Sudden Cardiac Death in DCM Patients

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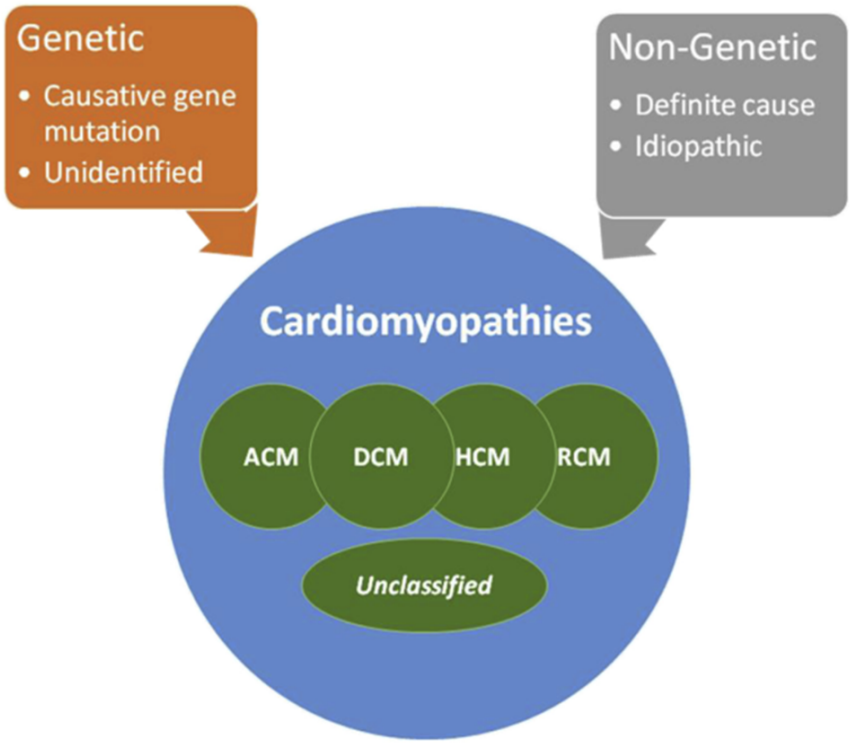
Cardiomyopathies

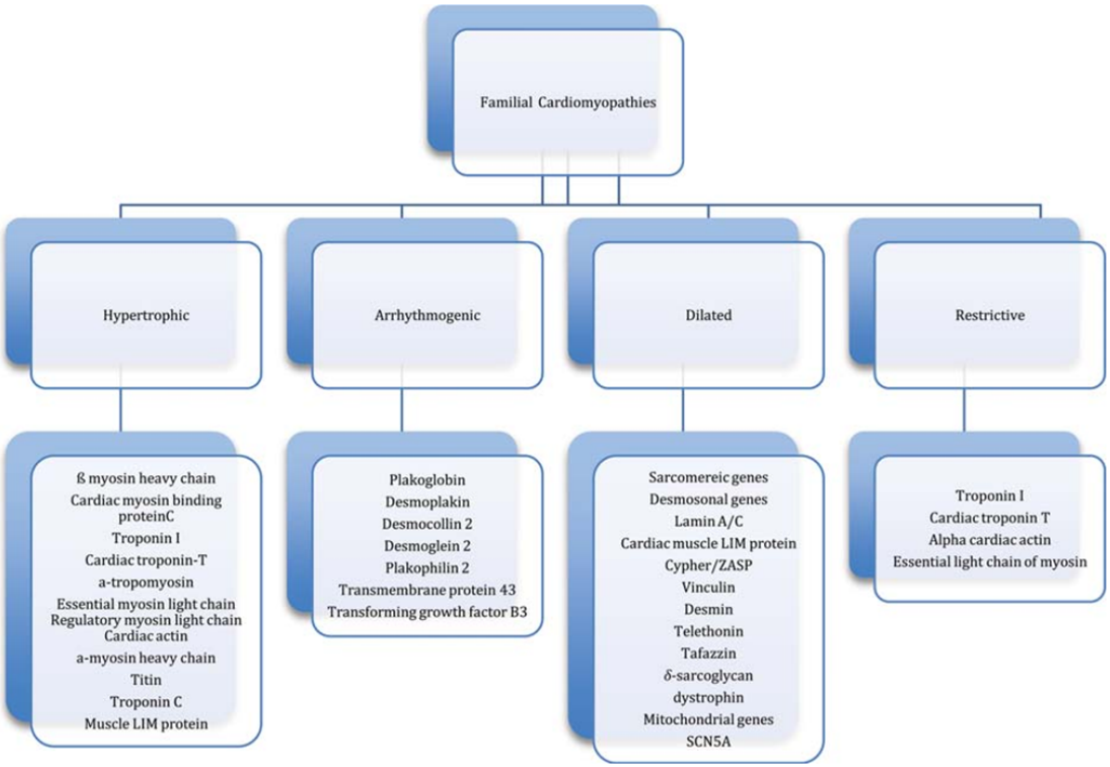


Bakalakos et al. 2018

Cardiomyopathies are a group of heterogeneous disorders. Different classifications exist. Based on the **ESC classification**, different morpho-functional phenotypes can be distinguished.

ACM: arrhythmogenic cardiomyopathy
DCM: dilated cardiomyopathy
HCM: hypertrophic cardiomyopathy
RCM: restrictive cardiomyopathies
Unclassified cardiomyopathies

Cardiomyopathies



Elliott et al. 2008

HCM and ACM

Primarily genetic diseases

DCM

Familial disease is reported in 20% to 35% of cases

Age of onset is typically between the ages of 20–50

DCM: Causes

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

DCM=dilated cardiomyopathy.

***Table 1*: Genetic causes of DCM[4]**

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

	Comments
(Continued from previous column)	
Inborn errors of metabolism	
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	--
Drugs	
Antineoplastic drugs	Anthracyclines, antimetabolites, alkylating agents, paclitaxel, hypomethylating agents, monoclonal antibodies, tyrosine kinase inhibitors, immunomodulating agents
Psychiatric drugs	Clozapine, olanzapine, chlorpromazine, risperidone, lithium, methylphenidate, tricyclic antidepressants, phenothiazines
Others	Chloroquine, all-trans retinoic acid, antiretroviral agents
Endocrinology	
Hypothyroidism	--
Hyperthyroidism	--
Cushing's and Addison disease	--
Pheochromocytoma	--
Takotsubo cardiomyopathy	Stress-related
Acromegaly	--
Diabetes mellitus	--
Electrolyte disturbances	
Hypocalcaemia	--
Hypophosphataemia	--

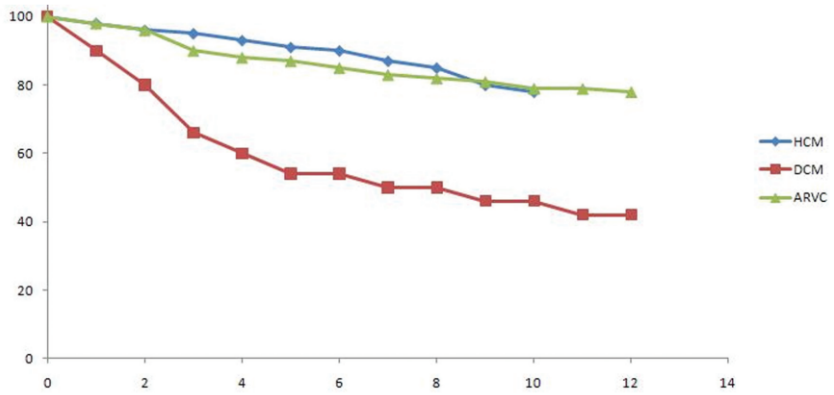
DCM=dilated cardiomyopathy. HPV=human papillomavirus.

***Table 2*: Other causes of DCM[4] by subtype, disease, or agent**

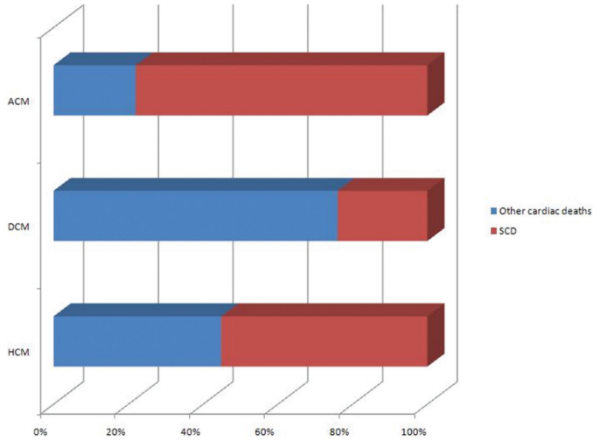
Weintraub et al. 2017

Cardiomyopathies

Survival (%) free of cardiac death or transplantation



Contribution of SCD to overall mortality in the pre-ICD era



"From the Aphorisms of Hippocrates to the sports fields of the twenty-first century, by both the lay public and medical community, the cardiomyopathies have been recognized as causes of sudden cardiac death."

Sen-Chowdhry and McKenna, 2012

DCM: Prognosis

Improved Long-Term Prognosis of Dilated Cardiomyopathy With Implementation of Evidenced-Based Medication

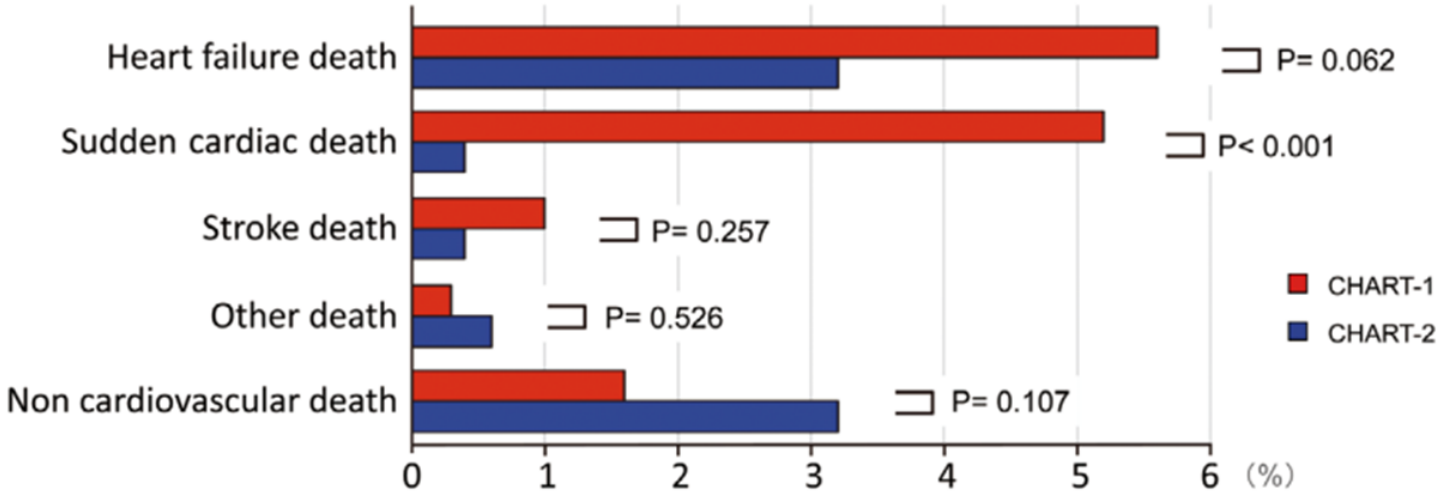
– Report From the CHART Studies –

- Prospective longitudinal observational studies which included 11.497 patients with chronic heart failure.
- CHART-1 (2000–2005), n=1,278
- CHART-2 (2006–2014), n=10,219

- Separate comparison of 306 and 710 DCM patients

Ushigome et al. 2015

DCM: Prognosis



Among the cardiovascular deaths, sudden death rate was significantly decreased from 5.2% in CHART-1 to 0.4% in CHART-2 (P<0.001).

Conclusions

Long-term prognosis of DCM patients has been improved, along with the implantation of evidence based medication in Japan.

Ushigome et al. 2015

DANISH: ICD in non-ischemic systolic heart failure

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

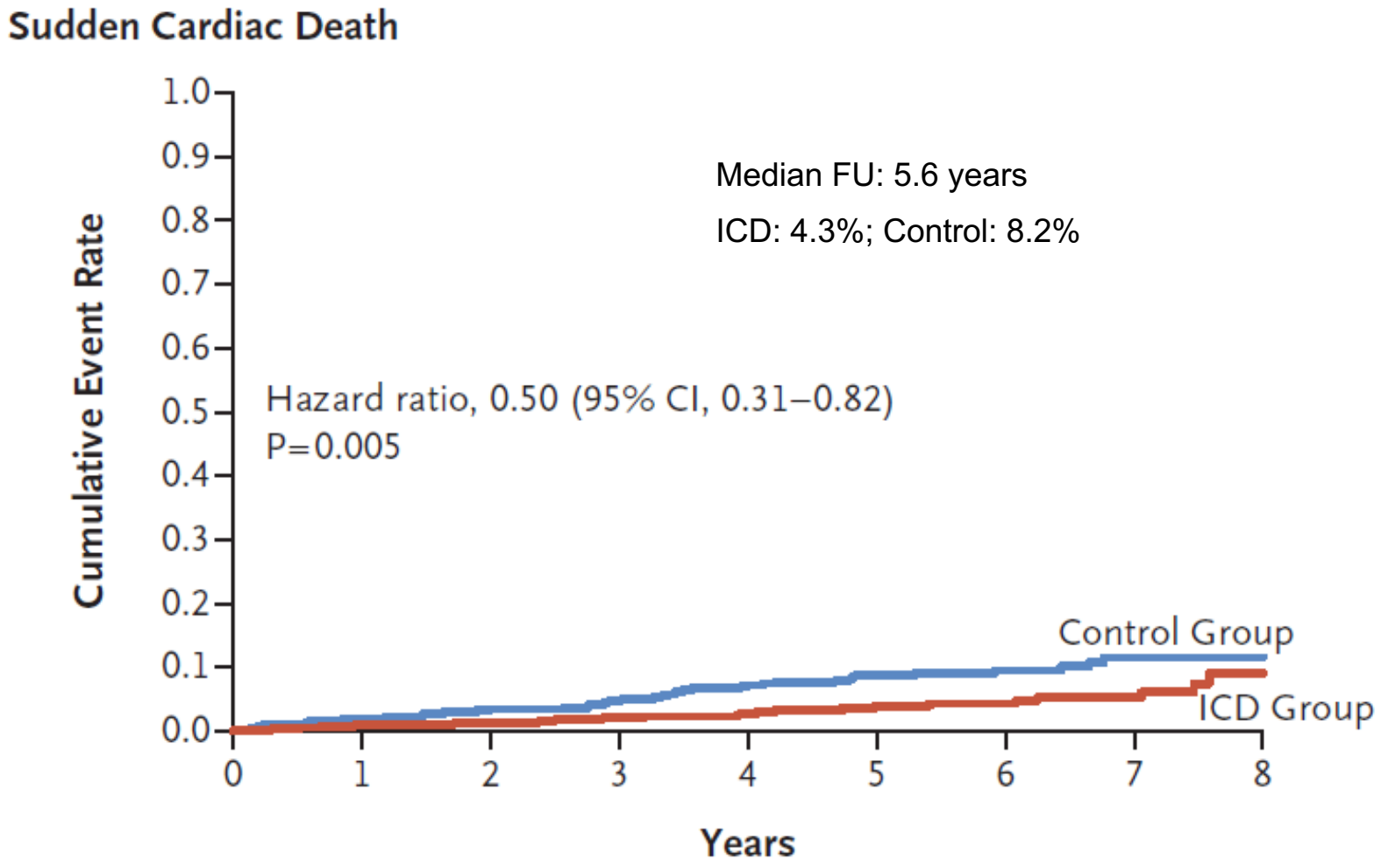
METHODS

In a randomized, controlled trial, 556 patients with symptomatic systolic heart failure (left ventricular ejection fraction, ≤35%) not caused by coronary artery disease were assigned to receive an ICD, and 560 patients were assigned to receive usual clinical care (control group). In both groups, 58% of the patients received CRT. The primary outcome of the trial was death from any cause. The secondary outcomes were sudden cardiac death and cardiovascular death.

Cause of heart failure „idiopathic“ in 76% of pts.

Kober et al. 2016

DANISH: ICD in non-ischemic heart failure



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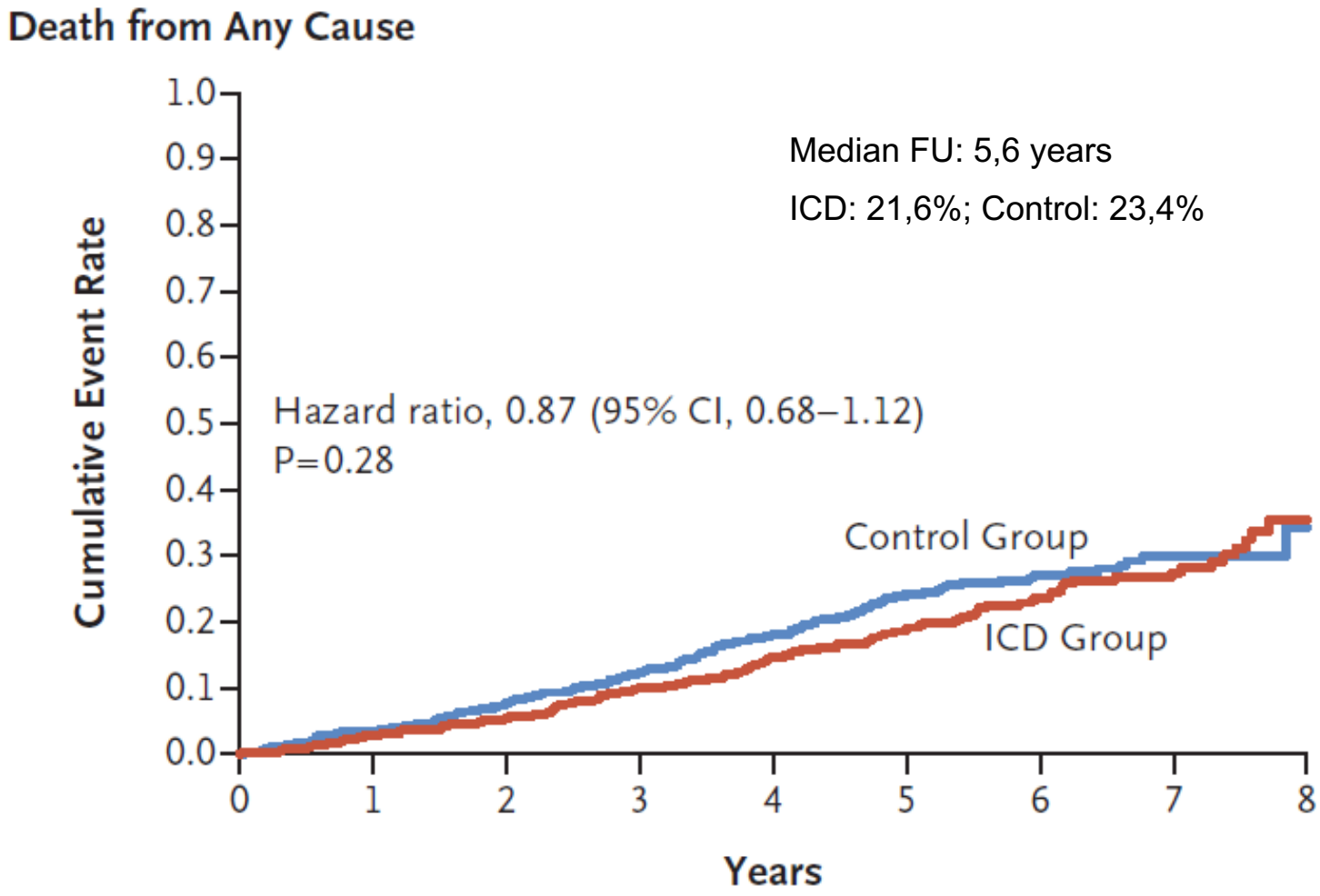

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CONCLUSIONS

In this trial, prophylactic ICD implantation in patients with symptomatic systolic heart failure not caused by coronary artery disease was not associated with a significantly lower long-term rate of death from any cause than was usual clinical care. (Funded by Medtronic and others; DANISH ClinicalTrials.gov number, NCT00542945.)

Kober et al. 2016

DANISH: ICD in non-ischemic systolic heart failure

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Defibrillator Implantation in Patients with Nonischemic Systolic Heart Failure

No distinction between acquired and inherited DCM!

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Kober et al. 2016

LMNA-DCM*

Long-Term Arrhythmic and Nonarrhythmic Outcomes of Lamin A/C Mutation Carriers

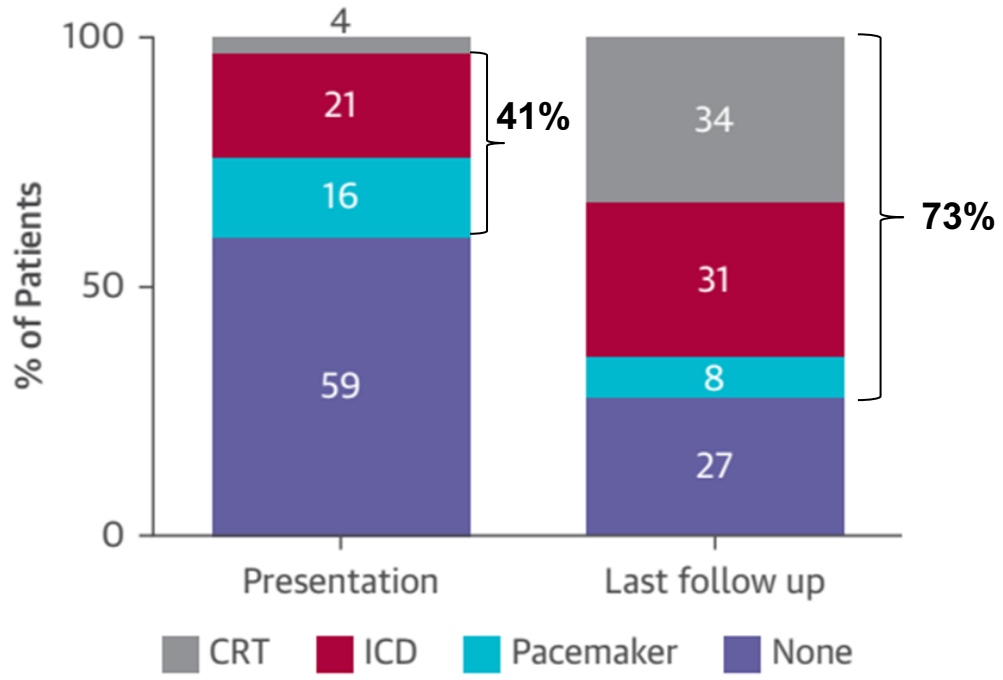
METHODS The incidence of AVB, AA, sustained VA, left ventricular systolic dysfunction (LVD) (= left ventricular ejection fraction ≤50%), and end-stage heart failure (HF) was retrospectively determined in 122 consecutive *LMNA* mutation carriers followed at 5 referral centers for a median of 7 years from first clinical contact. Predictors of VA and end-stage HF or death were determined.

- Mean age at first clinical contact: 41 +/-14 yrs
- LV-EF at first clinical contact: 53 +/- 14 %
  - Patients with LV-EF > 50%: 53%

Kumar et al. 2016

*Frequency of LMNA-related DCM: 5 - 10% of familial DCM and 2 - 5% of non-familial DCM

LMNA-DCM



The percentage of patients with implantable cardioverter-defibrillators (ICD) or cardiac resynchronization therapy (CRT) defibrillators increased substantially at follow-up.

Kumar et al. 2016

LMNA-DCM*

- 52 of 122 pts. (43%) developed sustained ventricular arrhythmia
  - 22 pts. (18%) experienced electrical storm

*Median FU: 7 yrs

- 58 of 122 pts. (48%) with primary prevention ICD therapy
  - 29 pts. (50%) appropriate ICD intervention
- 68 of 122 pts. pts. (56%) had CRT implantation
  - 30 pts. (44%) had heart transplantation
- 70 of 122 pts. (57%) with progression to endstage-HF
- 22 of 122 pts. (18%) died

Kumar et al. 2016

LMNA-DCM

REVIEW

Updated clinical overview on cardiac laminopathies: an electrical and mechanical disease

G. Peretto [a], S. Sala [a], S. Benedetti [b], C. Di Resta [c], L. Gigli [a], M. Ferrari [b,c], and P. Della Bella [a]

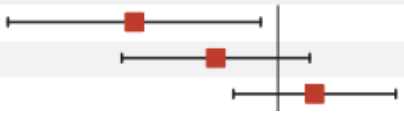
[…] it seems appropriate to implant a CRT-D every time a CRT-P is indicated […].

Peretto et al. 2018

DANISH: ICD in non-ischemic heart failure

Subgroup analysis accoreding to age

Subgroup	ICD Group	Control Group	Hazard Ratio (95% CI)	P Value	P Value for Interaction
	no. of events/total no.				
Age					0.009
<59 yr	17/167	34/181	0.51 (0.29–0.92)	0.02	
≥59 to <68 yr	36/173	50/202	0.75 (0.48–1.16)	0.19	
≥68 yr	67/216	47/177	1.19 (0.81–1.72)	0.38	



Kober et al. 2016

Making the Correct Diagnosis

Familial dilated cardiomyopathy diagnosis is commonly overlooked at the time of transplant listing

Evaluation of 73 pts. with ESHF from the United Network for Organ Sharing registry.

- 3 out 73 pts. diagnosed as having familial DCM
- after reevaluation 19 (26%) of pts. were found to have familial DCM

Conclusions

Despite decades of evidence supporting a genetic etiology of DCM […], the adoption of guidelines to screen patients for FDCM by clinicians has been slow. In this transplant population, in which at least one or more cardiologists has presumably evaluated each individual, the diagnosis of FDCM is missed in a large majority of cases.

Seidelmann et al. 2015

Conclusions

- Dilated cardiomyopathy are a heterogeneous group of acquired or inherited myocardial diseases.
- Heart failure and malignant arrhythmias represent major causes of death.
- Prospective studies taking the specific pathological/genetic substrate into consideration are urgently needed.

- *It is time for precision medicine and precision trials in heart failure!*

Making the Correct Diagnosis

Hidden in Heart Failure

Douglas Ewan Cannie,[1,2] Mohammed Majid Akhtar[1,2] and Perry Elliott[1,2]

Abstract

Current diagnostic strategies fail to illuminate the presence of rare disease in the heart failure population. One-third of heart failure patients are categorised as suffering an idiopathic dilated cardiomyopathy, while others are labelled only as heart failure with preserved ejection fraction. Those affected frequently suffer from delays in diagnosis, which can have a significant impact on quality of life and prognosis. Traditional rhetoric argues that delineation of this patient population is superfluous to treatment, as elucidation of aetiology will not lead to a deviation from standard management protocols. This article emphasises the importance of identifying genetic, inflammatory and infiltrative causes of heart failure to enable patients to access tailored management strategies.

Cannie et al. 2019