Medical management of LV aneurysm and subsequent cardiac remodeling: is it enough?

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Disclosures

- **Grants:** ALARM investigator received research grants by Abbott US and Orion Pharma

- **Horonaria:** received horonaria for advisory boards and lectures from Novartis, Pfizer, Menarini and Servier

- **Journals:** Associate Editor of EJHF

- **ESC HF GLs:** Member of task force
LV aneurysm: Main Clinical Consequences

- Cardiac remodeling
- Systolic cardiac dysfunction
- Ischemia/Angina
- Thromboembolic events
  (LV thrombus formation)
- Arrhythmias
  (ventricular tachycardias, sudden death)
- Cardiac rupture
LV aneurysm: Main diagnostic approaches

- Physical examination
- ECG
- Chest X rays
- ECHO (2-D, contrast, TEE)
- Radionuclide ventriculography
- Angiography
- MRI
The Influence of Apical Aneurysm on Left Ventricular Geometry and Clinical Outcomes: 3-Year Follow-Up Using Echocardiography

Echocardiography 2016;33:814–820

![Graphical representation of study findings](image)

**TABLE III**

Univariate and Multivariate Cox Proportional Hazards Analysis for the Prediction of an Adverse Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>Univariate</th>
<th>Multivariate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P-Value</td>
</tr>
<tr>
<td>Age</td>
<td>1.023 (0.986–1.061)</td>
<td>0.231</td>
</tr>
<tr>
<td>LV ejection fraction</td>
<td>0.960 (0.925–0.997)</td>
<td>0.033</td>
</tr>
<tr>
<td>E/e'</td>
<td>0.993 (0.938–1.052)</td>
<td>0.812</td>
</tr>
<tr>
<td>Presence of a large LVAA</td>
<td>2.872 (1.131–7.294)</td>
<td>0.027</td>
</tr>
</tbody>
</table>

LV = left ventricular; LVAA = left ventricular apical aneurysm.
Molecular and structural basis of cardiac remodeling in heart failure

- **CARDIAC INSULT**
  - pressure overload
  - hypoxia, ischemia, infection

- **MEDIATORS**
  - Increased wall stress
  - sub-endocardial ischemia
  - neurohormonal activation
  - cytokines/oxidative stress
  - iNOS expression

- **MOLECULAR/CELLULAR**
  - alterations in cardiomyocyte biology
  - cardiomyocyte loss (apoptosis, necrosis, auto-phagocytosis)
  - alterations in ECM turnover

- **STRUCTURAL/ FUNCTIONAL**
  - myocyte hypertrophy
  - myocyte slippage
  - cardiac fibrosis
  - cardiac dilatation
  - systolic/diastolic dysfunction

Neurohormonal model of HF

- Neurohormonal activation
  - RAAS, SNS
- Increased cytokine expression
- Immune and inflammatory changes
- Altered fibrinolysis

Ventricular remodeling

- Oxidative stress
- Apoptosis
- Altered gene expression
- Energy starvation

Injury to myocytes and extracellular matrix

- Electrical, vascular, renal, pulmonary muscle, and other effects

Heart failure

Remodeling following MI

Initial Infarct

Infarct Expansion (hours to days)

Global Remodeling (days to months)

Left ventricular (LV) remodeling after transmural anteroseptal myocardial infarction (MI): 2D echocardiographic evaluation at 1 week and 3 months.

Left Ventricular Aneurysm
LV remodeling: Independent determinant of post-MI survival

Treatment of remodelling

**Established**
- Accepted approaches *(Improve prognosis)*
  - ACEi (or ARBs) or ARNI
  - Beta blockers
  - Aldo antagonists
  - Ivabradine
  - CRTs
  - Revascularization in cases with viable cardiac tissue
  - Exercise training?

**Questionable/Future**
- Individualised therapy
  - BNP guided therapy?
  - Pharmacogenetics?
- Pharmacological interventions
  - MMP inhibition ?
  - Anabolics ?
- Cell technology
  - Manipulation of healing
- LVADs (plus drugs)
Evidence-Based Treatment for Heart Failure with Reduced LVEF

**Reduce Mortality**

- ACEI or ARB or LCZ696
- \( \beta \)-Blocker
- ivabradine
- MRAs

**Control Volume**

- Sodium Restriction*
- Diuretics*

**Treat Residual Symptoms**

- ICD*
- CRT ± an ICD*
- Hyd/ISDN*
- Digoxin*

**Enhance Adherence**

- Education
- Disease Management
- Performance Improvement Systems

**Treat Comorbidities**

- Aspirin*
- Warfarin*
- Statin*

*For select indicated patients.
Angiotensin Converting Enzyme Inhibitor Effects on Ventricular Volumes
Effects of Carvedilol on Left Ventricular Remodeling After Acute Myocardial Infarction
The CAPRICORN Echo Substudy

\[ \Delta = -6.7 \text{ml} \quad p = 0.41 \]

\[ \Delta = -9.2 \text{ml} \quad p = 0.031 \]

\[ \Delta = +2.6 \text{ml} \quad p = 0.053 \]

Heart Failure Progression

- Aldosterone
- Growth/Apoptotic Factors
- Ischemia & OFR
- Inflammation
- TNF-α
- Viral Injury
- Genetic Mutations
- MMPs
- Integrins
- Stretch
- Pressure/Volume Overload
- Phenotypic Transition
- Heart Failure Adverse Outcomes
Mineralocorticoid Receptor Antagonists (MRAs) in Heart Failure

**RALES** (LVSD, CHF severe symptoms)

**EPHESUS** (LVSD + HF after MI)

**Survival**
30% RR, P < 0.001

**Total Mortality**
15% RR, P = 0.008

![Graph showing survival and total mortality over time with Eplerenone and Placebo comparisons](image-url)
EPHESUS: Cardiovascular death / hospitalization

Early initiation

Late initiation

p = 0.01
HR = 0.85 (95%IC = 0.75 - 0.96)

p = 0.08
HR = 0.89 (95%IC = 0.78 - 1.01)
EPHESUS: Eplerenone Reduced Sudden Cardiac Death by 37% at 30 days

Pitt et al. JACC 2005;46;425-431
Mineralocorticoid Receptor Antagonists Modulate Galectin-3 and Interleukin-33/ST2 Signaling in Left Ventricular Systolic Dysfunction After Acute Myocardial Infarction
Anti-remodelling effect of canrenone in patients with mild chronic heart failure (AREA IN-CHF study)

SHIFT: Effect of ivabradine on primary outcome (CV death or HF hospitalization)

Hazard ratio = 0.76

\( P < 0.0001 \)

Effects of selective heart rate reduction with ivabradine on left ventricular remodelling and function: results from the SHIFT echocardiography substudy

European Heart Journal (2011) 32, 2507–2515
Impact of Ivabradine on Inflammatory Markers in Chronic Heart Failure

Journal of Immunology Research
Volume 2016, Article ID 6949320
Cardioprotective Effect of LCZ696 (sacubitril/valsartan) After Experimental Acute Myocardial Infarction

Gelatinolytic Activity 3 Days Post-MI

ESC congress 2017, Barcelona, Spain
**Summary**

1. LCZ696 significantly reduced death caused by cardiac rupture within 1 week after MI compared with vehicle and enalapril groups.

2. Echocardiography revealed that %FS was significantly improved in LCZ696 but not in enalapril, compared with that in vehicle group at 14 and 28 days after MI.

3. At 3 days after MI, expression of IL-1β, MMP-9 mRNA and MMP-9 activity in infarcted myocardium were significantly decreased in LCZ696 group compared with other two groups, and IL-6 mRNA were significantly decreased in LCZ696 compared with enalapril.

4. At 3 days after MI, plasma cGMP levels were significantly higher, and plasma aldosterone levels were significantly lower in the LCZ696 group than the other groups.

**ESC congress 2017, Barcelona , Spain**
Targeting Fibrosis for the Treatment of Heart Failure: A Role for Transforming Growth Factor-β

- MI
- HHD
- DIABETES

MI → HHD → DIABETES → Glucose, ROS, AngII (systemic) → Inflammation (chemokines, macrophages, neutrophils, cytokines) → TGF-β, AngII (cellular) → Fibroblast ↔ Myofibroblast

↑ collagen synthesis → Altered balance ↓ MMPs, ↑ TIMPs → Fibrosis → Myocardial stiffness

Graphs showing changes in left ventricular dimensions and matrix area, indicating potential therapeutic targets in heart failure.
Hydrogel anti-fibrotic interventions

**Fig. 4** The sequential IGF-1/HGF delivery using alginate hydrogel reduces fibrosis. **a** Representative photomicrographs of Masson’s trichrome staining (collagen-rich areas in blue and healthy myocardium in red), scar area. Bar = 500 μm. **b** Fibrotic content of the scar. *p < 0.05. (Reprinted from Ruvinov et al. [66])
Reverse remodeling in CRT trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>No. of patients</th>
<th>NYHA</th>
<th>Rx Duration</th>
<th>ΔLVEDD/V</th>
<th>ΔLVESD/V</th>
<th>ΔLVEF</th>
<th>ΔMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>MUSTIC [82]</td>
<td>34</td>
<td>III</td>
<td>12 mo.</td>
<td>↓−14% (D)</td>
<td>↓−18% (D)</td>
<td>–</td>
<td>↓−27%</td>
</tr>
<tr>
<td>MIRACLE-ICD [83]</td>
<td>369</td>
<td>III–IV</td>
<td>6 mo.</td>
<td>↓−6.2% (V)</td>
<td>–</td>
<td>↑+2.1%</td>
<td>↓−7.3%</td>
</tr>
<tr>
<td>CARE-HF [83]</td>
<td>813</td>
<td>III–IV</td>
<td>18 mo.</td>
<td>–</td>
<td>↓−21% (V)</td>
<td>↑+6.9%</td>
<td>↓−20%</td>
</tr>
<tr>
<td>REVERSE [84,85]</td>
<td>287</td>
<td>I–II</td>
<td>24 mo.</td>
<td>↓−30% (V)</td>
<td>↓−15% (V)</td>
<td>↑+3.8%</td>
<td>–</td>
</tr>
<tr>
<td>MADIT-CRT [86]</td>
<td>1820</td>
<td>I–II</td>
<td>2.4 yr.</td>
<td>↓−21% (V)</td>
<td>↓−35% (V)</td>
<td>↑+11%</td>
<td>–</td>
</tr>
</tbody>
</table>

Cardiovascular Therapeutics 30 (2012) 172–181
The three components of the Virchow's triad in left ventricular thrombus formation.

**LV regional wall akinesia & dyskinesia**

**Stasis**

**LV THROMBOSIS**

**Subendocardial injury with inflammatory changes**

**Hypercoagulability during ACS**

Ronak Delewi et al. Heart 2012;98:1743-1749
Sensitivities and specificities of different diagnostic modalities for the detection of left ventricular thrombus formation

<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOE</td>
<td>35%</td>
<td>90%</td>
</tr>
<tr>
<td>Routine clinical TTE</td>
<td>35–40%</td>
<td>90%</td>
</tr>
<tr>
<td>TTE (indication suspect LV thrombus)</td>
<td>60%</td>
<td>90%</td>
</tr>
<tr>
<td>CT</td>
<td>Comparable with TTE</td>
<td></td>
</tr>
<tr>
<td>Cine CMR</td>
<td>60%</td>
<td>90%</td>
</tr>
<tr>
<td>DE-CMR</td>
<td>88%</td>
<td>99%</td>
</tr>
</tbody>
</table>

*Heart* 2012;98:1743–1749.
Left ventricular (LV) thrombus formation on delayed gadolinium contrast cardiac MRI and transthoracic echocardiography.

Ronak Delewi et al. Heart 2012;98:1743-1749
Conditions that increase the risk of systemic embolization in patients with LV thrombus are:

(1) severe congestive heart failure,  
(2) diffuse LV dilatation and systolic dysfunction,  
(3) previous embolization,  
(4) advanced age,  
(5) presence of LV protruding or mobile thrombi  
(6) presence of AF
Embolic Potential, Prevention and Management of Mural Thrombus Complicating Anterior Myocardial Infarction: A Meta-Analysis

WARFARIN

ANTI-PLATELETS

JACC Vol. 22, No. 4
October 1993:1004–9
Medical treatment should contain:

- ACEi or ARBs or ARNI
- Beta blockers
- MRAs
- Ivabradine (in selected pts)
- ICD/CRT (in selected pts)
- Amiodarone (in selected pts)
- Anti-coagulant therapy (in the presence of thrombus and/or history of embolic events and/or AF)
Surgical treatment should be considered:

- In Large LV aneurysms / pseudoaneurysms
- In progressive cardiac remodeling despite OMT
- In LV aneurysms with recurrent severe arrhythmias (resistant to drugs)
- In LV aneurysms and recurrent embolic events despite medical therapy