including embolic stroke, heart failure and transplantation. SCD events occurred in five patients (1.2% or 0.2% per year). The authors conclude that patients with HCM surviving to an age above 60 are at low risk for HCM-related mortality and sudden death.

It has been suggested that conventional risk prediction algorithms do not apply to paediatric populations. In a paediatric cohort, judged clinically to be at high risk, appropriate ICD shocks were delivered in 19% of 224 patients followed for 4.3±3.3 years with an annual rate of 4.5% per year. However, as device-related complications occurred in 41% (especially lead complications and inappropriate shocks) of patients, more data in paediatric cohorts are required to determine the net benefit of ICD therapy in the young.
In a study comparing clinical screening and predictive genetic testing in children and adolescents, 90 patients with HCM and 361 relatives were followed for 12 years. In a group of 12 young mutation carriers without LV hypertrophy, at initial assessment only two developed HCM during the period of the study suggesting an unexpectedly low penetrance during adolescence, a period conventionally associated with the greatest rates of phenotype conversion. Importantly, the two cases were diagnosed at the ages of 26 and 28 years, emphasising the importance of screening beyond ado-

**Cost efficacy of family screening**

Economic models of genetic testing for the evaluation of families with HCM report that genetic testing is cost-effective when combined with conventional clinical screening. These models are based on the assumption that risk-algorithms from high risk populations can be applied to low risk populations detected through screening and that preventive treatment with ICDs is effective. Additionally, these models and many clinical screening programmes assume a relatively high disease penetrance.

Figure 4. O’Mahony et al. evaluated 334 patients with hypertrophic cardiomyopathy (HCM) at risk of sudden death treated with ICD. They conclude that HCM patients with an ICD have a significant cardiovascular mortality and are exposed to frequent inappropriate shocks and complications. Kaplan–Meier curves for survival free from cardiovascular mortality end-point (A) stratified according to device implantation for primary or secondary prevention, appropriate shocks (B) stratified according to impaired systolic function, inappropriate shocks (C), implant complications (D) stratified according to device complexity, implant complications in patients with single or dual-chamber ICDs (cardiac resynchronisation therapy patients excluded) (E), and implantable cardioverter-defibrillator-related adverse events (inappropriate shocks or implant complications) for the whole cohort (F).
sensitivity and specificity\textsuperscript{46,47}, there is a concern that they remain too sensitive in particular scenarios, most notably athletes and in people of black African ethnic origin, as many structural and electrographic changes considered normal in these groups are also minor diagnostic criteria for ARVC\textsuperscript{48,49}.

Novel methods to detect early phenotypic expression in ARVC have included immunohistochemical and electrophysiological approaches. A report suggested that immunohistochemical demonstration of reduced plakoglobin signal in myocardial biopsies has a sensitivity of 85\% and specificity of 57\% for ARVC. The authors suggested the test could be used in diagnosis\textsuperscript{50}, but the performance of the assay in prephenotypic cases—where it is most valuable—has not been assessed.

Another group of investigators observed a marked reduction in immunoreactive signal for plakoglobin at cardiac myocyte junctions in patients with sarcoidosis and giant cell myocarditis\textsuperscript{51}. This suggests new disease mechanisms involving desmosomal proteins in granulomatous myocarditis and implicates cytokines in dislocation of plakoglobin from desmosomes and in the development of arrhythmia in ARVC.

A recent study reported abnormalities in conduction repolarisation kinetics detected by invasive electrophysiological testing in 10 unrelated individuals and a mouse model with desmoplakin mutations\textsuperscript{52}. Notably, these abnormalities preceded overt structural changes.

Aetiology
ARVC is inherited as an autosomal dominant trait in up to 50\% of cases\textsuperscript{53} and incomplete penetrance (including age-dependent penetrance) and variable clinical expression are the norm. Over the last year, the genetic heterogeneity of ARVC has been underlined by reports of novel mutations in the genes for phospholamban, desmocollin-2, TMEM43, CTNNA3 (α T catenin) and a gene deletion in plakophilin-2\textsuperscript{54-60}. Additionally, mutations in genes hitherto associated with other cardiomyopathies have been reported in families and studies of individuals with ARVC. These include the non-desmosomal protein lamin A/C\textsuperscript{61}. The role of other genetic and epigenetic mechanisms on disease expression remains an area of active research\textsuperscript{62}.

Advances in genetics may improve the specificity of diagnostic algorithms in the future but data show that there are many challenges in the interpretation of sequence data. In a study of 427 controls and 93 ARVC probands\textsuperscript{63}, exons and splice acceptor/donor sites of PKP2, DSP, DSG2, DSC2 and TMEM43 were sequenced. Likely pathogenic mutations were identified in

ARRHYTHMOGENIC RIGHT VENTRICULAR CARDIOMYOPATHY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is clinically characterised by arrhythmia, SCD and progressive heart failure. Cardiomyocyte loss and replacement by fibrous or fibrofatty tissue are histological hallmarks of the disease. ARVC is caused by mutations in genes that encode constituents of the intercalated disc of cardiomyocytes in a large proportion of patients\textsuperscript{44}. Diagnosis requires integration of data from family members, genetic testing, electrocardiography and imaging techniques\textsuperscript{45}. SCD and treatment of symptomatic arrhythmia and heart failure are the major management challenges.

Clinical diagnosis of ARVC

While evidence suggests that recent modification of proposed diagnostic criteria has improved diagnostic sensitivity and specificity\textsuperscript{46,47}, there is a concern that they remain too sensitive in particular scenarios, most notably athletes and in people of black African ethnic origin, as many structural and electrographic changes considered normal in these groups are also minor diagnostic criteria for ARVC\textsuperscript{48,49}.

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58% of the ARVC cases, but were also found in 16% of the controls. The majority (43%) of the candidate mutations in cases were radical (ie, splice site, nonsense, inframe and frame-shift insertions and deletions) compared with only 0.5% of controls but the frequency of missense mutations was similar in cases (21%) and controls (16%). Other important findings were a higher frequency of candidate variants, in particular missense, in non-Caucasian versus Caucasian controls (19.44% vs 5.83%) and similar numbers of variants in the DSP, DSC2 and TMEM43 genes in the ARVC and control groups. These findings illustrate the conservative approach that must be followed when interpreting genetic variants in ARVC.

The use of iPSCs as a model of ARVC was recently described. Heterozygous mutant plakophilin-2 iPSC cardiomyocytes demonstrated exaggerated lipogenesis and apoptosis and calcium-handling deficits were detected in homozygous mutants. Greater understanding of these phenomena might lead to development of novel disease-modifying therapeutic strategies in the future.

Management strategies
Once ARVC has been diagnosed, management should include an assessment of SCD risk, indications for drug therapy and need for lifestyle changes. Although antiarrhythmic drugs such as amiodarone and sotalol are frequently prescribed to decrease arrhythmic burden, there is little evidence that these improve survival or alter the natural history of disease. The same is true for treatment of any associated LV systolic impairment with ACE inhibitors and β-blockers.

Physical exercise and competitive sport have been reported to increase the risk of sudden death and are consequently not recommended. More recently, exercise has been associated with increased disease penetrance and arrhythmic risk in individuals with a desmosomal mutation. Task force criteria were more likely to be met at follow-up and symptoms developed at a younger age in 56 endurance athletes carrying a mutation compared with more sedentary mutation carriers. These athletes also had a decreased lifetime survival free from ventricular tachycardia (VT)/ventricular fibrillation and heart failure. These findings correlate with preclinical observations in murine model of ARVC with plakophilin gene defects.

Catheter ablation to treat recurrent VT in ARVC has been associated with high recurrence rates but a recent multicentre study with focus on newer ablation strategies assessed recurrence of VT following radiofrequency ablation and effect on burden of VT. The authors report a significant reduction in VT burden and longer survival free of VT following epicardial ablation compared with an endocardial procedure. However, recurrence rates remain considerable with an overall freedom from VTof 47% at 1 year. These data suggest that catheter ablation may be helpful in a subgroup of patients with incessant or frequent VT refractory to medical therapy. Some data suggest that VT attributable to localised disease is a further potential indication.

Prevention of sudden death
Current AHA/ACC/ESC guidelines for the management of patients with ventricular arrhythmias and the prevention of SCD recommend ICD implantation in patients with ARVC who have documented sustained VT or ventricular fibrillation and are receiving optimal medical treatment. A recent literature review investigating outcomes and complications of ICD implantation in ARVC included 610 patients. During the 3.8-year follow-up, the authors report appropriate ICD interventions at a rate of 9.5% per year with inappropriate interventions (3.7%) and complications including lead malfunction, displacement and infection (20.3% rate of any complication). Once again, this underlines the need for appropriate risk stratification to minimise morbidity secondary to ICD-related complications. It is important to point out that the patients analysed in this review received an ICD for primary or secondary prevention. This could at least partially account for the high rate of appropriate interventions.

The incremental value and role of CMR in risk stratification were investigated in 69 patients with ARVC-associated mutations (83% with PKP-2 mutations) without prior sustained VT. Electrical abnormalities were found in 61% of patients of whom 48% also had an abnormal CMR (defined as presence of at least a minor task force criterion). Only a single patient (4%) without electrical abnormalities had an abnormal heart on imaging at baseline. Over a period of 5.8±4.4 years, episodes of sustained VT only occurred in patients with ECG and CMR abnormalities. The authors concluded that among mutation carriers the presence of both electrical and CMR abnormalities identified high risk patients. A similar study on prognosis in patients under evaluation for ARVC reports a positive predictive value of an abnormal CMR in 369 patients who fulfilled at least one minor or major diagnostic criterion for ARVC. The negative predictive value of a normal CMR was 98.8% over a follow-up of 4.3±1.5 years.
The search for biomarkers that allow early diagnosis and risk stratification is an active area of research. For example, low serum concentrations of Bridging integrator 1, a membrane-associated protein, were associated with ventricular arrhythmias and reduced functional status in a small cohort of 24 patients with ARVC. A novel strategy to risk prediction in ARVC-associated desmosomal mutation carriers proposes the use of pedigree evaluation, ECG and Holter information. Phenotypic characteristics were used in stratifying the risk of sustained VT. The investigators included 215 patients over a mean follow-up of 7 years. Patients were stratified according to repolarisation and depolarisation abnormalities on ECG. Event-free survival at 5 years was 33% in the high risk group versus 97% in the low risk group.

**DILATED CARDIOMYOPATHY**

Dilated cardiomyopathy (DCM) is one of the commonest heart muscle diseases in developed countries. It is defined as systolic impairment and LV dilatation in the absence of previous myocardial infarction. Research highlighting the importance of genetics in the aetiology of inherited and apparently acquired forms of DCM has been a prominent feature over the last few years. Standard symptomatic and prognostic heart failure treatments are the mainstay of patient management but more attention has been paid recently to the importance of aetiology in guiding the approach to management.

**Genetic subtypes of DCM**

A number of studies have examined the natural history of DCM caused by mutations in the lamin A/C gene (LMNA). This is associated with conduction disease, atrial arrhythmias, heart failure and sudden death and should be suspected when DCM is accompanied by elevated serum creatine kinase, conduction disease or frequent arrhythmias. In these patients, evidence suggests an ICD should be considered at a much lower threshold than in other cases of DCM. A multicentre cohort of 269 patients with LMNA mutation identified non-sustained VT, LVEF <45%, male gender and non-missense mutations as risk factors for malignant ventricular arrhythmias. Some authorities suggest ICD implantation should be considered following even mild cardiac expression.

A recent report suggests that titin (TTN) mutations are a common cause of DCM. TTN mutations have long been considered candidate causes of cardiomyopathy, but the size of the gene and the presence of many allelic variants have made it difficult to study. To overcome some of these difficulties, Herman and colleagues used next generation sequencing to analyse genomic TTN sequence for mutations that altered full-length cDNA (truncating mutations) in 792 subjects (312 DCM, 231 HCM and 249 controls). Truncating TTN mutations were found more frequently in DCM (27%) than in HCM (1%) or controls (3%). TTN mutations cosegregated with DCM in families with penetrant disease, but were also found in 18% of apparently sporadic cases. TTN sequencing is therefore likely to have a prominent role in the genetic evaluation of DCM patients in order to facilitate prephenotypic diagnosis, but the high frequency in controls and sporadic cases suggests that the majority of TTN mutants may yet prove to be susceptibility rather than causative factors.

The importance of epigenetic factors (ie, processes that alter gene activation without changing DNA sequence) has also been highlighted since 2011. In a study comparing genome-wide cardiac DNA methylation in patients with idiopathic DCM and controls, Haas et al detected differences in the methylation of genes implicated in heart failure pathways. These were associated with differences in mRNA expression, a finding further strengthened by studies in zebrafish. Epigenetics research is particularly advanced in cancer biology, contributing to potential therapeutic/diagnostic biomarker and therapeutic targets. Its potential in cardiovascular genetics is yet to be realised.

Genetic predisposition to inflammatory myocardial damage is also emerging as an important theme. The Coxsackie virus, a common cause of myocarditis, causes proteolysis of dystrophin in infected cardiomyocytes. Genetic defects of the dystrophin–glycoprotein complex, associated with muscular dystrophy, frequently cause a DCM where CMR findings are often indistinguishable from myocarditis. In another study, the presence of variants in Toll-like receptors which play a key role in the innate immune response were associated with poorer cardiac function in 158 patients. Finally, Meder et al present data associating the locus containing major histocompatibility genes (MHC I and II) with DCM. The authors identified multiple single nucleotide polymorphisms on chromosome 6p21. A specific locus was identified and an association was found with closely located genes encoding class I and class II major histocompatibility complex heavy chain receptors.

**Prediction of outcomes in DCM**

As in other cardiomyopathies, the role of CMR in predicting outcomes is an active area of study in DCM.
Recent evidence suggests that the presence of midwall LGE identifies a DCM cohort at increased mortality risk. During a median follow-up period of just over 5 years, 27% of 142 DCM with LGE patients died compared with 11% of 330 DCM patients without LGE. The pathophysiological basis of this difference is unclear.

Data describing the diagnostic and prognostic utility of CMR surrogate for other tissue abnormalities, such as oedema, diffuse fibrosis or myocyte disarray, are expected in the near future. Some of the most important data since 2011 have been in children with DCM. In a paediatric registry population of 1803 patients, a 5-year incidence rate of 29% for heart transplantation, 12.1% non-SCD and 2.4% for SCD are quoted. A risk stratification model for SCD based on echocardiography data had a sensitivity of 86% and 57% specificity. Significant factors were LV dilatation, age at diagnosis and posterior wall thinning.

Another study investigating 175 paediatric patients with DCM reports death or transplantation in 26% within 1 year of diagnosis with a survival free of death or transplant of 56% 20 years after diagnosis. An increased risk for death or transplant was associated with the age at diagnosis, presence of familial cardiomyopathy and lower baseline LV fractional shortening.

**Advances in treatment**

Stem cell therapy has been a major topic over the course of the last few years. A 5-year follow-up randomised controlled study of 110 patients with DCM shows improved LV function, improved exercise tolerance and greater long term survival in patients who underwent intracoronary stem cell transplantation. Total mortality was 14% in the stem cell group versus 35% in the controls with rates of pump failure of 5% versus 18%. There was no difference in rates of sudden death. A systematic review on 29 preclinical and 15 clinical studies scrutinised stem cell therapy as a treatment for DCM. The majority of studies showed a modest improvement of LVEF after cell therapy during follow-up. Due to the large heterogeneity in criteria for inclusion, procedure and outcome measure, the need for randomised controlled trials was stressed.

Effect of exercise has been evaluated in patients with DCM following an 8-week period of short term exercise. Significant improvement in cardiac function at rest and following exercise was reported with sedentary patients having the greatest improvement.

The importance of immune activation is another focus for therapy in DCM. Atorvastatin in a small dose reduced the levels of inflammatory cytokines (IL-6, TNF α), uric acid and N-terminal pro-brain natriuretic peptide in a small cohort of patients with DCM.

Overall evidence suggests improving survival in patients with idiopathic DCM. A study of 603 patients over three decades gives evidence for the impact of clinical guidelines on morbidity and mortality. Patients were subdivided in four enrolment periods and a 42% risk reduction per enrolment interval with regard to heart failure-related mortality and sudden death was reported.

**SUMMARY**

Cardiomyopathies continue to be an area of intense interest in the literature. While the spectrum of disease is considerable and continues to expand, the themes are very similar between cardiomyopathy subtypes, with great emphasis on accurate diagnosis, disease stratification and aetiology driven therapy. Advances in these areas will depend on discovery science and the application of omic technologies, but the greatest insights are likely to emerge from large scale multicentre collaborations. All the evidence suggests that the next few years will be one of considerable advance.

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