Dilated cardiomyopathy: diagnostic work-up, pathogenesis, prognosis and treatment

PhD thesis

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ACKNOWLEDGEMENTS

My work on the current thesis was performed at the cardiology ward at Oslo University Hospital, Rikshospitalet from October 2008 to June 2015, intercepted by two brief leaves of absence following the births of my two youngest children. During the first five years, I held a teaching position at the University of Oslo, alternating between teaching eager-to-learn medical students and fretting at slow patient recruitment. For the next six months, I received a scholarship from the grant provided by Inger and John Fredriksen, to whom I am grateful.

Foremost, I would like to thank my principle supervisor, Professor Lars Gullestad, whose door is (literally) always open, and whose enthusiasm I have relied heavily upon when progress has been slow or a manuscript has been rejected. He was the one who talked me into taking on this thesis, arguing that the data collection would be done in a matter of months, and he was the one who comforted me when this turned out to be as far from the truth as possible. (“But you are going to end up with a unique material and a large body of science to your name!”)

I would also like to thank my co-supervisor, Professor Svend Aakhus. When Lars’ unbridled enthusiasm and sometimes unrealistic expectations have had me crawling the walls of my shared (and, to the despair of my colleagues, severely disorganised and overcrowded) office, Svend has had a soothing effect with his cool, no-nonsense realism. Unlike Lars, Svend is a creature for details. Thus, as Lars provided ideas and pointed me in the general direction, Svend corrected my spelling mistakes and faulty statistics and above all tried to teach me how to perform state-of-the-art echocardiography.
The staff at the cardiology department has my gratitude for their patience and positive attitude whenever I came sauntering in to make their days longer and more difficult by recruiting patients for my project, requiring additional exams and extending the patients’ stay. In particular, I would like to thank secretary Anne Hegna for helping me organise the many diagnostic tests my patients went through, and nurse Maj-Britt Skaale for her invaluable contribution to data collection and interpretation. In general, a positive attitude towards research (and researchers!) permeates the walls of the department. The previous head of department, Dr Lars Aaberge, and his successor Professor Thor Edvardsen have no doubt inherited this mindset from their predecessors, but the cost-effectiveness demands of modern medicine makes it no mean task to maintain it, and I am grateful to them for providing a research friendly environment.

I extend my thanks to study nurses Rita Skårdal and Wenche Stueflotten for their contribution to the organisation of patient follow-up, blood sampling and storage, and for their general hospitality and smiling faces. I admire them for remembering my patients by name and family anecdotes, when all I could remember was the patient’s left ventricular end diastolic diameter.

Whereas research nowadays is usually performed within a scientific environment, it is at times lonely work. Many a day I have spent in front of the computer, reading other scientists’ work or despairing at my own. Luckily, I have been blessed with a number of good companions to share my fate, among whom I count Christian Eek, Jan Otto Beitnes, Mette Elise Estensen, Gabor Kunzt, Lene Anette Rustad, Wasim Zahid and Klaus Murbræch as good friends. Expert sonographers Johanna Andreassen and Richard Massey have contributed greatly to making my days brighter and my echocardiographic images less cloudy.
My home, obviously, is where my heart is, and it is with my good wife Line and my three children Marie, Erling and Tiril. Their love means the world to me, and without their support, I could not have written this thesis. Line has had to put up with my despair at a perceived lack of scientific progression, my irritation with obtuse reviewers and my coming home late and staying away from home in order to perform research and provide some hard earned extra income. She has done so with patience and grace, and for that, I am forever thankful.
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LIST OF PAPERS

1. Broch K, Andreassen AK, Hopp E, Leren TP, Scott H, Müller F, Aakhus S, Gullestad L. Results of comprehensive diagnostic work-up in “idiopathic” dilated cardiomyopathy (Submitted to Open Heart)


1 INTRODUCTION

1.1 Heart failure

Heart failure is a syndrome characterised by an impaired ability of the heart to fill or eject blood.¹ Heart failure may lead to symptoms of inadequate tissue perfusion, such as fatigue and lethargy (so-called “forward failure”), or congestion, including shortness of breath and peripheral oedema (often referred to as “backward failure”). All disorders affecting the structural and/or functional integrity of the heart, such as valvular, coronary or myocardial disease, can commence heart failure. Heart failure may also be precipitated by diseases affecting the heart indirectly, such as hypertension, pericardial disease or pulmonary disease.

Many of the conditions that may cause heart failure are to some extent reversible. However, once the burden of disease exceeds the compensatory capacity of the heart, the condition often progresses toward a common end stage.¹ The process whereby the myocardium undergoes structural changes in the face of perturbed loading conditions or myocardial disease is known as (adverse) remodelling.²,³ The pathophysiology behind this progressive deterioration is incompletely understood. Haemodynamic stress,⁴ neurocrine activation,⁵ and inflammation,⁶,⁷ all contribute to the ventricular dilation,⁸ loss of contractile elements⁹ and changes in the extracellular matrix composition¹⁰ observed in advanced heart failure.

Heart failure is a leading cause of morbidity and mortality in the Western world, affecting 2-3 % of the adult population.¹¹,¹² As the population ages, the prevalence is expected to increase over the next 20 years.¹¹ Current clinical guidelines¹²,¹³ take a generic approach to heart failure, paying little attention to inter individual differences in aetiology and pathophysiology.
This may partly be because the biology of the failing heart is incompletely understood, and partly because there is a lack of treatment strategies targeting many of the processes involved.

1.2 Dilated cardiomyopathy

Dilated cardiomyopathy is characterised by left ventricular dilation and dysfunction in the absence of coronary disease, valvular disease or hypertension.\textsuperscript{14} Approximately 10\% of heart failure cases are due to dilated cardiomyopathy.\textsuperscript{15}

![Echocardiographic apical 4-chamber image of one of the patients in the study, demonstrating the typical enlargement and ballooning of the left ventricle (LV).](image)

\textbf{Figure 1 Dilated cardiomyopathy}

Echocardiographic apical 4-chamber image of one of the patients in the study, demonstrating the typical enlargement and ballooning of the left ventricle (LV).
1.2.1 Definition

By the European Society of Cardiology (ESC)’s definition above, dilated cardiomyopathy is primarily a diagnosis based on phenotype, rather than aetiology (Figure 1). Accordingly, the ESC lists a whole array of potential causes of dilated cardiomyopathy, with widely differing pathogenic mechanisms. The American Heart Association (AHA) and the American College of Cardiology (ACC) have proposed a different classification of cardiomyopathies. In their guidelines, cardiomyopathies are firstly designated as either “primary” (i.e. predominantly involving the heart) or “secondary” to some systemic disease, and secondarily whether they are of a genetic, acquired or mixed aetiology. Although this latter classification of cardiomyopathies is attractive in the way that it pivots around the underlying pathogenesis of the disease, it poses several problems. Firstly, from a clinician’s point of view, the diagnostic work-up of a patient begins with the clinical appearance. Thus, a diagnostic system based on phenotype is operational when deciding what to do next in the diagnostic process. Secondly, most patients with dilated cardiomyopathy present with symptoms of heart failure, and as stated above, recommendations for treatment in heart failure do not take into account individual differences in aetiology or pathophysiology. Thirdly, one might argue that the categorisation of cardiomyopathies based on underlying causes is premature. Today, in the majority of patients with a dilated, dysfunctional left ventricle, in the absence of ischaemia and valvular or hypertensive disease, no particular cause is found, and the patients end up with a diagnosis of “idiopathic” dilated cardiomyopathy. For the above reasons, I adhere to the European definition of dilated cardiomyopathy in the following.
1.2.2 Aetiology

Dilated cardiomyopathy probably represents the end-stage phenotype of almost any kind of global insult to the myocardium, coronary heart disease and altered loading conditions excluded. Accordingly, the list of potential causes is long. The most common causes are listed in Table 1. However, in most patients, no particular aetiology is uncovered, and they are diagnosed with “idiopathic” dilated cardiomyopathy.

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Causes of dilated cardiomyopathy. The list is not exhaustive. Modified from Elliott et al.\textsuperscript{14} and Maron et al.\textsuperscript{16}

There are two prevailing theories regarding potential causes of idiopathic dilated cardiomyopathy. One holds that a proportion of the cases are secondary to myocardial inflammation, possibly subsequent to a (sub clinical) viral myocarditis.\textsuperscript{19,20} The other holds that most cases of dilated cardiomyopathy are hereditary, but that their genetic nature is hard to detect clinically due to incomplete penetrance and variable expressivity.

The former theory is supported by several observations. In murine models, viral myocarditis subsequently develops into dilated cardiomyopathy.\textsuperscript{21} The same development is observed in
some, but not all, human patients who have suffered from severe myocarditis. Moreover, viral nucleic acids are detectable in the myocardium of a substantial number of patients with dilated cardiomyopathy, and their presence may be associated with a poor prognosis. It has been proposed that in genetically disposed individuals, viral myocardial infection either remains unresolved or leads to an immunologic overreaction, and that the persistent inflammation begets left ventricular remodelling and heart failure.

On the other hand, recent studies have indicated that as many as 50% of patients with idiopathic dilated cardiomyopathy have familiar disease. Mutations in many different genes have been shown to cause dilated cardiomyopathy, most commonly with an autosomal dominant pattern of inheritance. Due to incomplete penetrance and variable phenotypes within families with dilated cardiomyopathy, the hereditary nature of the disease might easily escape detection. Current genetic screening tests are not in widespread use, and are directed towards the known genetic causes of dilated cardiomyopathy only. The mutations causing dilated cardiomyopathy that have been described so far, account for only a minority of the cases thought to be hereditary on the basis of their familiar occurrence.

We do not know why certain individuals with a given mutation develop clinical cardiomyopathy, while other carriers remain healthy or develop signs of the disease only detectable on specific examination. Neither do we know why it usually takes years to develop clinical disease, although the primary defect is inborn. It has been proposed that mechanical stress throughout life causes the development of DCM in individuals with a predisposing genetic variant.
1.2.3 Pathogenesis

Irrespective of the nature of the initiating pathogenic stimulus, the body responds to a compromised cardiac pump function with a number of compensatory mechanisms. These include neurohormonal activation, characterised by an increased activity of the renin-angiotensin-aldosterone axis, an elevated circulating concentration of catecholamines, and an increased sympathetic activity. In the heart, the wall stress induces the production and release of natriuretic peptides.

1.2.3.1 Left ventricular remodelling

The myocardium responds to the added strain by a process known as remodelling, whereby the macroscopic and ultrastructural architecture of the heart changes towards a dilated cardiomyopathy phenotype. On the macroscopic level, the left ventricle undergoes eccentric hypertrophy and dilation. A gradual replacement fibrosis often occurs, whereby functional cardiomyocytes undergo apoptosis or necrosis to be replaced by fibroblasts and extracellular matrix. The extracellular matrix itself undergoes several changes. Extracellular collagen deposition is increased, and at the same time, there is accelerated degradation of extracellular proteins, resulting in an increased matrix turnover. This is mirrored in the circulation by an increased concentration of collagen by-products and metalloproteinases. On the ultrastructural level, the protein composition of the myocyte is altered. Cardiomyocyte calcium handling is impaired, and with a return to a foetal gene expression program, there is isoform switching of sarcomeric proteins and modified metabolism.

1.2.3.2 Inflammation in dilated cardiomyopathy

There is a large body of evidence indicating that inflammation is involved in the pathogenesis of heart failure. Circulating levels of pro-inflammatory cytokines are elevated in heart failure irrespective of aetiology. Moreover, there is an association between the level of
inflammatory activity and prognosis in patients with recent-onset dilated cardiomyopathy.\textsuperscript{40} Auto-antibodies to key cardiac epitopes are at the core of certain forms of heart failure in murine models,\textsuperscript{41} and induction of inflammation may lead to overt heart failure in experimental settings.\textsuperscript{42,43} Accordingly, immunomodulation has been considered a promising treatment concept in heart failure.\textsuperscript{44} A few, small studies have demonstrated a favourable effect of anti-inflammatory treatment with intravenous immunoglobulin,\textsuperscript{45} immunoglobulin adsorption\textsuperscript{46} and pentoxifylline\textsuperscript{47,48} in patients with dilated cardiomyopathy. However, the results of major trials,\textsuperscript{49-51} especially those investigating anti TNF\(\alpha\) therapy,\textsuperscript{52,53} have been disappointing.

One reason for the lack of effect of anti-inflammatory treatment may be that patients with heart failure constitute such a heterogeneous population. Although circumstantial evidence suggests that many of these patients would benefit from immunosuppressive treatment, some patients may not. Indeed, it has been showed that in patients with virally infected myocardium, boosting the immune system with interferon leads to improved outcome.\textsuperscript{54} Thus, it may be that in this particular subgroup of patients with DCM, treatment with immunosuppressive agents is detrimental. This heterogeneity may have acted as a confounder in previous trials.

1.2.3.3 The role of ST2

ST2 is a receptor in the Interleukin (IL)-1 family. Discovered in 1989,\textsuperscript{55,56} it was long considered an orphan receptor. In 2005, however, ST2 was shown to bind IL-33.\textsuperscript{57} The binding of IL-33 to the membrane bound ST2 receptor induces a downstream cascade, ultimately activating nuclear factor \(\kappa B\)\textsuperscript{58,59} (Figure 2). Soluble ST2 (sST2) is a truncated receptor that lacks the transmembrane/ intracellular domains of membrane bound ST2.\textsuperscript{60} It arises by alternative splicing and is released into the circulation, where it acts as a decoy
receptor for IL-33. ST2 has been detected in many human tissues.\textsuperscript{61} ST2 is inducible in cardiac tissue,\textsuperscript{62} and is expressed in endothelial cells and vascular smooth muscle cells.\textsuperscript{63}
IL-33 binds to the ST2 receptor complex consisting of membrane bound ST2L and the IL1RAcP. This leads to the recruitment of MyD88 and IRAK4. The latter autophosphorylates to initiate a cascade of intracellular kinases that ultimately leads to activation of NFκB and MAPKs. This again leads to transcription of inflammatory cytokines and regulation of cell proliferation. Soluble ST2 (sST2) sequesters IL33, preventing its interaction with the IL1RL1 receptor complex. Modified from Broch et al64

Figure 2 ST2 signalling
IKB, Inhibitor of nuclear factor κB; IKK, Inhibitor of nuclear factor κB kinases; IL1RACp, Interleukin-1 receptor accessory protein, IL33, Interleukin-33; IRAK4, Interleukin-1 receptor associated kinase 4; MAPK, mitogen activated protein kinase; MyD88, Myeloid differentiation primary response gene 88; sST2, soluble ST2; ST2L, membrane bound ST2; TRAF6, TNF receptor associated factor 6.

Not surprisingly, given its similarity to the IL-1 system, IL-33/ST2 signalling plays a role in inflammatory diseases,65-68 where it seems to be pivotal to certain immune responses involving TH2 helper cells.57,65,69,70 On the other hand, in 2002 Weinberg and colleagues found that ST2 was up regulated in cardiomyocytes subjected to mechanical stress, and that levels of circulating sST2 increased substantially after myocardial infarction.62 Subsequently, the IL33/ST2 axis has been shown to protect against maladaptive hypertrophy and fibrosis secondary to aortic banding,71 and against hypoxia-induced apoptosis.72 Serum concentrations of sST2 are elevated in cardiac disease and are associated with mortality in acute coronary syndromes.73-75 In heart failure, ST2 levels correlate with markers of disease severity, such as left ventricular ejection fraction,76-78 New York Heart Association functional class77 and left ventricular filling pressure.76 More importantly, sST2 has been shown to be an independent predictor of outcome in patients with heart failure.64

1.2.4 Prognosis in dilated cardiomyopathy

Outcome in dilated cardiomyopathy depends on the aetiology. In the idiopathic form of the disease, the prognosis is generally better than in patients with ischaemic heart failure.18,79 Five year mortality is substantial, however, ranging from more than 50 % in early reports80 to approximately 25 % in recent reports.79,81 Survival differs due to various inclusion criteria in different trials. In addition, there has probably been a real improvement in outcome as treatment for heart failure has advanced over the last decades with the introduction of drugs
inhibiting major neuroendocrine axes and the use of devices to resynchronise left ventricular contraction and treat ventricular arrhythmias.\textsuperscript{82,83}

\subsection*{1.2.5 Treatment}

The recommended therapy for dilated cardiomyopathy does not differ from that advocated for heart failure in general, where inhibitors of the major neuroendocrine axes are the mainstay of treatment.\textsuperscript{84} Several large studies have shown that in mixed heart failure populations (i.e. including patients with non-ischaemic as well as ischaemic heart failure), treatment with angiotensin converting enzyme inhibitors (ACEIs) and/or angiotensin II receptor blockers (ARBs) confers a survival benefit.\textsuperscript{85,86} Likewise, there are several, large studies to show that beta receptor antagonists (beta blockers) improve the outcome in patients with heart failure and dilated cardiomyopathy,\textsuperscript{87-89} and that aldosterone antagonists provide an added survival benefit in patients with heart failure who remain symptomatic after the up-titration of drugs inhibiting the renin-angiotensin and sympathetic neurohormonal axes.\textsuperscript{90,91} Furthermore, implantable cardioversion defibrillators (ICDs) reduce the number of sudden deaths in high-risk patients with dilated cardiomyopathy,\textsuperscript{79,81} and cardiac resynchronisation therapy (CRT) have been shown to improve outcome in patients with dilated cardiomyopathy and wide QRS complexes.\textsuperscript{92-94}

Statins reduce the number of cardiovascular events in patients with, or at risk of developing, coronary disease.\textsuperscript{95,96} Statins are inhibitors of 3-hydroxy 3-methylglutaryl coenzyme A reductase, the rate-limiting enzyme in cholesterol synthesis, and effectively reduce serum cholesterol levels. It is hotly debated whether the cardioprotective effects of statins are due to cholesterol reduction only. Statins also possess anti-inflammatory and matrix stabilizing properties,\textsuperscript{97} and the relative risk reduction observed in statin trials has been independent of
baseline cholesterol levels.\textsuperscript{95} Also, the effect on clinical endpoints is associated with a
treatment-induced reduction in the C-reactive protein serum concentration.\textsuperscript{98} Whereas the two
major trials assessing the effect of statins in heart failure failed to show a positive effect on
the clinical outcome,\textsuperscript{99,100} several small, randomised trials have shown that treatment with a
statin could lead to improved left ventricular function and a reduction in markers of
inflammation in patients with dilated cardiomyopathy.\textsuperscript{101-104}
AIMS OF THE THESIS

We aimed to explore the yield of a comprehensive baseline diagnostic evaluation, the pathogenesis, the prognosis, and treatment options in patients with dilated cardiomyopathy. From the outset, we hypothesised that dilated cardiomyopathy results from an environmental insult in a genetically disposed individual, whereby inappropriate inflammation and metabolic derangement ultimately lead to myocardial remodelling and ensuing heart failure. In this thesis, we wanted to answer the following questions:

1) What are the causes of initially unexplained dilated cardiomyopathy, and what are the diagnostic and therapeutic yields of an extensive diagnostic work-up?
2) What are the determinants of the novel biomarker ST2 in patients with dilated cardiomyopathy, and are sST2 levels associated with outcome in these patients?
3) What is the prognosis in patients with dilated cardiomyopathy treated according to contemporary, evidence based guidelines, and what are the determinants of left ventricular remodelling and cardiovascular events and mortality in this population?
4) Can the hydroxymethylglutaryl-CoA reductase inhibitor rosuvastatin contribute to reverse left ventricular remodelling in patients with dilated cardiomyopathy through effects on inflammation and matrix remodelling?
3 PATIENTS AND METHODS

The first three papers derive from a prospective cohort study performed at our tertiary care university hospital. The fourth paper, on rosuvastatin for dilated cardiomyopathy, describes a randomised, controlled trial dubbed the EVRICA study (“Effect of rosuvastatin on left Ventricular Remodeling and inflammatory markers in Idiopathic dilated Cardiomyopathy”) This trial was initiated before the above-mentioned cohort study was designed. We recruited some of the patients enrolled in the latter study from the cohort population, but many were included at Oslo University Hospital before recruitment to the cohort study had started, and some were enrolled at Drammen Hospital, Vestre Viken Hospital Trust, Drammen and St Olav’s Hospital, Trondheim University Hospital, Trondheim.

Both studies comply with the Declaration of Helsinki and were approved by the Regional Committee for Medical and Health Research Ethics (REK Sør-Øst). All patients provided written, informed consent.

3.1 Patient population, paper I, II and III

For the cohort study, we included consecutive patients aged 18 or above with a referral diagnosis of dilated cardiomyopathy, or with signs or symptoms that turned out to be caused by non-ischaemic, non-valvular, and non-congenital heart failure. Inclusion criteria were an end diastolic left ventricular internal diameter ≥ 6.5 cm and a left ventricular ejection fraction < 40 %. Exclusion criteria were

- ischaemic, hypertensive or valvular aetiology as judged by patient history, physical examination, echocardiography and coronary angiography
- other known or suspected causes of heart failure, such as myocarditis, metabolic disease, toxins, radiotherapy or poorly controlled tachycardia
- inotropic or mechanical support at admittance
- implantable cardiac devices
- severe concomitant disease such as infections, connective tissue disease, pulmonary disease, cancer, serious psychiatric disease, life threatening ventricular arrhythmias, severe kidney failure or severe hepatic failure
- referral specifically for heart transplantation

From the 13th of October 2008 to the 16th of November 2012, a total of 265 patients admitted to our tertiary care cardiology department were evaluated for participation, of whom 169 were excluded from and 102 included in the study cohort. Figure 3 is a flow-chart depicting patient selection, inclusion and follow-up.
Some patients had several reasons for exclusion from participation

Figure 3 Patient selection and follow-up

Patients screened for participation (n = 265)

- Known or suspected cause of dilated cardiomyopathy* (n = 37)
  - Intra cardiac device (n = 54)
  - Reduced life expectancy due to non-cardiac disease (n = 7)
  - Compliance deemed poor (n = 12)

- Ischaemic heart failure (n = 9)

- LVEF above 40% or left ventricular internal diameter below 6.5 cm / 3.3 cm indexed (n = 29)

- Primary valvular heart disease (n = 8)

- Referral specifically for heart transplant evaluation (n = 36)

- Required mechanical or inotropic support (n = 17)

- Not included for administrative reasons (n = 5)

- Unwilling to participate (n = 3)

Included (n = 102)

- Transplanted or on LVAD (n = 3)

Follow-up after 6 months (n = 97)

- Lost to short term follow-up (n = 2)

Follow-up after 13 months (n = 95)

- Lost to short term follow-up (n = 4)

Transplanted (n = 6), dead due to worsening heart failure (n = 2), dead due to other reasons (n = 2)

Alive and transplant-free after median follow-up 3.5 (2.2 – 4.4) years (n = 89)
3.2 Patient population, paper IV

For the EVRICA trial, patients aged 18 to 80 years were eligible. In brief, the inclusion criteria were symptomatic heart failure, a left ventricular ejection fraction < 40 % and no current use of statins or indication for statins. Criteria for exclusion included decompensated heart failure; heart failure of ischaemic aetiology; haemodynamically significant valvular disease not considered secondary to ventricular dilation; recent or planned surgical procedures or operations; significant concomitant disease such as infection, severe pulmonary disease or connective tissue disease; acute or chronic liver disease; or contraindications to statin therapy defined as hypersensitivity to any statin, alanine transaminase ≥ 2 times the upper limit of normal, serum creatinine ≥ 2 mg/dL, an unexplained creatine kinase ≥ 3 times the upper limit of normal, current or planned pregnancy, or breast feeding. According to the study protocol, we aimed to include all together 75 patients, but due to slow recruitment and a low number of dropouts, the recruitment was stopped after the enrolment of 72 patients. The trial flow chart and population characteristics are presented in paper IV.

3.3 Study Procedures papers I through III

At baseline, participants underwent physical examination; blood tests including screening for known monogenic causes of dilated cardiomyopathy; echocardiography; cardiac magnetic resonance imaging; exercise testing with measurement of peak oxygen uptake; and right-sided cardiac catheterisation with endomyocardial biopsy. After 6 months, physical examination, blood tests and echocardiography were repeated. One year after inclusion, a second follow-up was performed including physical examination, blood tests, echocardiography, exercise testing with measurement of peak oxygen uptake, and magnetic resonance imaging.
3.4 Study procedures, paper IV

Paper 4 describes a multicentre, randomised, double blind, placebo-controlled trial designed to assess the effect of rosuvastatin on left ventricular function in patients with DCM. It was conducted at three sites in Norway. At baseline, all participants underwent physical examination, blood tests, echocardiography and, unless contraindicated, cardiac magnetic resonance imaging. Patients were then randomised in a 1:1 fashion to receive 10 mg of rosuvastatin or matching placebo once a day in a double blind fashion. Physical examination, blood tests, echocardiography and cardiac magnetic resonance imaging were repeated after six months of intervention.

3.5 Imaging

3.5.1 Echocardiography

Echocardiography was performed mainly with Vivid 7, and in a few instances E9, ultrasound scanners (GE Vingmed Ultrasound, Horten, Norway). We examined the patients in the lateral recumbent position after > 5 minutes of rest. Three heartbeats were recorded with each registration. Cine loops comprising ultrasound raw data were digitally stored and later analysed off line using Echo-Pac (GE Vingmed). 2D parameters and conventional Doppler parameters were measured according to current recommendations.\textsuperscript{105,106} Valvular regurgitations were graded as mild, moderate or severe by visual assessment.\textsuperscript{107} Left ventricular ejection fraction (LVEF) was measured by Simpson’s biplane method.\textsuperscript{105}

3.5.2 Magnetic resonance imaging

Magnetic resonance imaging was performed with Siemens 1.5 tesla scanners (Siemens Avanto and Siemens Sonata; Siemens Medical Systems, Erlangen, Germany). Left ventricular
long and short axis images were acquired using a prospectively ECG-triggered, segmented, balanced steady-state free precession gradient-echo cine sequence with minimum echo and repetition times, 6 mm slice thickness, 4 mm short-axis interslice gap, a spatial resolution of 1.9 mm x 1.3 mm, and a temporal resolution of 30-35ms. The endocardial borders were traced manually using a PACS workstation (Sectra Medical Systems AB, Linköping, Sweden). Left and right ventricular volumes and ejection fractions were calculated by short axis slice summation. In the cohort study participants, images with late gadolinium enhancement (LGE) were acquired 10 to 20 minutes after intravenous injection of 0.2 mmol/kg of gadoterat meglumine (Guerbet, Villepinte, France) unless contraindicated due to a reduced glomerular filtration rate. The total volume of late myocardial enhancement was quantified from visual analysis of short axis slices covering both ventricles (Figure 4).

![Cardiac magnetic resonance imaging with late Gadolinium enhancement](image)

**Figure 4** Cardiac magnetic resonance imaging with late Gadolinium enhancement

The image shows typical, mid-wall late enhancement (arrow) reflecting the septal fibrosis often seen in patients with dilated cardiomyopathy
3.5.3 Image analysis

All image analysis was performed off-line. The analyses were performed in a blinded manner and without knowledge of the results of the other image modalities. For the cohort study, the echocardiograms were analysed by two researchers, Klaus Murbræch and Kaspar Broch. Individual exams were de-identified and randomised, and image analysis was performed blinded to patient characteristics and to whether the exam was performed at baseline or follow-up. Repeatability was excellent, with an intra-observer intraclass correlation coefficient for left ventricular ejection fraction of 0.95 (95 % confidence interval 0.93 – 0.97), and an inter observer coefficient of 0.93 (0.89 – 0.95).

3.6 Measurement of peak oxygen consumption

Maximal, upright, symptom-limited exercise testing was performed using an electrically braked bicycle ergo meter at a constant cadence of 60 rpm. The test employed an individualised, stepwise protocol, with the load incrementally increased every minute. Based on the patient’s age, gender, size, physical shape and symptoms, an expected maximum load was estimated for each patient, and the test was designed to reach this load after approximately 10 minutes. The test was discontinued at patient exhaustion (defined as an inability to keep the pedalling rate steady at 60 rpm) or at the occurrence of arrhythmia, chest pain, dizziness or other symptoms causing severe patient discomfort.

Simultaneous gas exchange and haemodynamic monitoring was performed on a Cardiovit CS-200 unit (Schiller, Baar, Switzerland) using a Ganshorn PowerCube gas analyser (Ganshorn, Niederlauer, Germany). Peak VO\textsubscript{2} was defined as the VO\textsubscript{2} achieved at maximum load at the
end of the exercise. Heart rate was recorded continuously by 12 lead electrocardiography, and
blood pressure was recorded at regular intervals throughout the test with a semi-automated
recorder. Perceived exertion was rated using the Borg’s RPE scale.\(^\text{108}\)

### 3.7 Right-sided heart catheterisation

We performed right-sided heart catheterisation using a Swan–Ganz pulmonary artery
thermodilution catheter (Baxter Health Care Corp, Santa Ana, CA). Patients were not required
to fast. The following pressures were recorded: right atrial mean pressure, systolic pulmonary
artery pressure, mean pulmonary artery pressure, and mean pulmonary capillary wedge
pressure. The wedge position was verified by observing the typical changes in waveforms,
and by fluoroscopy. We measured cardiac output by the thermodilution technique, and cardiac
index was calculated by dividing cardiac output with body surface area. Septal right
ventricular endomyocardial biopsies were obtained for viral RNA/DNA detection, and
conventional and electron microscopy. In addition, for each patient two biopsies were snap
frozen and stored for future analyses.

### 3.8 Viral genome detection

We extracted total nucleic acid from the endomyocardial biopsy specimens and performed
real-time polymerase chain reaction assays for the detection of Enteroviruses (including
Coxsackievirus and Echovirus), Adenovirus, Human Parvovirus B19, Epstein-Barr virus,
Cytomegalovirus, and Human herpes virus 6 as described elsewhere.\(^\text{109}\)
3.9 Conventional and electron microscopy

We fixed endomyocardial specimens with formalin, embedded the specimens in paraffin, and sliced them into 5-μm sections. They were then stained with haematoxylin and eosin as well as haematoxylin phloxine saffron and Congo stains for light microscopic examination. In addition, we fixed biopsy fragments with glutaraldehyde and examined by electron microscopy.

3.10 Blood sampling and laboratory analysis

Peripheral blood samples were obtained in the non-fasting state and collected in glass tubes containing ethylenediamine tetraacetic acid, immediately centrifuged and analysed by routine laboratory methods. We determined concentrations of N-terminal pro-B-type natriuretic peptide by an electrochemiluminescence immunoassay (Roche proBNP II, Roche Diagnostics, Basel, Switzerland). Levels of C-reactive protein were determined on a MODULAR Analytical platform, P800 module (Roche Diagnostics) using a particle-enhanced immunoturbidimetric assay (Tina-Quant CRP Gen.3, Roche Diagnostics).

Plasma for the measurement of sST2 was stored at −80°C and thawed once for analysis. Soluble ST2 was measured with the Presage® ST2 Assay (Critical Diagnostics, San Diego, CA) as described by Dieplinger et al. Soluble tumour necrosis factor receptor type 1, osteoprotegerin, soluble glycoprotein 130, matrix metalloproteinase-9 and monocyte chemotactic protein-1/CCL2 were analysed by enzyme immunoassays obtained from R&D Systems (Minneapolis, MN). Procollagen type I and III N-terminal pro-peptides were analysed by radioimmunoassays (UniQ PINP RIA and UniQ PIIINP RIA, Orion Diagnostica, Espoo, Finland). Von Willebrand factor was determined by an enzyme immunoassay as
previously reported. Inter-and intra-assay coefficients of variation were < 10 % for all biochemical analyses.

3.11 Statistics

All statistical analyses were performed in IBM SPSS for Windows (IBM Corp., Armonk, NY, USA) Values are presented as mean ± standard deviation, median (interquartile range) or no (%) as appropriate. Baseline characteristics stratified by sST2 tertiles were analysed using one way ANOVA for symmetric, continuous variables, Kruskal-Wallis test for asymmetric continuous variables, and χ² test for categorical variables. Temporal changes were assessed with dependent Student’s t-tests or analysis of variance (ANOVA) for normally distributed parameters, or by Wilcoxon’s or Friedman’s test for categorical parameters. Associations between baseline characteristics and sST2, and between baseline parameters and left ventricular ejection fraction at follow-up, were assessed by bivariate and multiple linear regression. Associations between baseline values and the time to death or transplantation were assessed by Cox regression. Skewed parameters were log transformed prior to analyses. Differences in numerical outcome variables between patients treated with rosvastatin and patients treated with placebo were analysed using analysis of covariance (ANCOVA), adjusting for baseline values. The number of adverse events was compared across treatment groups by Poisson regression. All end point analyses were performed according to the intention-to-treat principle.
4 SUMMARY OF RESULTS:

4.1 Paper I

In paper 1, we show that there are but modest diagnostic and therapeutic yields of performing an extensive diagnostic work-up in patients with no suspected cause of dilated cardiomyopathy based on patient history, clinical examination, coronary angiography and echocardiography. Out of 102 patients with “idiopathic” dilated cardiomyopathy, only 15 received an aetiology-specific diagnosis based on genetic screening, magnetic resonance imaging, and endomyocardial biopsies (Table 2).

Table 2 Diagnostic yield and therapeutic consequences of additional testing in “idiopathic” dilated cardiomyopathy

<table>
<thead>
<tr>
<th>Diagnostic test</th>
<th>Diagnostic yield</th>
<th>Therapeutic consequences</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac MRI</td>
<td>Two patients diagnosed with non-compaction cardiomyopathy</td>
<td>Oral anticoagulation initiated and ICDs implanted</td>
</tr>
<tr>
<td>MRI with gadolinium contrast</td>
<td>Two patients diagnosed with cardiomyopathy in association with systemic inflammatory disease</td>
<td>Appropriate immunosuppressant therapy initiated</td>
</tr>
<tr>
<td>Right-sided cardiac catheterisation</td>
<td>None</td>
<td>No direct therapeutic consequences. Haemodynamic data can be used to optimise diuretic treatment</td>
</tr>
<tr>
<td>Endomyocardial biopsy</td>
<td>Two patients diagnosed with cardiac sarcoidosis* and ATTR-amyloidosis, respectively</td>
<td>Patient with sarcoidosis treated with prednisone</td>
</tr>
<tr>
<td>Exercise test with measurement of peak oxygen consumption</td>
<td>None</td>
<td>Ventricular arrhythmia prompted ICD implantation in two patients. Peak oxygen consumption one of several parameters used in stratification for heart transplantation.</td>
</tr>
<tr>
<td>Twenty-four hour electrocardiogram</td>
<td>None</td>
<td>No direct consequences. Detection of non-sustained ventricular tachycardia strengthens the case for ICD implantation</td>
</tr>
<tr>
<td>Genetic screening</td>
<td>Ten patients diagnosed with possible disease-causing mutations</td>
<td>Finding prompted ICD implantation in one patient. Allowed for family screening.</td>
</tr>
</tbody>
</table>

* This patient was also diagnosed on cardiac MRI with late gadolinium enhancement. MRI = magnetic resonance imaging; ICD = implantable cardioverter-defibrillator
4.2 Paper II

In this paper, we demonstrate that levels of circulating, soluble ST2 are associated with the level of haemodynamic stress, but not with potential aetiological factors in patients with dilated cardiomyopathy (Figure 5).

Figure 5 Associations between sST2 and haemodynamic variables

Scatter plots illustrating the association between log-transformed soluble ST2 (ln(sST2)) and heart rate (panel A), right atrial pressure (panel B), left ventricular ejection fraction (panel C) and pulmonary capillary wedge pressure (panel D). All p-values < 0.001. Adapted from Broch et al.\textsuperscript{113}
4.3 Paper III

Symptomatic and left ventricular improvement occurred within a year in a large proportion of patients referred to our tertiary care centre due to dilated cardiomyopathy. Moreover, we found that their medium to long-term prognosis was favourable. A short duration of symptoms and a relatively preserved left ventricular volume were predictors of a reasonably good left ventricular function after one year. Determinants of the improvement in left ventricular ejection fraction are presented in Figure 6. A small subgroup of patients with particularly severe heart failure went on to receive cardiac allografts or died from progressive heart failure.
Figure 6 Determinants of left ventricular functional improvement

The improvement in left ventricular ejection fraction is independent of the presence of a monogenic aetiology (A), viral persistence (B), atrial fibrillation (C) or late Gadolinium enhancement (D), but improved significantly more in patients with a duration of symptoms below median (F). There was a trend towards a more pronounced improvement in patients with a severely dilated ventricle from the outset (E), but these patients had a worse left ventricular ejection fraction to start with. Boxes: 25 – 75 percentiles, whiskers 2.5 – 97.5 percentiles.
4.4 Paper IV

Paper IV shows that rosuvastatin does not contribute to left ventricular improvement in well-treated, stable patients with symptomatic heart failure due to dilated cardiomyopathy. Neither does rosuvastatin affect the serum levels of markers of inflammation or matrix remodelling in this population (Figure 7).

![Graph showing changes in LVEF and LDL cholesterol](image)

**Figure 7 Changes in left ventricular ejection fraction and LDL cholesterol**

The left panel illustrates the change in left ventricular ejection fraction (LVEF) stratified by treatment allocation. There was no difference in the change in LVEF between the two groups as analysed by an independent group t-test ($p = 0.94$). The right panel illustrates the change in LDL cholesterol stratified by treatment allocation. The fall in LDL cholesterol occurred in patients allocated to rosuvastatin ($p < 0.001$). Boxes: 25-75 percentiles; whiskers: 10-90 percentiles. Modified from Broch et al. 114
5 DISCUSSION

In this thesis, we show that the clinical value of diagnostic evaluation beyond careful history taking, physical examination, routine blood sampling, echocardiography and coronary angiography is limited in patients with “idiopathic” dilated cardiomyopathy. Serum levels of sST2 seem to reflect the level of haemodynamic stress, rather than aetiological factors, in these patients. Moreover, their short- and medium term prognosis is favourable, and substantially better than some previous reports have indicated. Statins do not have a place in the routine treatment of patients with dilated cardiomyopathy.

We took care to include patients with a definite dilated cardiomyopathy only. Current guidelines define dilated cardiomyopathy as left ventricular dilation and dysfunction in the absence of coronary disease, valvular disease or hypertension, but the degree of left ventricular dysfunction and dilation required to make the diagnosis is not specified. There is no consensus on what is the ideal cut-point for discerning dilated cardiomyopathy from normal hearts. The upper limit of the normal left ventricular diameter (defined as the average + 2 standard deviations) is 5.8 cm in males and 5.2 cm in females, corresponding to 3.0 and 3.1 cm/1.73 m², respectively. To err on the safe side, in the cohort study we used 3.2 cm/m² or, in very large patients (who were not included in the above reference materials), an absolute value of 6.5 cm.

Several important randomised trials, starting with the ground-breaking SOLVD investigations, have used an LVEF cut-point of 35 %. This is also true of the more recent “device trials” such as DEFINITE. However, a number of major trials, including CIBIS, the cardiomyopathy-specific MDC trial, CHARM-Alternative and recently PARADIGM-HF have used 40 % as a cut-off. Moreover, current guidelines use 40 % as a cut-point for
recommending pharmacological intervention. We therefore chose a cut-off of 40% for left ventricular ejection fraction when designing the EVRICA trial as well as the cohort study.

An in-depth medical assessment may serve many purposes. First and foremost, we examine our patients in order to deliver correct therapy. If the aetiology is known, causal therapy may be provided. A thorough evaluation may also yield prognostic information that can be important for deciding whether to supply prophylactic therapies such as ICDs, how closely to monitor the patients, and how to inform the patients and their kin. On another level, a meticulous diagnostic work-up may help care providers better to understand disease pathophysiology, and ultimately help devise new treatment/follow-up strategies. This latter purpose is best served when the examinations are performed in a controlled study setting.

“Dilated cardiomyopathy” is a morphologically based diagnosis that covers myocardial diseases of widely different aetiologies. However, most cases are labelled “idiopathic”, meaning that the potential for cause-directed therapy remains unexploited. Many methods have been used for diagnostic investigation of patients with dilated cardiomyopathy. However, to our knowledge, the value of each of these methods has not been systematically explored. We assessed the diagnostic and therapeutic yield of a comprehensive, multi-modality work-up in dilated cardiomyopathy. The results could impact diagnostic strategies for a relatively common disease. However, despite a “state of the art” diagnostic evaluation, extensive testing did not reveal the cause of the heart failure in but a minority of our patients. Naturally, this does not mean that the other patients do not have a cause for their myocardial dysfunction, but rather serves to point out that our understanding of the aetiology in dilated cardiomyopathy remains inadequate.
Genetic testing holds the promise to revolutionise the field of cardiology. In the case of monogenic diseases, such as some cases of familial dilated cardiomyopathy, the approach should theoretically be straightforward. However, in reality, there are several difficulties with genetic testing as of today. One problem is that the distinction between a disease-causing mutation and an innocent polymorphism can be difficult to make. As de novo mutations are frequent and penetrance often incomplete, family history cannot necessarily be relied upon to ascertain the pathophysiological importance of a particular mutation. In some cases, as in early truncation of the protein in question, an assumption of clinical significance can be made with some certainty. In other cases, prediction programs can be used. We used, and compared, two such prediction programs, PolyPhen2 (http://genetics.bwh.harvard.edu/pph2/) and SIFT (http://sift.jcvi.org/). As evident from Table 3 in our article no 1, there is not complete agreement between the predictions made by these programs, and the results must be interpreted with care.

On the other hand, unless an exploratory whole genome analysis is performed, the genetic tests are restricted to genes already known to be involved in the pathogenesis of dilated cardiomyopathy. Thus, mutations affecting genes that are not known to affect cardiac function will not be discovered by the tests in use. Some of our patients had quite an impressive family history including several family members with early onset heart failure, yet negative results on genetic screening. This considered the proportion of our patients with monogenic aetiology is probably underestimated.

None of our patients had primary myocarditis as defined by the Dallas criteria. However, the sensitivity of these criteria for detecting myocarditis has been questioned, and more subtle inflammation may have been present in a substantial proportion of our patients. We
found late enhancement, potentially representing fibrosis\textsuperscript{123} or areas of inflammation,\textsuperscript{124} in approximately one third of our patients. This finding has been shown to herald an adverse prognosis in patients with dilated cardiomyopathy.\textsuperscript{123,125,126} However, we did not find late enhancement to be of prognostic importance in our patients. On the same note, viral persistence was present in a sixth of our patients, but was not associated with outcome. Previous studies have produced conflicting results regarding the clinical significance of biopsy-proven myocardial viral persistence.\textsuperscript{24,127-129} Moreover, in the few studies to look for traces of viral genome in the myocardium of patients free from heart failure, there has been a similar prevalence of “viral persistence” in subjects without heart failure as in patients with heart failure,\textsuperscript{130,131} calling into question the aetiological association between viral persistence and dilated cardiomyopathy. Our results suggest that endomyocardial biopsy should be performed in patients with dilated cardiomyopathy only when a specific aetiology is suspected, or when the suspicion of primary inflammatory disease has been raised by magnetic resonance imaging with Gadolinium late enhancement.

An important part of the diagnostic evaluation in patients with heart failure is cardiac imaging. Whereas magnetic resonance imaging is widely regarded as the “gold standard” for determining cardiac dimensions and volumes,\textsuperscript{132-135} echocardiography is the primary tool when assessing most patients with cardiac disease. Echocardiography enables a comprehensive evaluation of haemodynamic features as well as cardiac structure, is readily available, relatively cheap, and can be used bedside. On the other hand, the use of gadolinium contrast in magnetic resonance imaging allows for the identification of myocardial disease not detectable by echocardiography, such as inflammation, subtle scarring and fibrosis.
I have mainly relied on echocardiography when describing the patient population in this thesis. First, all of the patients were examined with echocardiography, whereas for various reasons magnetic resonance imaging was not performed in some patients at baseline. At follow-up, magnetic resonance imaging could not be done in a substantial portion of our patients due to the large number of implantable intracardiac devices. Moreover, some of the shortcomings of echocardiography, such as the limited resolution and tendency to underestimate intracardiac volumes, can be overcome by the use of new equipment and careful image acquisition and analysis. Figure 8 demonstrates the very high agreement between echocardiography and magnetic resonance imaging in our patients.
Figure 8 Left ventricular end diastolic volume and ejection fraction

Panel A depicts left ventricular end diastolic volume (LVEDV) and panel B left ventricular ejection fraction (LVEF) by echocardiography and magnetic resonance imaging. The data from baseline and follow-up are pooled. The Pearson correlation coefficients between results obtained by magnetic resonance imaging and results obtained by echocardiography were 0.91 (p < 0.001) for LVEDV and 0.88 (p < 0.001) for LVEF.
The aetiology in dilated cardiomyopathy is heterogeneous, and the pathophysiology is complex. There is a growing understanding that the “one treatment fits all” paradigm that exists today should probably yield to individually tailored treatment. Biomarkers hold the promise to help pinpoint patient-specific pathophysiological pathways and guide treatment.

Soluble ST2 is a cardiac biomarker that has been approved by the Food and Drug Administration, and some regard it as “ready for prime time”. We believe that it is crucial to know what a biomarker actually reflects, before it is used extensively in clinical practice.

Soluble ST2 is secreted by cardiomyocytes subjected to mechanical stress, but the source of the elevated serum levels measured in patients with heart failure remains unsettled. Our results show that the level of haemodynamic deterioration, more specifically right atrial pressure and resting heart rate, are important determinants of sST2 levels. These findings, when viewed in the light of basic science reports suggesting that the sST2 in heart failure is not primarily released by cardiomyocytes, imply that sST2 may be a marker of congestion, rather than myocardial disease. This fact possibly limits its potential usefulness as a therapeutic target.

Outcome in the heart failure population at large has improved with the introduction of treatment targeted at neurohormonal activation, malignant arrhythmias and dyssynchrony, but remains dismal. On the other hand, there are several reports of rapid and sustained improvement in patients with dilated cardiomyopathy, especially in patients with a short duration of symptoms. In the late 1990ies, McNamara and colleagues observed a seemingly impressive effect of intravenous immunoglobulin in patients with recent-onset dilated cardiomyopathy. However, from the controlled trial that followed, it was apparent that the improvement in left ventricular ejection fraction occurred independently of treatment assignment: There was as large an improvement in controls as in patients assigned to active
Moreover, the overall survival rate in the subsequent IMAC trial was surprisingly high. Since then, there has been a growing awareness of the fact that a large proportion of patients presenting with “idiopathic” dilated cardiomyopathy and a short duration of symptoms experience substantial symptomatic and left ventricular improvement.

Judging from reports over the last three decades, there has been an unequivocal, and quite impressive, improvement in the long-term survival of patients with dilated cardiomyopathy with time. This improvement is probably, at least in part, due to the beneficial effect of current, evidence based pharmacological treatment. Our very good results concerning median-to-long-term, heart transplant-free survival must be viewed in the light of the very tight adherence to recommended therapy in our population. On the other hand, this fact raises the bar for the introduction of new therapeutic interventions: A new drug would have to not only facilitate myocardial function, it would have to do so on top of the already substantial improvement in left ventricular ejection fraction and survival conferred by existing therapy. On this background, a new therapeutic intervention would probably have to target some of the pathways that are not addressed by current, guideline-recommended therapy, such as inflammation or ultrastructural remodelling.

The anti-inflammatory effect of statins has been widely studied, and a recent meta-analysis concluded that statins can improve left ventricular ejection fraction in patients with heart failure. The pleiotropic effects of statins are, however, not universally acknowledged. Our results suggest that statins do not affect ejection fraction, markers of inflammation or matrix turnover in patients with dilated cardiomyopathy. We believe that this trial provides an important contribution to the scientific evidence pertaining to the pleiotropic effects of statins, and specifically call into question the clinical relevance of these effects.
Limitations

We present data from a well-characterised, extensively examined, prospective cohort subjected to meticulous follow-up and little loss of data. However, the number of patients was limited, and the inclusion criteria were strict, making broad generalisations to the entire population of patients with dilated cardiomyopathy difficult. On the other hand, as the diagnosis “dilated cardiomyopathy” covers such a heterogeneous disease, as far as both aetiology and clinical manifestations are concerned, a very fastidious characterisation and reporting of the actual sample at hand is required for the results to be reproducible.

Contraindications, technical difficulties and a very few complications precluded some diagnostic test from being performed or analysed. We cannot exclude the possibility that a few more aetiological diagnoses could have been made had every diagnostic option been exhausted in every patient. The battery of genetic tests was limited, and did not include primers for titin, truncations of which are known to be a common cause of dilated cardiomyopathy.\textsuperscript{142} For administrative reasons, we were unable to perform immunohistochemistry on biopsy specimens. Immunohistochemistry is more sensitive than conventional light microscopic examination with regard to detecting subtle inflammation,\textsuperscript{40} and might have been useful to identify sub-clinical myocarditis.

The EVRICA trial was small, but the results were unequivocal, and unlikely to change substantially with a larger number of subjects. Nonetheless, the study was underpowered to detect small, but potentially relevant changes in inflammatory activity, extracellular matrix remodelling and left ventricular function.
6 CONCLUDING REMARKS

In this thesis, my co-authors and I have shed new light on the value of comprehensive aetiological evaluation, the involvement of a putative pathogenic pathway, the prognosis and aspects of treatment in dilated cardiomyopathy. More specifically, we show that:

1) The clinical value of diagnostic evaluation beyond careful history taking, physical examination, routine blood sampling, echocardiography and coronary angiography is modest in patients with “idiopathic” dilated cardiomyopathy.

2) Serum levels of sST2 seem to reflect the level of haemodynamic stress, rather than aetiological factors, in these patients.

3) With contemporary, evidenced based therapy, a majority of patients experience left ventricular reverse remodelling along with a substantial and clinically significant symptomatic and functional improvement. A short duration of symptoms on presentation is associated with LV functional improvement, suggesting that patients with DCM should receive a complete diagnostic work-up and evidence-based therapy as soon as possible. Their short- and medium term prognosis is favourable, but a minority of patients presenting with particularly severe HF subsequently die from HF or need orthotopic heart transplantation.

4) Statins do not contribute to reverse left ventricular remodelling in patients with dilated cardiomyopathy, and should not have a place in the routine treatment of these patients.
Reference List


55. Tominaga S. A putative protein of a growth specific cDNA from BALB/c-3T3 cells is highly similar to the extracellular portion of mouse interleukin 1 receptor. *FEBS Lett* 1989;258:301-304.


collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 2012;14:803-869.


105. Lang RM, Bierig M, Devereux RB, Flachskampf FA, Foster E, Pellikka PA, Picard MH, Roman MJ, Seward J, Shanewise J, Solomon S, Spencer KT, St John SM,


