Advanced topics in general cardiology: Cardiomyopathy and Cardio-Oncology

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Declarations

- Support for educational events: Astra Zenaca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Pfizer, Sanofi, Servier, Shire, Gore, Alnylam

- Speaker fees: Novartis, Sanofi, Astra Zenaca, Bayer, Roche

- Advisory boards: Vifor

- Grant for HF service support: Servier
Content

• European Exam in General Cardiology

• Revision sources

• Exam question technique

• Cardiomyopathy

• Cardio-oncology
European Exam in General Cardiology

- 120 questions in 3 hours
- Clinical stem followed by ‘best of five’ answer
- **No more** than an assessment of adequate core cardiology knowledge.
- **Part** of the assessment strategy for higher specialist trainees in cardiology.
- **Not an exit exam** and not an assessment of overall competence.
- No negative marking. The pass-mark is criterion referenced and usually around 60% correct answers.
- The pass-rate is usually between **85-95%** of candidates.
- Passmark for my exam was 61% (or 72 questions correct) 2012.
Question topics

Category 1 – Valvular and Myocardial Disease (~ 20% of questions)
15 Valvular disease | 16 Infective endocarditis | 10 Myocardial Disease | 17 Heart Failure

Category 2 - Ischaemic Heart Disease (~ 20% of questions)
4 Invasive cardiac imaging | 7 Cardiovascular Disease Protection i) risk factors iii) dyslipidaemia iv) diabetes | 8 Acute Coronary Syndromes | 9 Chronic IHD | 19 Rehabilitation and exercise physiology

Category 3 - Rhythm Disorders (~ 20% of questions)
2 Basic Investigations – ECG, ambulatory ECG, exercise testing | 20 Arrhythmias | 21 Atrial fibrillation | 22 Syncope | 23 Sudden Cardiac Death and Resuscitation

Category 4 – Imaging and Adult Congenital Heart Disease (~ 20% of questions)
13 Adult congenital heart disease | 14 Heart disease in pregnancy | 3 Non-invasive imaging

Category 5 - General (~ 20% of questions)
1 Clinical skills history and examination | 24 Diseases of the Aorta and Trauma | 25 Peripheral Vascular Disease | 11 Pericardial disease | 12 Cardiac tumours | 18 Pulmonary hypertension | 5 Clinical Genetics | 6 Clinical Pharmacology | 7 Cardiovascular Disease Protection ii) hypertension | 26 Venous thrombo-embolism | 27 The Cardiac Consult (Non-cardiac disease and the heart)
Relevant revision

- How to succeed in the EEGC: a guide for trainees and their trainers

- 2014 ESC HCM Guidelines

- 2016 ESC DCM position statement
  - European Heart Journal (2016) 37, 1850–1858

- 2010 ARVC Task Force Criteria
  - doi/full/10.1161/CIRCULATIONAHA.108.840827

- ESC Position Paper on cancer treatments and cardiovascular toxicity
  - European Heart Journal (2016) 37, 2768–2801
Cardiomyopathies

**Cardiomyopathy**

- **Hypertrophic**
  - Diastolic dysfunction
  - Risk of sudden death in young athletes
  - Thickened left ventricular wall

- **Dilated**
  - Enlargement of all cardiac chambers
  - Systolic dysfunction

- **Restrictive**
  - Rigid ventricular walls
  - Diastolic dysfunction

Most common type: Dilated
A 57 year old female attends your CMR list for a cardiomyopathy study shortly after a recent hospital admission. Her coronary arteries at that time were normal. What is the diagnosis?
Question
Question

What is the diagnosis?

A. Dilated cardiomyopathy
B. Apical hypertrophic cardiomyopathy
C. TakoTsubo cardiomyopathy
D. Arrhythmogenic cardiomyopathy
E. Athletic adaptation
A few weeks earlier
Cardiomyopathies

- HCM
- DCM
- ARVC
- RCM
- Unclassified

Familial/Genetic vs. Non-familial/Non-genetic

- Unidentified gene defect
- Disease sub-type*
- Idiopathic
- Disease sub-type*

Thanks to Dr Claire Turner
Hypertrophic cardiomyopathy

CAV3, GLA, MYL2, PRKAG2

Dilated cardiomyopathy

ACTC1, ACTN2, LAMP2, MYBPC3, MYH7, PLN, TNNI3, TNNT2, TPM1, TTR

DES TTN

ABCC9, CRYAB, LMNA, RBM20, TAZ

Thanks to Dr Claire Turner
Hypertrophic cardiomyopathy
CAV3, GLA, MYL2, PRKAG2

Arrhythmogenic cardiomyopathy
DSC2, DSG2, DSP, JUP, PKP2, RYR2, TMEM43

Dilated cardiomyopathy
ABCC9, CRYAB, LMNA, RBM20, TAZ

Heterogeneous

Thanks to Dr Claire Turner
Cardiac disorders

- Heterogenous in a cohort but mostly monogenic (autosomal dominant) in a family
- Few or no common mutations
- If in 1 individual > 1 gene implicated = di/oligogenic

Thanks to Dr Claire Turner
Genetic heterogeneity

- Described genes
  - LQT approx 20 genes
  - Brugada approx 20
  - CPVT > 7 genes
  - HCM > 30+ genes
  - DCM > 100’s of genes
  - ARVC > 9 genes

- Routine “panel” tests
  - 16 genes
  - 18 genes
  - 7 genes
  - 17 genes
  - 28 genes
  - 9 genes

Thanks to Dr Claire Turner
Hypertrophic Cardiomyopathy

• Defined by a wall thickness ≥15 mm in one or more LV myocardial segment

• HCM in first-degree relatives of patients with unequivocal disease (LVH ≥15 mm) is based on LV wall thickness ≥13 mm

• That is not explained solely by loading conditions
Hypertrophic Cardiomyopathy (HCM)

- Most common inherited cardiovascular condition in the world (1:500)
- Unexplained hypertrophy of the left +/- right ventricle
- Myocyte hypertrophy and disarray, interstitial fibrosis
- Shortness of breath, chest pain, syncope and sudden cardiac death
- Most common cause of sudden death in athletes
- Common feature in all types of HCM is the \textbf{variable expression of the phenotype}
- Autosomal dominant
  Genes encoding sarcomeric proteins

Thanks to Dr Martina Muggenthaler
Diverse aetiology of hypertrophic cardiomyopathy

- **Sarcomeric protein gene mutation**
  - 40-60%

- **Unknown**
  - ~25-30%

- **Other genetic and non-genetic causes**

  - Inborn errors of metabolism
  - Glycogen storage diseases:
    - Pompe
    - Danon
  - AMP-Kinase (PRKAG2)
  - Carnitine disorders
  - Lysosomal storage diseases
    - Anderson-Fabry
  - Neuromuscular diseases
    - Friedreich's ataxia
    - FHL1
  - Mitochondrial diseases
    - MELAS
    - MERFF
  - Malformation Syndromes
    - Noonan
    - LEOPARD
    - Costello
    - CFC
  - Amyloidosis
    - Familial ATTR
    - Wild type TTR (senile)
    - AL amyloidosis
  - Newborn of diabetic mother
  - Drug-induced
    - Tacrolimus
    - Hydroxychloroquine
    - Steroids

The majority of cases in adolescents and adults are caused by mutations in sarcomere protein genes.
Schematic summarising the general approach to the diagnosis of hypertrophic cardiomyopathy

Clinical evaluation
- Pedigree
- Signs
- Symptoms
- ECG
- Cardiac Imaging
- Laboratory

Diagnostic red flags
- Features suggesting a specific disease?

Genetic testing
- Consider genetic testing
  - Definite disease causing sarcomere protein gene mutation
  - No definite disease causing sarcomere protein gene mutation identified

Further specialised tests & multidisciplinary input
- No cause identified

Specific genetic/acquired disorder

Notes: 1. Counselling is essential before and after testing for genetic disease. 2. Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM to enable cascade genetic screening of their relatives. 3. For recommendations on individual investigations see relevant sections.
Treatment of Hypertrophic Cardiomyopathy

- Improve symptoms
  - Medical
  - Surgical

- Sudden cardiac death risk
  - Assessment
  - Device decision

- Family screening
Protocol for the assessment and treatment of left ventricular outflow tract obstruction

2-D and Doppler echocardiography at rest, Valsalva and standing

- Maximum provoked peak LVOTO ≥ 50 mm Hg
  - See 9.1 Symptomatic left ventricular outflow tract obstruction

- Maximum provoked peak LVOTO < 50 mm Hg
  - Asymptomatic*
    - Repeat echocardiography 1 year
  - Symptomatic
    - Exercise stress echocardiography
      - Maximum provoked peak LVOTO ≥ 50 mm Hg
        - See 9.1 Symptomatic left ventricular outflow tract obstruction
      - Maximum provoked peak LVOTO < 50 mm Hg
        - Medical therapy (see 9. Management of symptoms and complications)

*Exercise echocardiography may be considered in individual patients when the presence of a LVOT gradient is relevant to lifestyle advice and decisions on medical treatment.

LVOT = left ventricular outflow tract obstruction.
**Treatment of left ventricular outflow tract obstruction: General measures**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arterial and venous dilators, including nitrates and phosphodiesterase inhibitors, should be avoided if possible in patients with resting or provicable LVOTO.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Restoration of sinus rhythm or appropriate rate control should be considered before considering invasive therapies in patients with new-onset or poorly controlled atrial fibrillation.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Digoxin is not recommended in patients with resting or provicable LVOTO.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
# Medical treatment of left ventricular outflow tract obstruction

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-vasodilating β-blockers, titrated to maximum tolerated dose, are recommended as first-line therapy to improve symptoms in symptomatic patients with resting or provoked LVOTO.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Verapamil, titrated to maximum tolerated dose, is recommended to improve symptoms in symptomatic patients with resting or provoked LVOTO, who are intolerant or have contra-indications to β-blockers.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Disopyramide, titrated to maximum tolerated dose, is recommended in addition to a β-blocker (or, if this is not possible, with verapamil) to improve symptoms patients with resting or provoked LVOTO.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Disopyramide, titrated to maximum tolerated dose, may be considered as monotherapy to improve symptoms in symptomatic patients with resting or provoked LVOTO (exercise or Valsalva manoeuvre) taking caution in patients with—or prone to—AF, in whom it can increase ventricular rate response.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>β-Blockers or verapamil may be considered in children and asymptomatic adults with resting or provoked LVOTO, to reduce left ventricular pressures.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
# Medical treatment of left ventricular outflow tract obstruction (Cont.)

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-dose loop- or thiazide diuretics may be used with caution in symptomatic LVOTO, to improve exertional dyspnoea.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Diltiazem, titrated to maximum tolerated dose, should be considered in symptomatic patients with resting or provoked(^a) LVOTO, who are intolerant or have contra-indications to β-blockers and verapamil to improve symptoms.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Oral or i.v. β-blockers and vasoconstrictors should be considered in patients with severe provable LVOTO presenting with hypotension and pulmonary oedema.</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

\(^a\)Provocation with Valsalva manoeuvre, upright exercise or oral nitrates if unable to exercise.

\(^b\)QTc interval should be monitored during up-titration of disopyramide and the dose reduced if it exceeds 480 ms.
## Septal reduction therapy

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>It is recommended that septal reduction therapies be performed by experienced operators, working as part of a multidisciplinary team expert in the management of HCM.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Septal reduction therapy to improve symptoms is recommended in patients with a resting or maximum provoked LVOT gradient of $\geq 50$ mm Hg, who are in NYHA functional Class III–IV despite maximum tolerated medical therapy.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Septal reduction therapy should be considered in patients with recurrent exertional syncope caused by a resting or maximum provoked LVOTO gradient $\geq 50$ mm Hg despite optimal medical therapy.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Septal myectomy, rather than SAA, is recommended in patients with an indication for septal reduction therapy and other lesions requiring surgical intervention (e.g. mitral valve repair/replacement, papillary muscle intervention).</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>Mitral valve repair or replacement should be considered in symptomatic patients with a resting or maximum provoked LVOTO gradient $\geq 50$ mm Hg and moderate-to-severe mitral regurgitation not caused by SAM of the mitral valve alone.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Mitral valve repair or replacement may be considered in patients with a resting or maximum provoked LVOTO gradient $\geq 50$ mm Hg and a maximum septal thickness $\leq 16$ mm at the point of the mitral leaflet-septal contact or when there is moderate-to-severe mitral regurgitation following isolated myectomy.</td>
<td>IIb</td>
<td>C</td>
</tr>
</tbody>
</table>
Septal reduction therapy

Courtesy of Dr Sam Mohiddin
Flow chart for ICD implantation

**PRIMARY PREVENTION**

Recommended assessment:
- History
- 2-D/Doppler echocardiogram
- 48-hour ambulatory ECG

HCM Risk-SCD variables:
- Age
- Family history of sudden cardiac death
- Unexplained syncope
- Left ventricular outflow gradient
- Maximum left ventricular wall thickness
- Left atrial diameter
- NSVT

HCM Risk-SCD Score

**SECONDARY PREVENTION**

- Cardiac arrest due to VT or VF
- Spontaneous sustained VT causing syncope or haemodynamic compromise

Life expectancy >1 year

ICD recommended

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*a Use absolute values for LVOT gradient, MLVWT and left atrial dimension.

## Risk of Sudden Cardiac Death

### HCM Risk-SCD Calculator

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Input</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>Maximum LV wall thickness</td>
<td></td>
</tr>
<tr>
<td>Left atrial size</td>
<td></td>
</tr>
<tr>
<td>Max LVOT gradient</td>
<td></td>
</tr>
<tr>
<td>Family History of SCD</td>
<td></td>
</tr>
<tr>
<td>Non-sustained VT</td>
<td></td>
</tr>
<tr>
<td>Unexplained syncope</td>
<td></td>
</tr>
</tbody>
</table>

- **Age**: Age at evaluation
- **Maximum LV wall thickness**: Transsthoracic Echocardiographic measurement
- **Left atrial size**: Left atrial diameter determined by M-Mode or 2D echocardiography in the parasternal long axis plane at time of evaluation
- **Max LVOT gradient**: The maximum LV outflow gradient determined at rest and with Valsalva provocation (irrespective of concurrent medical treatment) using pulsed and continuous wave Doppler from the apical three and five chamber views. Peak outflow tract gradients should be determined using the modified Bernoulli equation: \( \text{Gradient} = 4V^2 \), where \( V \) is the peak aortic outflow velocity
- **Family History of SCD**: History of sudden cardiac death in 1 or more first degree relatives under 40 years of age or SCD in a first degree relative with confirmed HCM at any age (post or ante-mortem diagnosis)
- **Non-sustained VT**: 3 consecutive ventricular beats at a rate of 120 beats per minute and <30s in duration on Holter monitoring (minimum duration 24 hours) at or prior to evaluation
- **Unexplained syncope**: History of unexplained syncope at or prior to evaluation

### Risk of SCD at 5 years (%): [ ]

### ESC recommendation: [ ]

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O’Mahoney C 2014 EHJ  
Flow chart for ICD implantation

- **HCM-Risk SCD Score**
  - **LOW-RISK**
    - 5-year risk < 4%: ICD generally not indicated
  - **INTERMEDIATE RISK**
    - 5-year risk ≥4% - <6%: ICD may be considered
  - **HIGH-RISK**
    - 5-year risk ≥6%: ICD should be considered

*ICD not recommended unless there other clinical features that are of potential prognostic importance and when the likely benefit is greater than the lifelong risk of complications and the impact of an ICD on lifestyle, socioeconomic status and psychological health.*
David Frost's late son not told of heart condition inherited from father

Miles Frost family says he was not told he was at risk of hypertrophic cardiomyopathy, as they set up fund to help others with congenital disorder

Sir David Frost’s son was not told that he was at risk from a rare genetic disorder inherited from his father before his unexpected death at the age of 31 last summer.
Question

John and Claire are expecting their first child. They have come to see you and want to know what the risk is for their unborn child to be affected by the same condition that John has.
Which of the following is true?

A. The unborn child’s risk of being affected is 25%
B. If the unborn child is a girl, the risk of being affected is 0%. If the unborn child is a boy, the risk of being affected is 50%.
C. If the unborn child is a girl, the risk of being affected is 25%. If the unborn child is a boy, the risk of being affected is 100%.
D. The unborn child’s risk of being affected is 50%.
E. If the unborn child is a girl, the risk of being affected is 50%. If the unborn child is a boy, the risk of being affected is 100%
## Genetic testing in probands

<table>
<thead>
<tr>
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<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing is recommended in patients fulfilling diagnostic criteria for HCM, when it enables cascade genetic screening of their relatives.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>It is recommended that genetic testing be performed in certified diagnostic laboratories with expertise in the interpretation of cardiomyopathy-related mutations.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>In the presence of symptoms and signs of disease suggestive of specific causes of HCM, genetic testing is recommended to confirm the diagnosis.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Genetic testing in patients with a borderline(^a) diagnosis of HCM should be performed only after detailed assessment by specialist teams.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Post-mortem genetic analysis of stored tissue or DNA should be considered in deceased patients with pathologically confirmed HCM, to enable cascade genetic screening of their relatives.</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

\(^a\)Borderline: left ventricular wall thickness 12 – 13 mm in adults; left ventricular hypertrophy in the presence of hypertension, athletic training, valve disease.
Genetic and clinical testing of adult relatives

<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Cascade genetic screening, after pre-test counselling, is recommended in first-degree adult relatives of patients with a definite disease-causing mutation.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Clinical evaluation, employing ECG and echocardiography and long-term follow-up, is recommended in first-degree relatives who have the same definite disease-causing mutation as the proband.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>First-degree relatives who do not have the same definite disease-causing mutation as the proband should be discharged from further follow-up but advised to seek re-assessment if they develop symptoms or when new clinically relevant data emerge in the family.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>When no definite genetic mutation is identified in the proband or genetic testing is not performed, clinical evaluation with ECG and echocardiography should be considered in first-degree adult relatives and repeated every 2-5 years (or 6-12 monthly if non-diagnostic abnormalities are present).</td>
<td>IIa</td>
<td>C</td>
</tr>
</tbody>
</table>

Proband = usually the first family member to be diagnosed with the condition.
Flow chart for the genetic and clinical screening of probands and relatives

Genetic testing

- Definite mutation
  - Cascade genetic test
    - Mutation positive ± clinical phenotype
      - Long-term follow-up
    - Mutation negative
      - Discharge
  - HCM
    - Long-term follow-up
- Variant of unknown/uncertain significance
  - Do segregation analysis where possible
- No mutation
  - Reconsider other genocopies/phenocopies
    - Cascade clinical screening
      - Normal
        - Repeat screening at intervals
      - HCM
        - Long-term follow-up

HCM = hypertrophic cardiomyopathy.
Cascade genetic test = screening of first degree relatives of patients already diagnosed with HCM.
A 70 year old man presents with progressively increasing breathlessness and clinical signs of fluid overload. He has a history of hypertension controlled with 2 agents.

What is the most likely diagnosis?
A. Hypertensive cardiomyopathy
B. Hypertrophic cardiomyopathy
C. Anderson-Fabry disease
D. Cardiac amyloidosis
E. Cardiac iron deposition
Question?
A 70 year old man presents with progressively increasing breathlessness and clinical signs of fluid overload. He has a history of hypertension controlled with 2 agents.

What is the most likely diagnosis?

A. Hypertensive cardiomyopathy
B. Hypertrophic cardiomyopathy
C. Anderson-Fabry disease
D. Cardiac amyloidosis
E. Cardiac iron deposition
Question

A 50 year old woman has experienced symptoms over the last 2 years and been investigated for a cardiomyopathy. Presuming her 20 year old son is currently unaffected, what is the repeat interval for screening?

A. 3-5 years
B. Symptom based
C. 1 year
D. 2 years
E. Don’t know - need more info
Question
Question

A 50 year old woman has experienced symptoms over the last 2 years and been investigated for a cardiomyopathy. Presuming her 20 year old son is currently unaffected, what is the repeat interval for screening?

A. 3-5 years
B. Symptom based
C. 1 year
D. 2 years
E. Need more info
Dilated cardiomyopathy

Left ventricular or biventricular systolic dysfunction and dilatation that are not explained by abnormal loading conditions or coronary artery disease.

Systolic dysfunction
- abnormal LV ejection fraction, measured using any modality and shown either by two independent imaging modalities or on two distinct occasions by the same technique, preferably echocardiography or CMR.

Left ventricular dilatation
- is defined by LV end-diastolic (ED) volumes or diameters 2SD from normal according to normograms (Z scores 2 standard deviations) corrected by body surface area (BSA) and age, or BSA and gender.

Pinto et al. EHJ 2016, doi:10.1093/eurheartj/ehv727
DCM Clinical Spectrum

Preclinical or Early Phase

(Relative of patients with DCM or Hypokinetic Non Dilated CM)

- No cardiac expression (Mutation carrier and/or AHA positive)
  (no LV abn, no arrhythmia)
  \( (DCM_{\text{ND-NH-Mut+AHA}^+}) \)

- Isolated Ventricular Dilation
  (Dilation/no Hypokinesia)*\(^\wedge\)
  \( (DCM_{D-NH}, \text{with or without mut+AHA}^+) \)

- Arrhythmic CM
  (Arrhythmias or conduction defect)
  \( (DCM_{\text{ND-NH-A/CD},\text{with or without mut+AHA}^+}) \)

Clinical Phase

- Hypokinetic Non Dilated CM
  (Hypokinesia/no Dilation)
  \( (HNDC \text{ or } DCM_{ND-H}^-) \)

- Dilated CM
  (LV Dilation + Hypokinesia)
  \( (DCM_{D-H}) \)

Progressive expression of the phenotype

*Shown by two independent imaging modalities, \(^\wedge\)mutation carrier or not; anti-heart autoantibody (AHA) positive or negative
Overview of dilated cardiomyopathy criteria in probands and relatives

Summary of diagnostic criteria for DCM

INDEX CASE
- DCM (Dilated LV & reduced EF)
- HNDC (EF <45% & no dilation)
  - Familial
  - Non familial

RELATIVE

Criteria as for index cases?
  yes → Definitive disease (DCM/HNDC)
  no → Major criteria for relatives? (dilated LV OR LV EF 45–50%)

  yes → + ≥1 minor criterion? Or mutation carrier?
  no → ≥2 minor without mutation carrier? OR 1 minor criterion + mutation carrier?

  yes → Probable disease
  no → Possible disease

Probable disease
Possible disease
No disease
Investigation of DCM

• Huge number of causes
• Guided by history
• Progressive process (remember common things are common)
• Don’t forget to keep an open mind though!
• Idiopathic/familial (20-50%)
• Treatment predominantly as per heart failure guidelines
Late gadolinium enhancement – diagnosis and prognosis?

IHD

DCM

HCM

Myocarditis

Sarcoid

Amyloid

White JA et al. Cardiology Clinics, 2007; 25(1), 71-95
Arrhythmogenic Right Ventricular Cardiomyopathy or Arrhythmogenic Cardiomyopathy

Special Report

Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia
Proposed Modification of the Task Force Criteria

Background — In 1994, an international Task Force proposed criteria for the clinical diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) that facilitated recognition and interpretation of the frequently non-specific clinical features of ARVC/D. This enabled confirmatory clinical diagnosis in index cases through exclusion of phenotypes and provided a standard on which clinical research and genetic studies could be based. Structurally, histological, electrocardiographic, arrhythmic, and familial features of the disease were incorporated into the criteria, subdivided into major and minor categories according to the specificity of their association with ARVC/D. At that time, clinical experience with ARVC/D was dominated by symptomatic index cases and sudden cardiac death victims—hence the overt or severe end of the disease spectrum. Consequently, the 1994 criteria were highly specific but lacked sensitivity for early and familial disease.

Methods and Results — Revision of the diagnostic criteria provides guidance on the use of emerging diagnostic modalities and advances in the genetics of ARVC/D. The criteria have been modified to incorporate new knowledge and technology to improve diagnostic sensitivity, but with the important requisite of maintaining diagnostic specificity. The approach of classifying structural, histological, electrocardiographic, arrhythmic, and genetic features of the disease as major and minor criteria has been maintained. In this modification of the Task Force criteria, quantitative criteria are proposed and abnormalities are defined on the basis of comparison with normal subject data.

Conclusion — The present modifications of the Task Force Criteria represent a working framework to improve the diagnosis and management of this condition.


Key Words: arrhythmogenic, cardiac — arrhythmogenic right ventricular cardiomyopathy/dysplasia — death, sudden, cardiac — diagnosis — echocardiography — electrocardiography — magnetic resonance imaging

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a dominantly inherited myocardial disorder that is characterized pathologically by fibromyocardial replacement of the right ventricle (RV) myocardium. In the early stage of the disease, structural changes may be absent or subtle and confined to a localized region of the RV, typically the inflow tract, outflow tract, or apex of the RV, the “triangle of dysplasia.” Progression to more
Arrhythmogenic Right Ventricular Cardiomyopathy or Arrhythmogenic Cardiomyopathy

- Epsilon wave (most specific finding, seen in 30% of patients)
- T wave inversions in V1-3 (85% of patients)
- Prolonged S-wave upstroke of 55ms in V1-3 (95% of patients)
- Localised QRS widening of 110ms in V1-3
- Paroxysmal episodes of ventricular tachycardia with a LBBB morphology
Arrhythmogenic Right Ventricular Cardiomyopathy or Arrhythmogenic Cardiomyopathy

ARVC with LV involvement
<table>
<thead>
<tr>
<th>Domain</th>
<th>Major criteria</th>
<th>Minor criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history</td>
<td>• ARVD confirmed in a first-degree relative</td>
<td>• History of ARVD in a first-degree relative in whom it was not possible to determine whether the current Task Force Criteria is met</td>
</tr>
<tr>
<td></td>
<td>• ARVD confirmed at surgery or autopsy in a first-degree relative</td>
<td>• Premature death at &lt;35 years of age due to suspected ARVD</td>
</tr>
<tr>
<td></td>
<td>• Pathogenetic mutation in a gene associated with ARVD</td>
<td>• ARVD confirmed pathologically or by current Task Force criteria in a second-degree relative</td>
</tr>
<tr>
<td>ECG abnormalities</td>
<td>• Epsilon wave (reproducible low-amplitude signals between end of QRS complex and beginning of T-wave in leads V1 to V3)</td>
<td>• Late potentials by signal-averaged ECG in ≥1 of 3 parameters in an absence of QRS ≥110 ms</td>
</tr>
<tr>
<td></td>
<td>• Inverted T-waves in leads V1 to V3 in individuals &gt;14 years of age in the absence of RBBB and QRS ≥120 ms</td>
<td>• Filtered QRS duration ≥114 ms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Duration of terminal QRS &lt;40 µV and ≥38 ms</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Root-mean-square voltage of terminal QRS &lt;40 ms and ≤20 µV</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Terminal activation duration of QRS ≥55 ms measured between the nadir of the S wave and the end of the QRS complex, including R', in V1, V2, or V3, without RBBB</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• T-wave inversion in V1 and V2 in individuals &gt;14 years of age in the absence of RBBB, or in V4 to V6</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• T-wave inversion in leads V1 to V4 in individuals &gt;14 years of age in the presence of complete RBBB</td>
</tr>
<tr>
<td>Arrhythmias</td>
<td>• Nonsustained or sustained VT with a LBBB morphology with superior axis (negative or indeterminate QRS in leads II, III, and aVF and positive in aVL)</td>
<td>• Nonsustained or sustained VT of RVOT configuration, LBBB morphology with inferior axis (positive QRS in leads II, III, and aVF and negative in aVL) or of unknown axis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• 500 ventricular extrasystoles within 24 h on Holter monitoring</td>
</tr>
<tr>
<td>Tissue characteristics</td>
<td>• Fibro-fatty replacement of the myocardium on endomyocardial biopsy</td>
<td>• Residual myocytes &lt;60% by morphometric analysis (or &lt;50% if estimated) with fibrous replacement of the RV free wall myocardium in &gt;1 sample, with or without fatty replacement of tissue on endomyocardial biopsy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Residual myocytes 60%-75% morphometric analysis (or 50%-65% if estimated) with fibrous replacement of the RV free wall myocardium in &gt;1 sample, with or without fatty replacement of tissue on endomyocardial biopsy</td>
</tr>
</tbody>
</table>
**Modified Task Force Criteria for ARVC**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Major Criteria</th>
<th>Minor Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Echocardiography</strong></td>
<td>Regional RV akinesia, dyskinesia, or aneurysm</td>
<td>Regional RV akinesia, dyskinesia, and one of the following at end diastole:</td>
</tr>
<tr>
<td></td>
<td>PLAX RVOT $\geq 32$ mm (corrected for body size [PLAX/BSA] $\geq 19$ mm/m$^2$)</td>
<td>o PLAX RVOT $\geq 32$ and $&lt;36$ mm (corrected for body size [PLAX/BSA] $&gt;18$ and $&lt;21$ mm/m$^2$)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o PLAX RVOT $\geq 29$ and $&lt;32$ mm (corrected for body size [PLAX/BSA] $&gt;16$ and $&lt;19$ mm/m$^2$)</td>
</tr>
<tr>
<td></td>
<td>Fractional area change $\leq 33%$</td>
<td>o Fractional area change $&gt;33%$ and $\leq 40%$</td>
</tr>
<tr>
<td><strong>MRI</strong></td>
<td>Regional RV akinesia or dyskinesia or dyssynchronous RV contraction and one of the following:</td>
<td>Regional RV akinesia or dyskinesia and one of the following:</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o Ratio of RV end-diastolic volume to BSA $\geq 110$ mL/m$^2$ (male) or $\geq 100$ mL/m$^2$ (female)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o RV ejection fraction $\leq 40%$</td>
</tr>
<tr>
<td></td>
<td></td>
<td>o RV ejection fraction $&gt;40%$ and $\leq 45%$</td>
</tr>
<tr>
<td><strong>RV angiography</strong></td>
<td>Regional RV akinesia, dyskinesia, or aneurysm</td>
<td>Regional RV akinesia, dyskinesia, or aneurysm</td>
</tr>
</tbody>
</table>

**Definite:** 2 major or 1 major and 2 minor or 4 minor from different categories

**Borderline:** 1 major and 1 minor or 3 minor from 3 different categories

**Possible:** 1 major or 2 minor criteria from different categories

---

*Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia, Volume: 121, Issue: 13, Pages: 1533-1541*
Histological examination of ACM: normal findings within the RV vs pathological criteria for ACM
Pattern of ventricular involvement in ACM

Biventricular Involvement 141/202 (70%)

RV: 26/202 (13%)  LV: 35/202 (17%)

RVAL 64%  RVOT 48%
RVS 32%  LVS 32%
RVPW 43%  LVPW 68%
LVAL 58%
Classification of competitive sport according to static and dynamic component

- **I. Low (<20% MVC)**
  - Cricket n=1

- **II. Moderate (20-50% MVC)**
  - Rugby n=5
  - Gaelic football n=1

- **III. High (>50% MVC)**
  - Martial arts n=3
  - Triathlon n=2
  - Rowing n=1
  - Cycling n=2

- **A. Low (<40% Max O2)**
- **B. Moderate (40-70% Max O2)**
- **C. High (>70% Max O2)**

Increasing Dynamic Component

Sudden Death and Left Ventricular Involvement in Arrhythmogenic Cardiomyopathy, Volume: 139, Issue: 15, Pages: 1786-1797, DOI: (10.1161/CIRCULATIONAHA.118.037230)
Prediction of sustained ventricular arrhythmia in ARVC

5-year event-free survival (n = 528)
Overall

Model for 5-year risk prediction

- Sex: x 0.49
- Age: x -0.022
- Recent syncope: x 0.66
- Non-sustained VT: x 0.81
- Ln(24h PVC count): x 0.17
- Leads with T-wave inv.: x 0.11
- RVEF: x -0.025

\[ 1 - 0.802^{\text{exp}()} = 5 \text{ year risk} \]

5-year event-free survival (n = 528)
Per predicted risk group

European Heart Journal, ehz103, https://doi.org/10.1093/eurheartj/ehz103
Prediction of sustained ventricular arrhythmia in ARVC

Age at diagnosis
41
Enter the age at which the patient fulfilled ARVC diagnosis as per 2010 modified Task Force Criteria (Marcus et al. 2010)

Sex
- Male
- Female

Cardiac syncope (<6 months)
- Yes
- No
Specify if the patient experienced syncope suspected to be caused by cardiac arrhythmia in the 6 months prior to diagnosis.

Number of inverted T-waves
3
Specify the total number of inverted T-waves in precordial and inferior leads on standard 12-lead ECG.

Maximum 24 hours PVC count
8000
Enter the maximum number of PVCs measured in 24 hours by ECG/Holter monitoring.

History of non-sustained VT
- Yes
- No
Specified as a recorded ventricular tachycardia (>100bpm) ending spontaneously within 30 seconds.

Right ventricular ejection fraction (%)
50
As measured by cardiac MRI.

As measured by cardiac MRI.

Calculate

Risk of sustained ventricular arrhythmia
- 40.8% within 5 years
- 26.9% within 2 years
- 17.6% within 1 year

Reset

Please consider the following limitations:
- The calculator should not be used in patients with prior sustained ventricular arrhythmia or sudden cardiac arrest.
- The calculator is designed to provide predictions based on the clinical characteristics of ARVC patients at time of their diagnosis (as per 2010 TFC).
- Caution should be exercised when interpreting the result for pediatric patients <14 years of age.

For more information, read the disclaimer and the European Heart Journal publication.

Problems with the calculator? Contact us

www.arvcrisk.com
Cardio-Oncology
75 year old male under investigation for weight loss and diarrhoea. An abdominal mass is identified and surgery is planned. A murmur is heard at the pre-op check and an echo request. You are asked to review the images.

What is the next most appropriate investigation to confirm the diagnosis?

A. Right and left heart catheter
B. Cardiac MRI
C. Urinary free cortisol levels
D. Urinary 5-hydroxyindoleacetic acid levels
E. Transoesophageal echo
Question

75 year old male under investigation for weight loss and diarrhoea. Clinical signs of right heart failure and a murmur. The gastroenterologist requests an Echo and you are asked to review.

What is the next most appropriate investigation to confirm the diagnosis?

A. Right and left heart catheter
B. Cardiac MRI
C. Urinary free cortisol levels
D. Urinary 5-hydroxyindoleacetic acid levels
E. Transoesophageal echo
Cardio-Oncology

With thanks to Dr A Ghosh
http://www.acc.org/latest-in-cardiology/articles/2017/10/24/08/43/how-to-build-a-cardio-oncology-service
Cardiac problems in cancer treatment

- **Chemotherapy**
  - Heart failure, cardiac ischaemia, arrhythmias, pericarditis

- **Radiotherapy**
  - CAD, fibrosis of valves, pericardium and myocardium

With thanks to Dr A Ghosh
Br J Hosp Med 2017
We’re doing great so what’s the problem?

changes in survival, 1971-72 to 2010-11

Estimated Number of Cancer Survivors in the US

With thanks to Dr A Ghosh Maddams 2012; DeSantis 2014
Mechanism of cytotoxicity and potential preventive therapies

Bloom Circ HF 2016
## Type 1 and Type 2 effects

### Table 1: Characteristics of type I and II CTRCD

<table>
<thead>
<tr>
<th>Characteristic agent</th>
<th>Type I</th>
<th>Type II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical course and typical response to antiremodeling therapy (β-blockers, ACE inhibitors)</td>
<td>May stabilize, but underlying damage appears to be permanent and irreversible; recurrence in months or years may be related to sequential cardiac stress</td>
<td>High likelihood of recovery (to or near baseline cardiac status) in 2–4 months after interruption (reversible)</td>
</tr>
<tr>
<td>Dose effects</td>
<td>Cumulative, dose related</td>
<td>Not dose related</td>
</tr>
<tr>
<td>Effect of rechallenge</td>
<td>High probability of recurrent dysfunction that is progressive; may result in intractable heart failure or death</td>
<td>Increasing evidence for the relative safety of rechallenge (additional data needed)</td>
</tr>
<tr>
<td>Ultrastructure</td>
<td>Vacuoles; myofibrillar disarray and dropout; necrosis (changes resolve over time)</td>
<td>No apparent ultrastructural abnormalities (though not thoroughly studied)</td>
</tr>
</tbody>
</table>
Assessing and managing cardiac risk

Which cancer patients are at increased risk for developing cardiac dysfunction?

Recommendation 1

Cancer diagnosis

Start of treatment

End of treatment

Which preventative strategies minimize risk before initiation of therapy?

Recommendation 2

What strategies minimize risk during potentially cardiotoxic therapy?

Recommendation 3

What are the preferred surveillance / monitoring approaches during treatment in patients at risk for cardiac dysfunction?

Recommendation 4

What are the preferred surveillance / monitoring approaches after treatment in patients at risk for cardiac dysfunction?

Recommendation 5

Armenian et al: JCO 2016
### Table 1: Incidence of left ventricular dysfunction associated with chemotherapy drugs^{10–21}

<table>
<thead>
<tr>
<th>Chemotherapy agents</th>
<th>Incidence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Anthracylicines (dose dependent)</strong></td>
<td></td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin) 400 mg/m²</td>
<td>3–5</td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin) 550 mg/m²</td>
<td>7–26</td>
</tr>
<tr>
<td>Doxorubicin (Adriamycin) 700 mg/m²</td>
<td>18–48</td>
</tr>
<tr>
<td>Idarubicin (&gt;90 mg/m²)</td>
<td>5–18</td>
</tr>
<tr>
<td>Epirubicin (&gt;900 mg/m²)</td>
<td>0.9–11.4</td>
</tr>
<tr>
<td>Mitoxantrone &gt;120 mg/m²</td>
<td>2.6</td>
</tr>
<tr>
<td>Liposomal anthracyclines (&gt;900 mg/m²)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Alkylation agents</strong></td>
<td></td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>7–28</td>
</tr>
<tr>
<td>Ifosfamide &lt;10 g/m²</td>
<td>0.5</td>
</tr>
<tr>
<td>Ifosfamide 12.5–16 g/m²</td>
<td>17</td>
</tr>
<tr>
<td><strong>Antimetabolites</strong></td>
<td></td>
</tr>
<tr>
<td>Clofarabine</td>
<td>27</td>
</tr>
<tr>
<td><strong>Antimicrotubule agents</strong></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>2.3–13</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>&lt;1</td>
</tr>
<tr>
<td><strong>Monoclonal antibodies</strong></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>1.7–20.1^{78a}</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1.6–4^{14b}</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>0.7–1.2</td>
</tr>
</tbody>
</table>

### Table 2: Factors associated with risk of cardiotoxicity following treatment with anthracyclines^{a}

<table>
<thead>
<tr>
<th>Risk factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Cumulative dose</td>
</tr>
<tr>
<td>• Female sex</td>
</tr>
<tr>
<td>• Age</td>
</tr>
<tr>
<td>- &gt;65 years old</td>
</tr>
<tr>
<td>- Paediatric population (&lt;18 years)</td>
</tr>
<tr>
<td>• Renal failure</td>
</tr>
<tr>
<td>• Concomitant or previous radiation therapy involving the heart</td>
</tr>
<tr>
<td>• Concomitant chemotherapy</td>
</tr>
<tr>
<td>- alkylation or antimicrotubule agents</td>
</tr>
<tr>
<td>- immuno- and targeted therapies</td>
</tr>
<tr>
<td>• Pre-existing conditions</td>
</tr>
<tr>
<td>- Cardiac diseases associating increased wall stress</td>
</tr>
<tr>
<td>- Arterial hypertension</td>
</tr>
<tr>
<td>- Genetic factors</td>
</tr>
</tbody>
</table>

^{a} Anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin) or anthracenedione (mitoxantrone).
Can we prevent it? OVERCOME

90 patients with haem malignancies randomised to enalapril and carvedilol or placebo

Bosch et al. 2013 JACC
Can we prevent it? PRADA

A

Effect of Candesartan Treatment
Difference in change in LVEF (95% CI) from baseline to EOS

Sample
- n = total/candesartan/not candesartan
- All patients (n = 109/57/52)
- Age > median (n = 55/28/27)
- Age ≤ median (n = 54/29/25)
- Current smoker (n = 19/11/8)
- Not current smoker (n = 90/46/44)
- Hypertension (n = 8/6/2)
  - No hypertension (n = 101/51/50)
- BMI > median (n = 51/20/31)
  - BMI ≤ median (n = 58/37/21)
- Trastuzumab (n = 25/13/12)
  - No trastuzumab (n = 84/44/40)
- No radiation (n = 24/14/10)
  - Left sided radiation (n = 40/23/17)
  - Right sided radiation (n = 45/20/25)

P-values for interaction
- P = 0.47
- P = 0.76
- P = 0.41
- P = 0.09
- P = 0.28
- P = 0.43

Can we prevent it? PRADA

Can we prevent it? Statins

628 women with breast cancer and anthracycline treatment
Continuous statin treatment or not.

Seicean et al. 2012 JACC
Can we prevent it? MANTICORE

**Women with HER2 +ve breast cancer – Trying to prevent Herceptin related LVSD**


<table>
<thead>
<tr>
<th>Measure</th>
<th>Placebo (n = 30)</th>
<th>Perindopril (n = 33)</th>
<th>Bisoprolol (n = 31)</th>
<th>ANOVA P</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEDVI, mL/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>76 ± 13*</td>
<td>67 ± 14</td>
<td>69 ± 10</td>
<td>.01</td>
</tr>
<tr>
<td>Post-cycle 4</td>
<td>77 ± 10</td>
<td>71 ± 10†</td>
<td>76 ± 11†</td>
<td>.09</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>+2 ± 9</td>
<td>+4 ± 9</td>
<td>+7 ± 8</td>
<td>.07</td>
</tr>
<tr>
<td>Post-cycle 17</td>
<td>79 ± 12</td>
<td>74 ± 16†</td>
<td>76 ± 14†</td>
<td>.27</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>+4 ± 11</td>
<td>+7 ± 14</td>
<td>+1 ± 10</td>
<td>.06</td>
</tr>
<tr>
<td>LVEF, %</td>
<td></td>
<td></td>
<td></td>
<td>.55</td>
</tr>
<tr>
<td>Baseline</td>
<td>61 ± 5</td>
<td>62 ± 5</td>
<td>62 ± 4</td>
<td></td>
</tr>
<tr>
<td>Post-cycle 4</td>
<td>54 ± 5*†</td>
<td>59 ± 6†</td>
<td>59 ± 4†</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−7 ± 5*</td>
<td>−4 ± 4</td>
<td>−4 ± 5</td>
<td>.01</td>
</tr>
<tr>
<td>Post-cycle 17</td>
<td>56 ± 4*†</td>
<td>59 ± 6†</td>
<td>61 ± 4</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>−5 ± 5*</td>
<td>−3 ± 4</td>
<td>−1 ± 5</td>
<td>.001</td>
</tr>
<tr>
<td>LVESVI, ml/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>30 ± 7*</td>
<td>25 ± 6</td>
<td>26 ± 5</td>
<td>.01</td>
</tr>
<tr>
<td>Post-cycle 4</td>
<td>35 ± 7*†</td>
<td>29 ± 8†</td>
<td>31 ± 5†</td>
<td>.002</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>6 ± 5</td>
<td>4 ± 5</td>
<td>5 ± 5</td>
<td>.31</td>
</tr>
<tr>
<td>Post-cycle 17</td>
<td>35 ± 8*†</td>
<td>30 ± 8†</td>
<td>30 ± 6†</td>
<td>.006</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>6 ± 5</td>
<td>5 ± 6</td>
<td>4 ± 4</td>
<td>.37</td>
</tr>
<tr>
<td>LV MASSi, g/m²</td>
<td></td>
<td></td>
<td></td>
<td>.62</td>
</tr>
<tr>
<td>Baseline</td>
<td>53 ± 8</td>
<td>52 ± 7</td>
<td>51 ± 7</td>
<td></td>
</tr>
<tr>
<td>Post-cycle 4</td>
<td>55 ± 8†</td>
<td>53 ± 7</td>
<td>53 ± 8</td>
<td>.28</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>2 ± 5</td>
<td>1 ± 5</td>
<td>1 ± 5</td>
<td>.58</td>
</tr>
<tr>
<td>Post-cycle 17</td>
<td>53 ± 8†</td>
<td>52 ± 8</td>
<td>52 ± 6</td>
<td>.61</td>
</tr>
<tr>
<td>Change from baseline</td>
<td>0 ± 7</td>
<td>0 ± 5</td>
<td>1 ± 5</td>
<td>.91</td>
</tr>
</tbody>
</table>

**NOTE.** All values expressed as means ± SD unless indicated. Abbreviations: LVEDVI, indexed left ventricular end diastolic volume; LVEF, left ventricular ejection fraction; LVESVi, indexed left ventricular end systolic volume; LV MASSi, indexed left ventricular mass. *P < 0.05 compared with other groups. †P < 0.05 from baseline.
Can we treat it?

- 201 pts with anthracycline related cardiomyopathy (EF<45%)
- Treated promptly with enalapril and carvedilol
- Mean FU 36+/−27 mths
- Complete LVEF recovery 42%
- Partial LVEF recovery 13%
- No recovery 45%

Cardinale et al. 2010 JACC
NCRI Traffic lights

A. Patient assessment
- LVEF value
  - > LLN
  - ≤ LLN
  - > 0.40
  - ≤ 0.40
- LVEF decrease during trastuzumab
  - < 0.10
  - ≥ 0.10
- Signs or symptoms
  - None
  - Any

LVEF = left ventricular ejection fraction
LLN = lower limit of normal

B. Pre-chemotherapy
- Treatment
  - Standard CT
- Start ACEi
  - NO
- Cardiology
  - NO
- Consider CT*
  - YES
  - REFER

*Consider non-anthraclycline chemotherapy (CT)

C. Post-chemotherapy
- Trastuzumab
  - Start trastuzumab
  - Defer until 'green'*
  - Not recommended
- Start ACEi
  - NO
  - YES
- Cardiology
  - NO
  - REFER

*For patients with LVEF < LLN, cardiac function should be optimised and reassessed 3 months later

D. During trastuzumab
- Trastuzumab
  - Continue
  - STOP*
- Start ACEi
  - NO
  - YES
- Cardiology
  - NO
  - REFER
- Additional monitoring
  - 6–8 weeks after first amber End of treatment
  - Within 6 weeks then as clinically indicated

*May restart if ‘green’ after consideration of risk vs benefit

Jones et al. NCRI UK recommendations. Br J Ca 2009
Current practice?

Royal Devon & Exeter Oncology Department Guideline
Cardiac monitoring for breast cancer patients receiving adjuvant or neo-adjuvant trastuzumab (Herceptin)

HER2+ breast cancer requiring adjuvant/neo-adjuvant chemotherapy

Cardiac history and examination
If BP>140/85 consider starting ACEi
Baseline ECG
Baseline urgent full echo pre-chemo (within 1-2/52)

LVEF>50%
Standard chemotherapy
Repeat echo prior to starting Herceptin

LVEF <50%
Consider non-anthracycline chemotherapy
Start ACEi
Refer to cardiology
Repeat echo prior to starting Herceptin
Only start Herceptin if LVEF >50%


Suggestion for ACEi initiation and monitoring:
Ramipril 1.25mg od, titrating up by doubling every 2 weeks to maintenance of 2.5-10mg od (max dose 5mg if CrCl<60)
BP and U&E should be checked within 2 weeks of initiation and any change in dose. Recheck at 1, 3 and 6 months on maintenance dose, then at least 6 monthly thereafter.
Current practice?

**LVEF >50%**
- Start Herceptin
- Echo at 4 and 8 months

**LVEF 40-50% or >10% drop**
- Defer Herceptin until LVEF >50%
- Start ACEi
- Refer to Cardiology
- Echo in 6 weeks

**LVEF <40% or signs of CCF**
- No Herceptin
- No further monitoring
- Start ACEi
- Refer to Cardiology

**LVEF >50%**
- Continue Herceptin
- No further monitoring

**LVEF 40-50% or >10% drop**
- Defer Herceptin until LVEF >50%
- Start ACEi
- Refer to Cardiology
- Echo in 6 weeks
- On-going monitoring as recommended by cardiology

**LVEF <40% or signs of CCF**
- No Herceptin
- Stop Herceptin
- Start ACEi
- Refer to Cardiology
- Echo in 6 weeks
- Only restart Herceptin if LVEF >50% and benefit outweighs risk

Suggestion for ACEi initiation and monitoring:
- Ramipril 1.25mg od, titrating up by doubling every 2 weeks to maintenance of 2.5-10mg od (max dose 5mg if CrCl<60)
- BP and U&E should be checked within 2 weeks of initiation and any change in dose.
- Recheck at 1,3 and 6 months on maintenance dose, then at least 6 monthly thereafter.

Cardio-Onc Conclusions

• Increasing survival from cancer
• Increasing potential impact from cardiac toxicity
• Manage risk at each stage of treatment
• Remember full assessment for causes
• Modest benefit from ACE-I/BB but little or no harm – start early
Thank you

and GOOD LUCK!
BJCA Spring Meeting 2019 - Cardiology to the core

Advanced topics in general cardiology: Cardiomyopathy and Cardio-Oncology

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