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Revascularization of ischemic LV dysfunction: past, present and future

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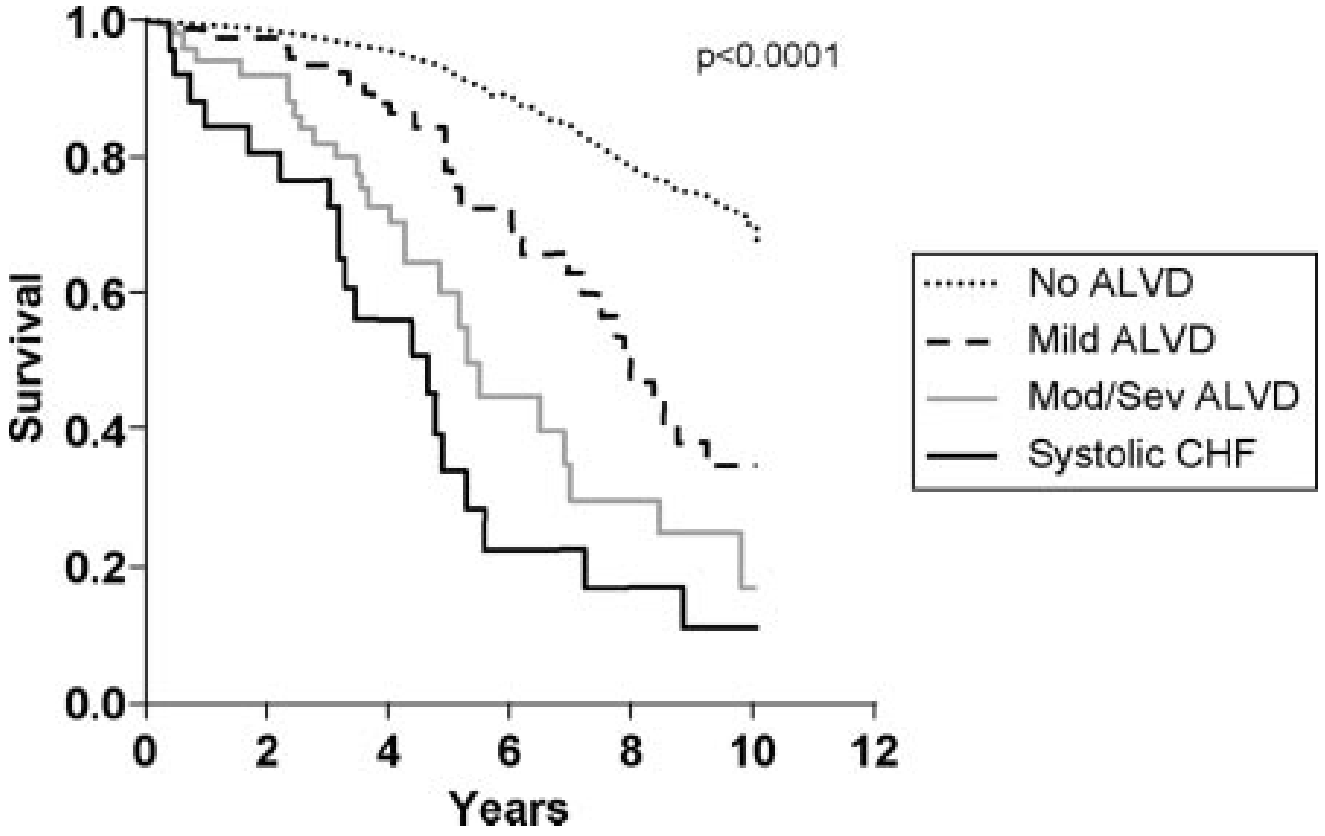
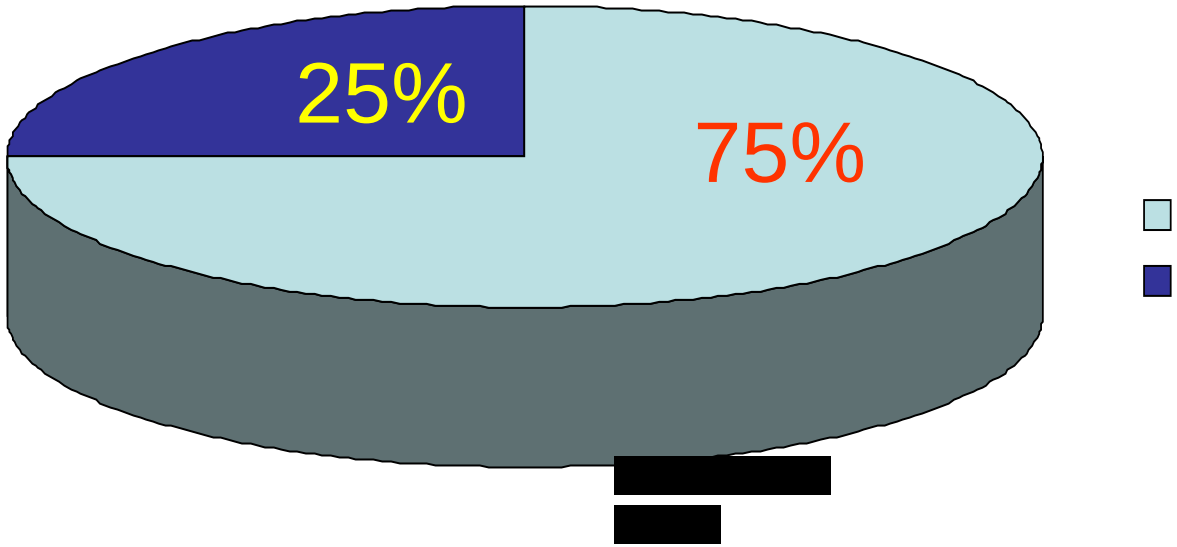
Advances in Cardiovascular Arrhythmias
and Great Innovations in Cardiology
XXIV Giornate Cardiologiche Torinesi ”

Framingham Study on 4257 participants and an assessment of their risk of progression from asymptomatic LVSD to clinical HF



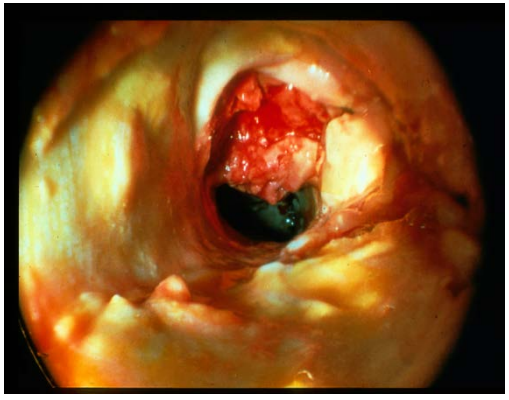
(Circulation. 2006;113:2851-2860.)

Aethiology of heart failure

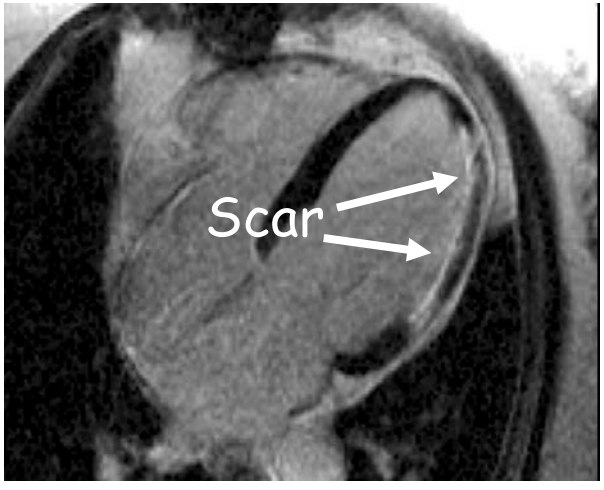


Mechanisms of post-ischemic LV dysfunction

Coronary atherosclerosis/
Vulnerable plaque



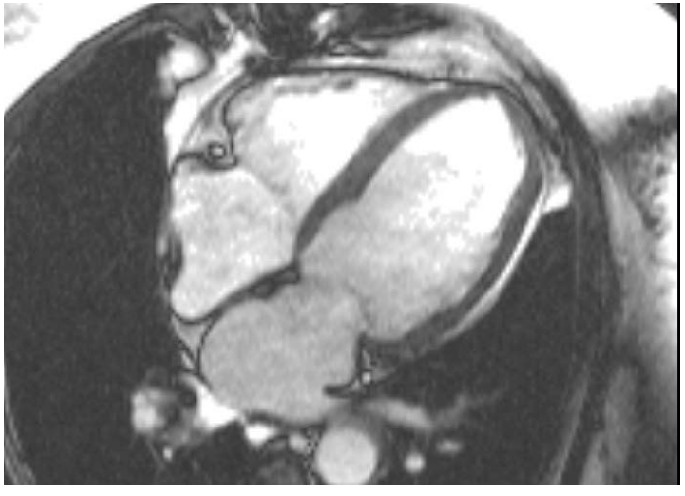
Thrombosis/
myocardial infarction



Late GAD CMR

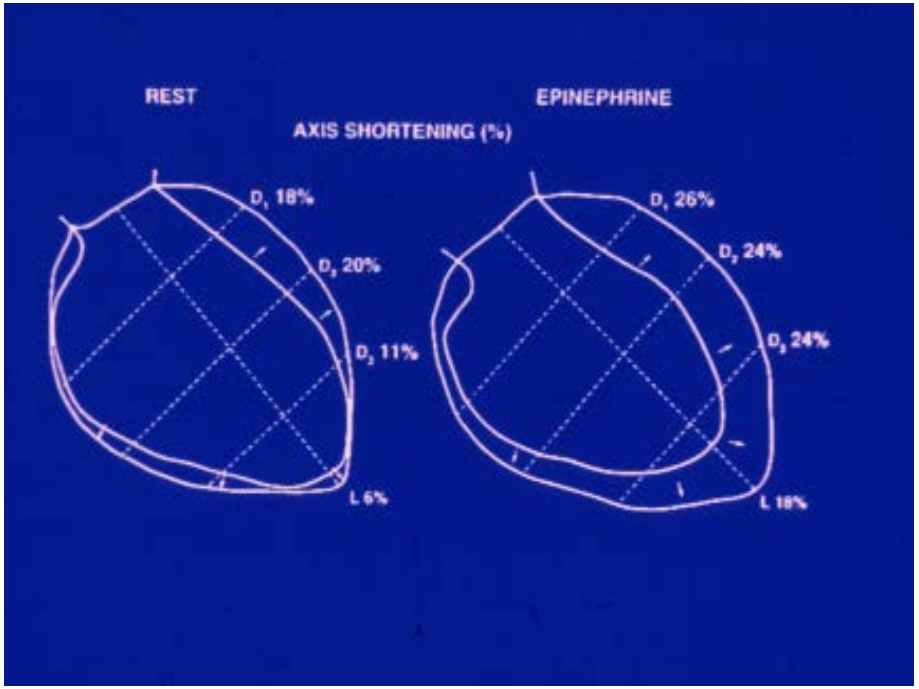
Loss of contraction

Ventricular dilatation
and remodelling



- LV dysfunction in patients with CAD is not always an irreversible process, as LV function may improve substantially after CABG

Gorlin's "epinephrine ventriculogram"

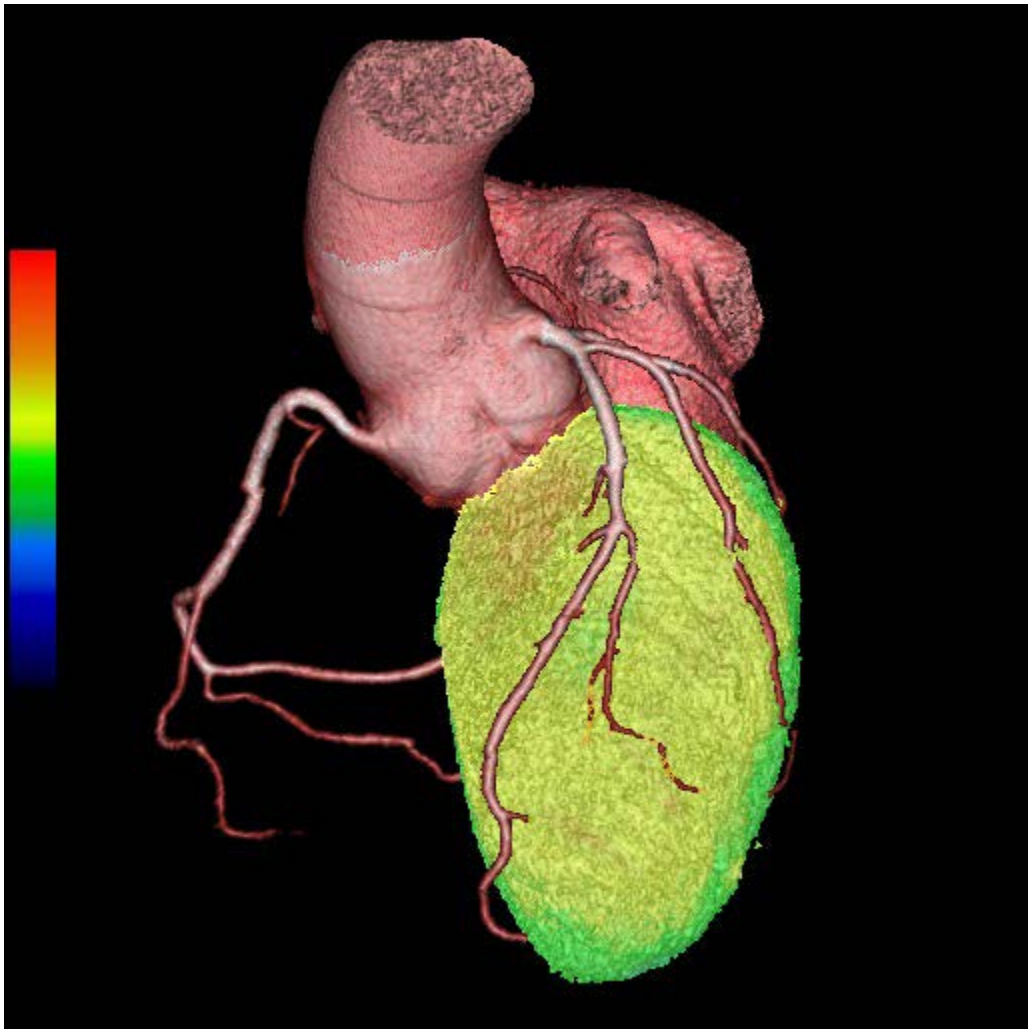


Studies by Gorlin et al. using a cathecholamine stress, showed that the asynergic LV could improve its function with inotropic stimulation. This was the forerunner of DSE.
(Circulation 1974;49:1063-71)

Hibernating myocardium

In 1978 Diamond et al. suggested that:

"…ischemic non infarcted myocardium can exist in a state of function hibernation"



Am Heart J 1978; 95; 204-9

Hibernating myocardium

"…there is a prolonged subacute or chronic stage of myocardial ischemia that is frequently not accompanied by pain and in which *myocardial contractility and metabolism and ventricular function are reduced to match the reduced blood supply*"

Rahimtoola SH. Circulation 1985; 72:V123-35.
Rahimtoola SH. Am Heart J 1989; 117:211-21.

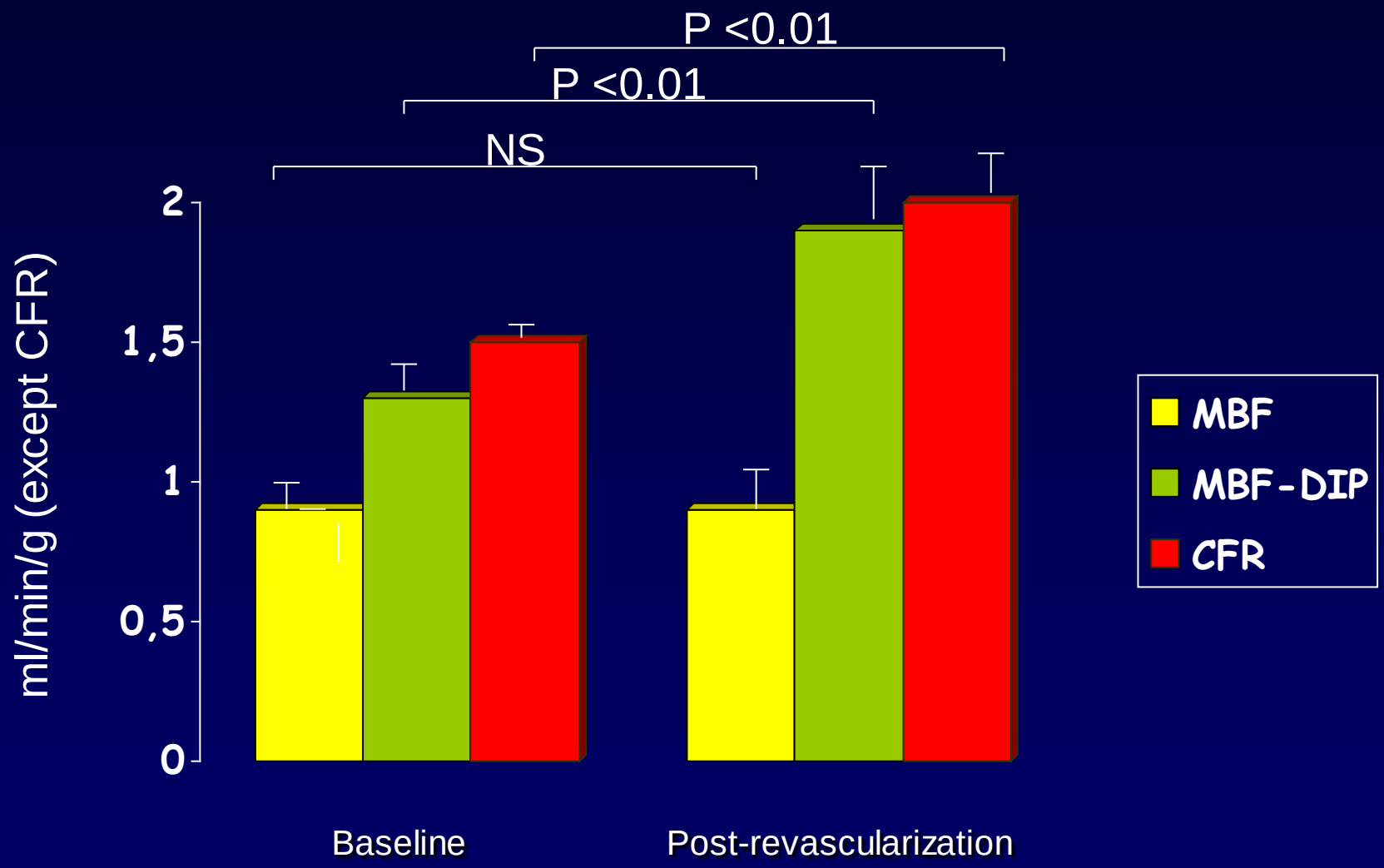
Hibernating myocardium

More recently, a number of studies in which regional myocardial blood flow was *quantified* non-invasively by PET have demonstrated that:

- *in most patients transmural blood flow to hibernating segments is within the range of values seen in healthy volunteers*
- *a reduction of about 20% can be found in some cases*

Camici et al. Circulation 1997; 96: 3205-3214
Wijns, Vatner & Camici N Engl J Med 1998; 339:173-181

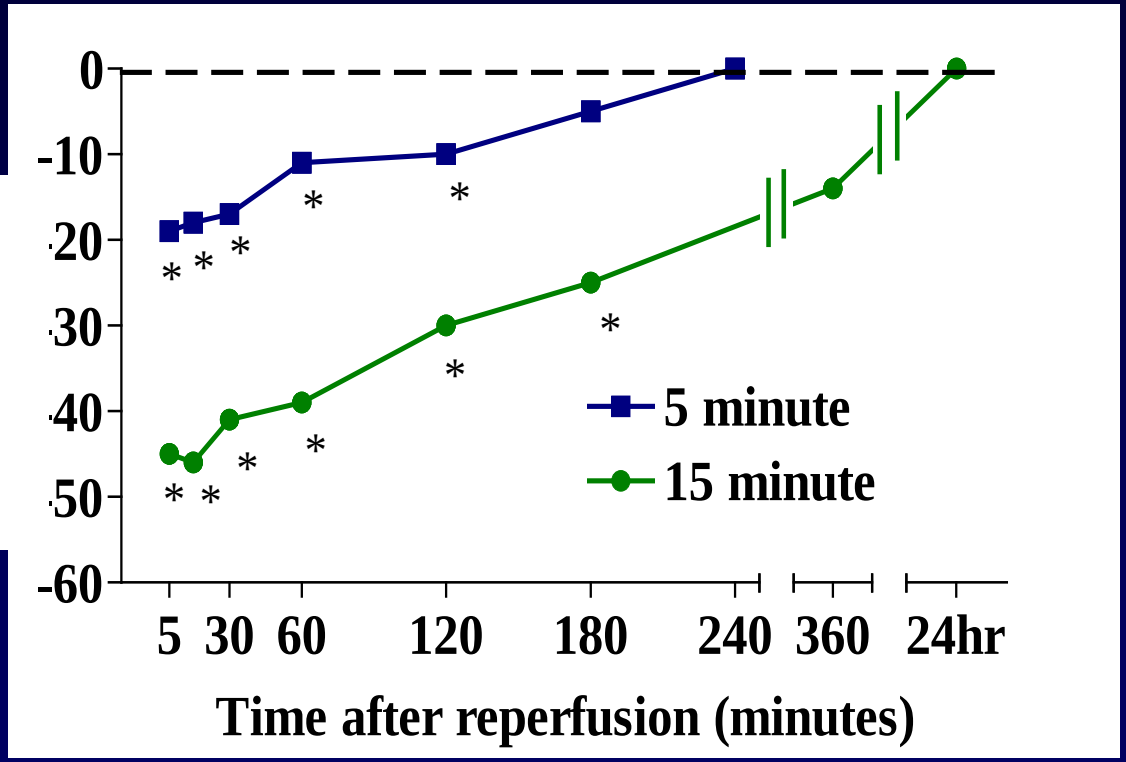
MBF and CFR in hibernating myocardium



Pagano et al. Heart 2001; 85:208-212

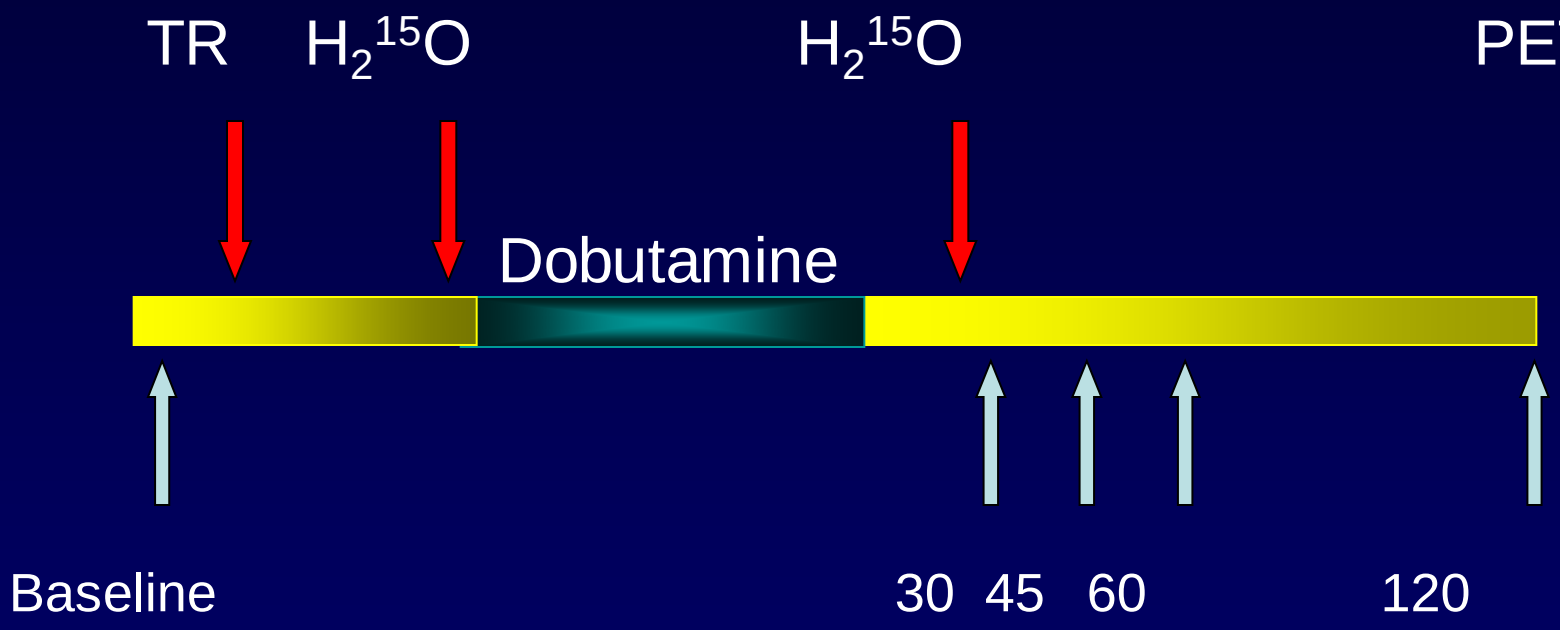
Myocardial stunning

Transient acute ischemia is associated and followed by a prolonged, but reversible, contractile dysfunction *(stunning)*



Heyndrickx et al. J Clin Invest 1975

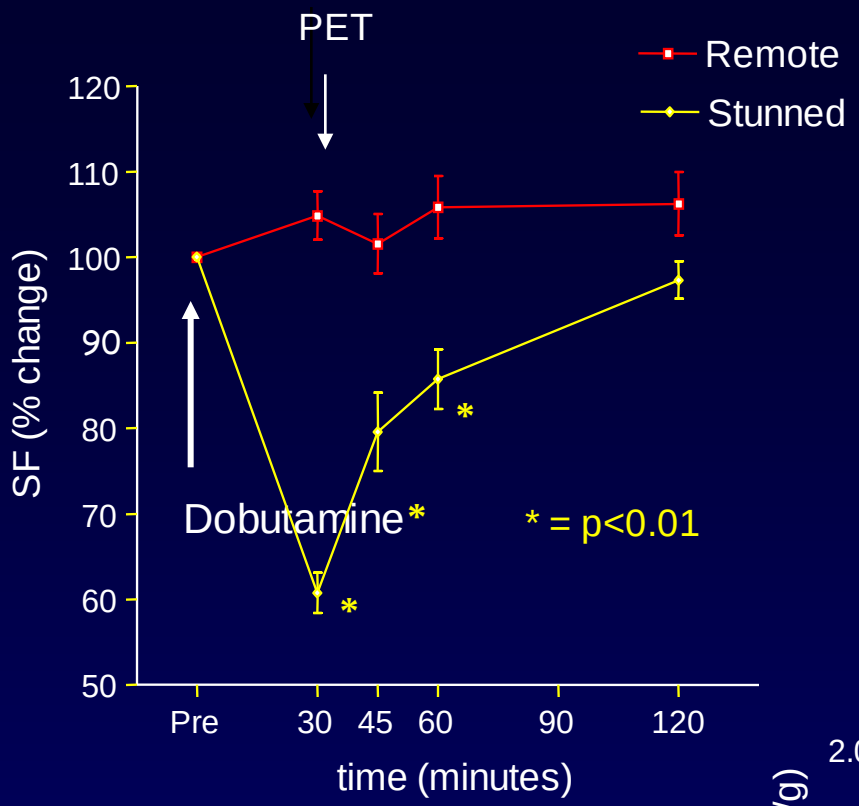
Myocardial stunning in patients with CAD (PET + echo)



Echo data acquisition: time in minutes

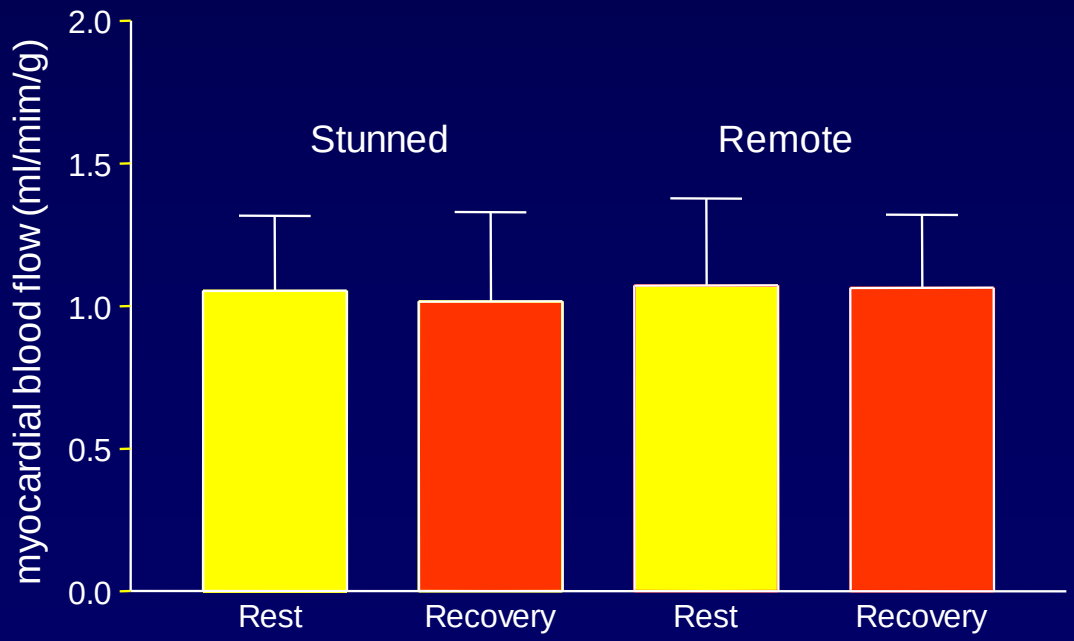
Barnes et al. J Am Coll Cardiol 2002; 39: 420-427

Stunning in pts with CAD



Regional LV Function (Echocardiography)

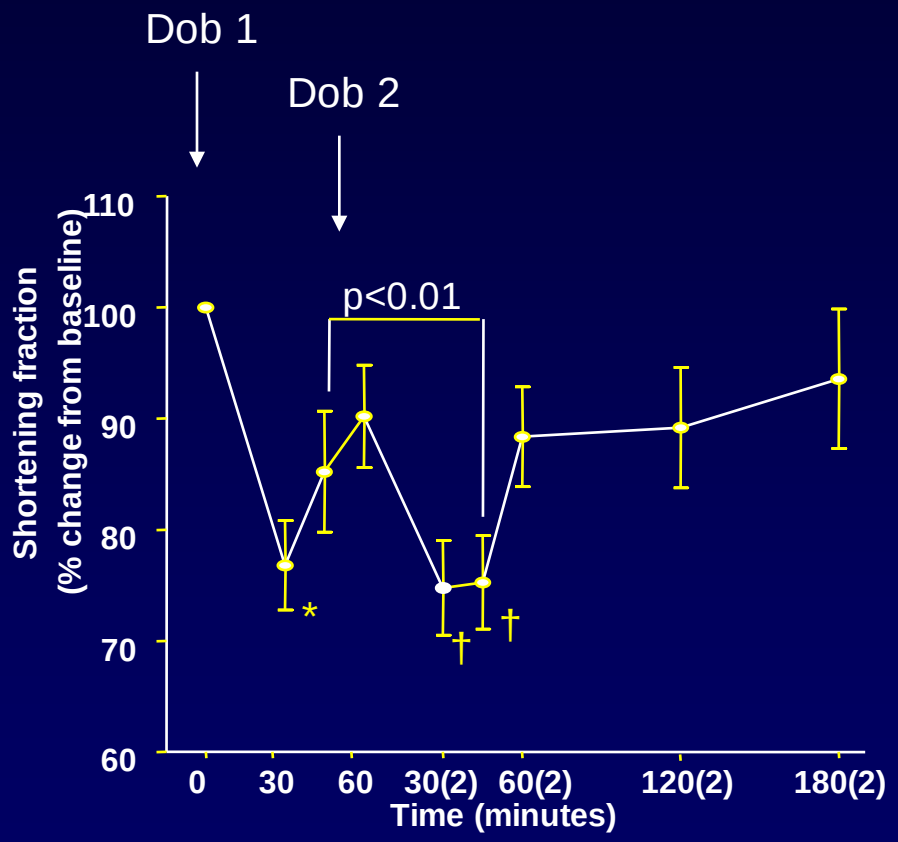
Regional Myocardial Blood Flow (PET)



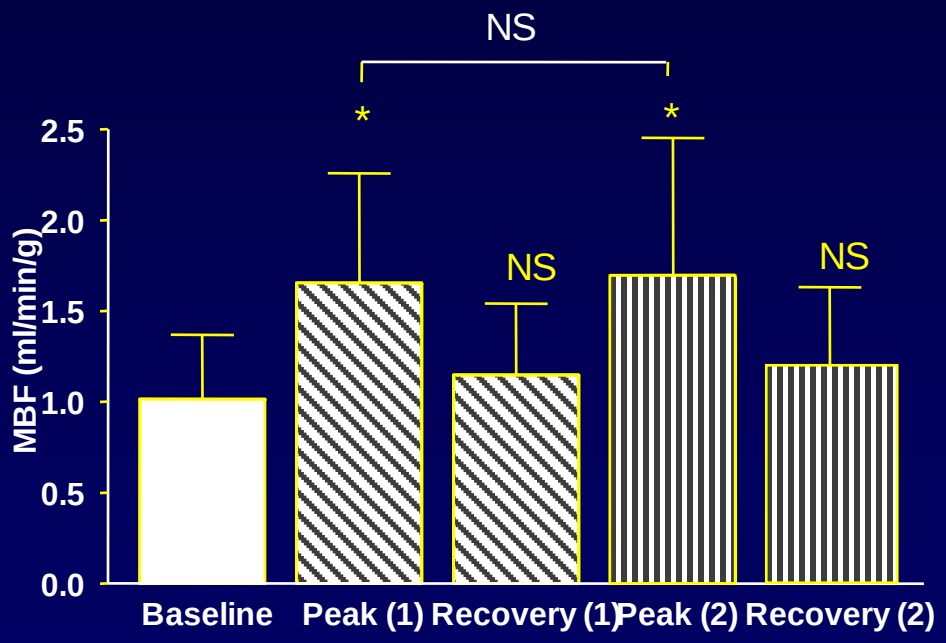
J Am Coll Cardiol 2002; 39: 420-427

“Repetitive” stunning and hibernation

Echo

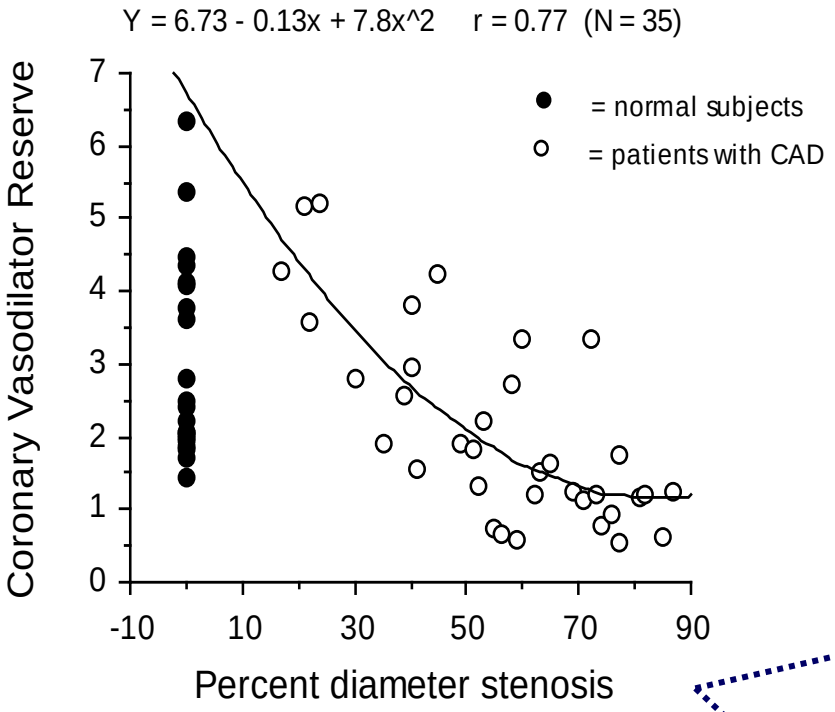


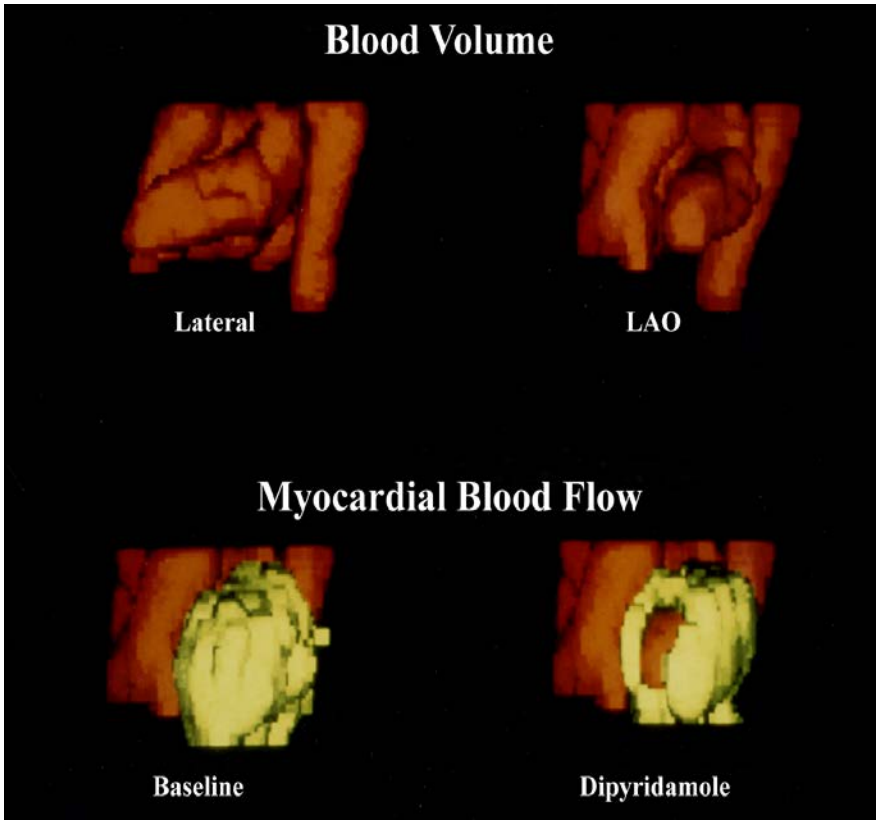
PET



Barnes et al. Am J Physiol 2002; 282: H1603-H1608

Stenosis severity vs. flow reserve





Severe stenoses which limit flow reserve can lead to demand ischemia for increases in cardiac work as those associated with daily life

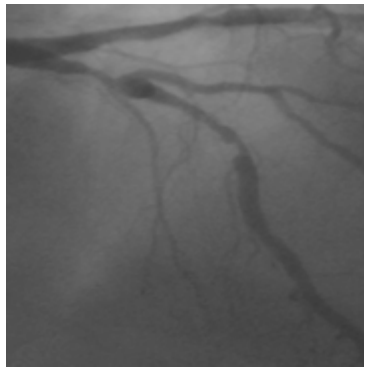
Uren et al. New Engl J Med 1994; 330: 1782-1788

The “repetitive” stunning hypothesis

- Patients with CAD have repeated episodes of ischemia, often silent, followed by stunning that is cumulative
- This could lead to hibernating myocardium
- Revascularisation by restoring flow-reserve would reduce ischemia and stunning

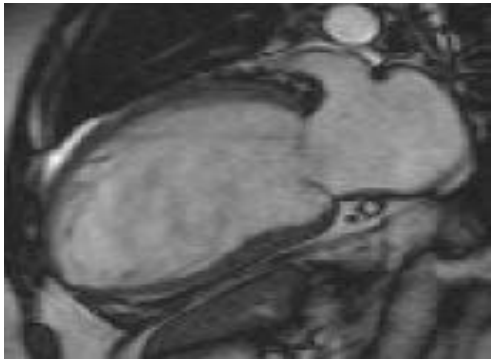
Camici et al. Circulation 1997; 96: 3205-3214
Wijns, Vatner & Camici N Engl J Med 1998; 339:173-181

1 Coronary atherosclerosis/ Flow limiting stenosis



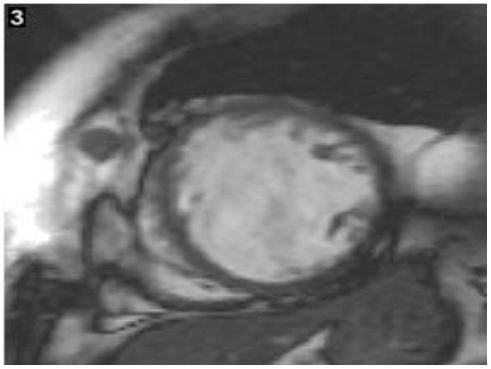
2 Repetitive ischemia and stunning

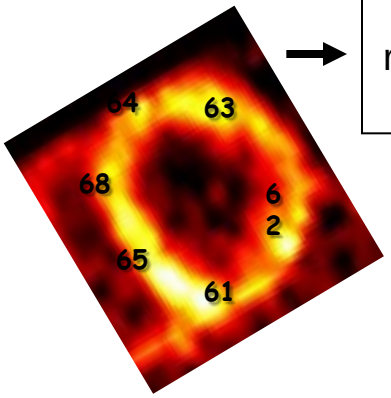
Recovery of contractility and wall thickening with reverse remodelling



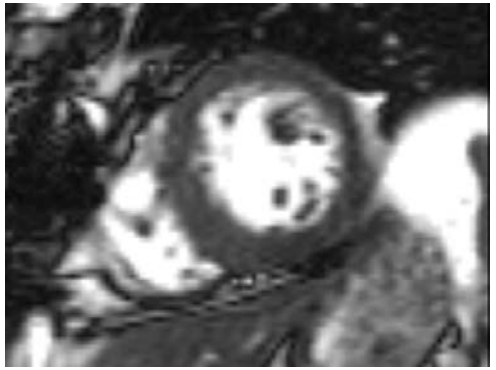
Chronic stunning/hibernation 3

Evidence of viability by PET 4





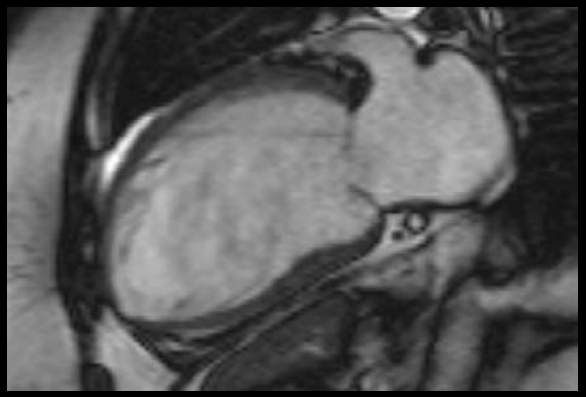
Complete revascularization by CABG 5



- LV dysfunction in patients with CAD is not always an irreversible process, as LV function may improve substantially after CABG
- Assessment of myocardial viability is often used to predict improvement in LV function after CABG and thus select patients for CABG

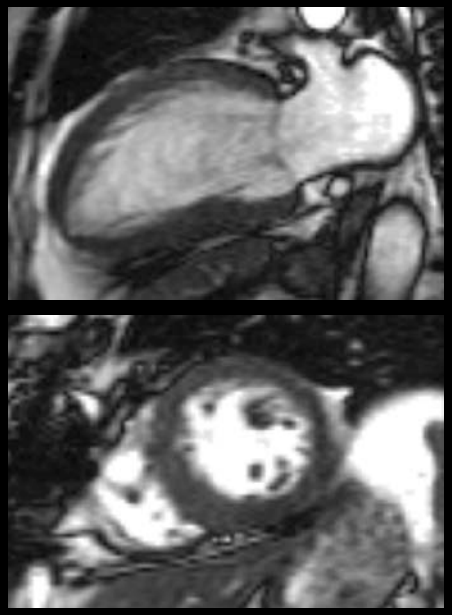
The prototype patient with chronic LV dysfunction and hibernating myocardium

72 year old lady
Arterial hypertension
Three vessel CAD
No history of previous AMI
Severe global LV dysfunction
LVEF 25%
Moderate mitral regurgitation

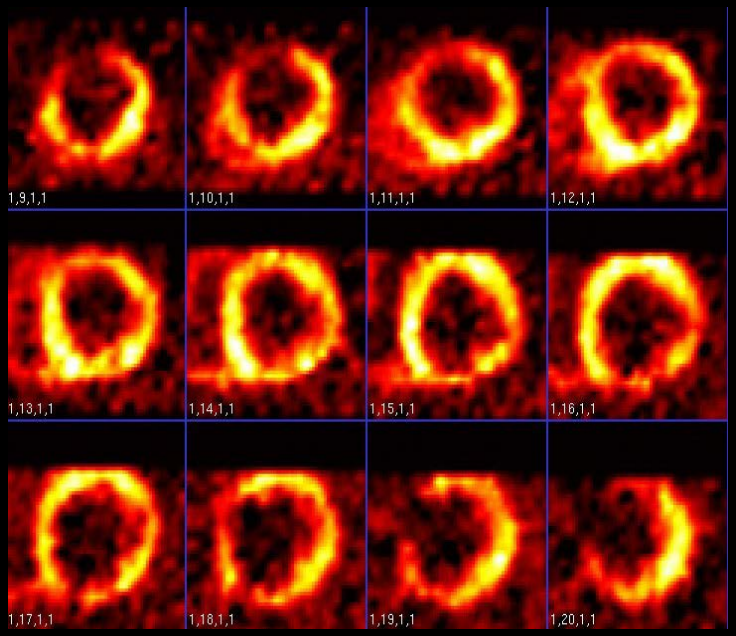


According to conventionally accepted echo criteria LV-WT <5-6 mm is considered typical of non viable tissue

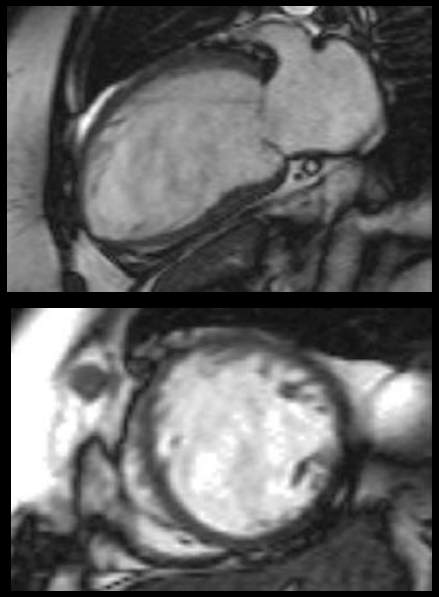
The prototype patient with chronic LV dysfunction and hibernating myocardium



Six months after bypass
LV EF 38 %

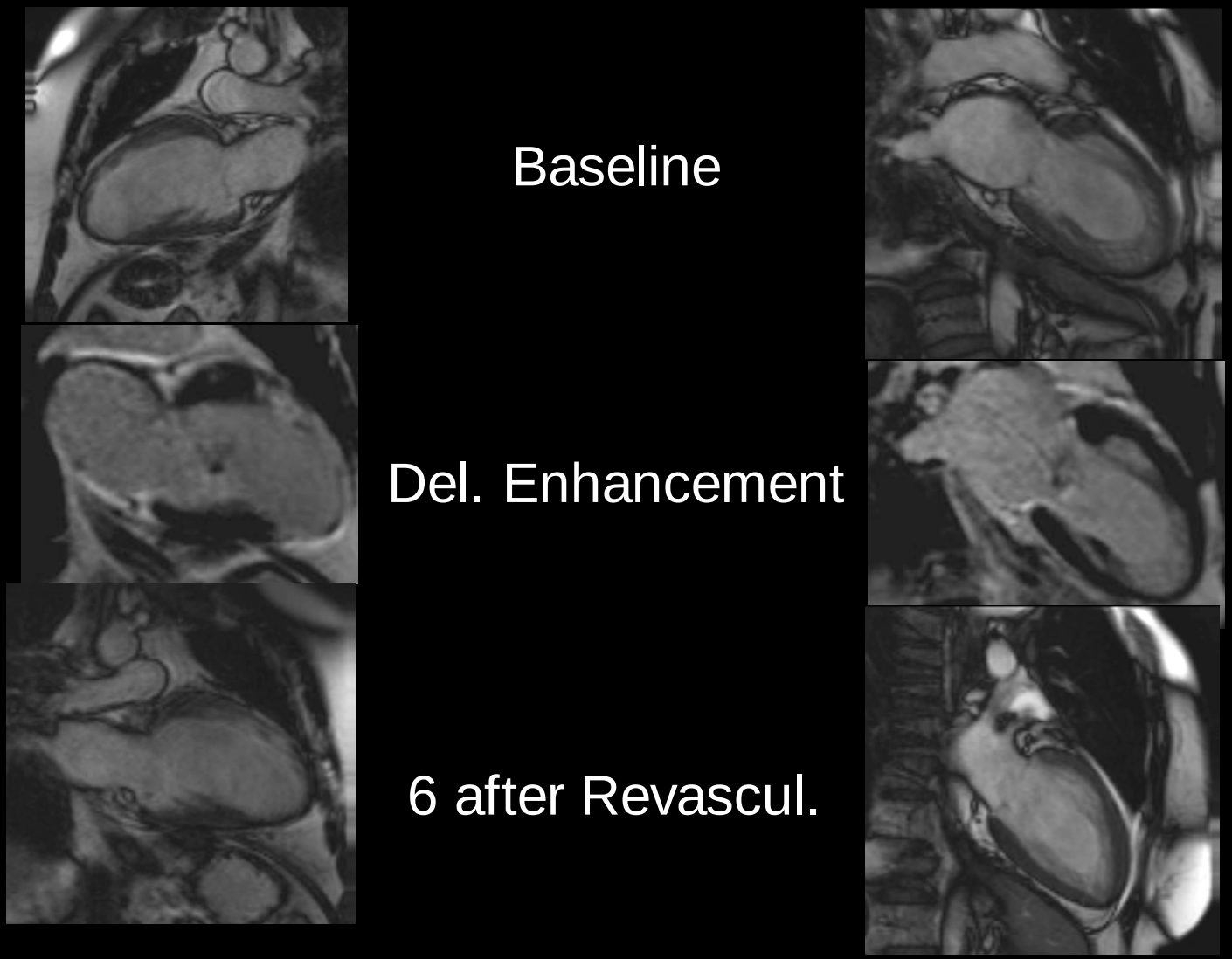


PET-FDG during euglycemic hyperinsulinemic clamp shows Preserved viability in entire LV



Baseline
LV EF 25 %

Viable vs. non-viable myocardium



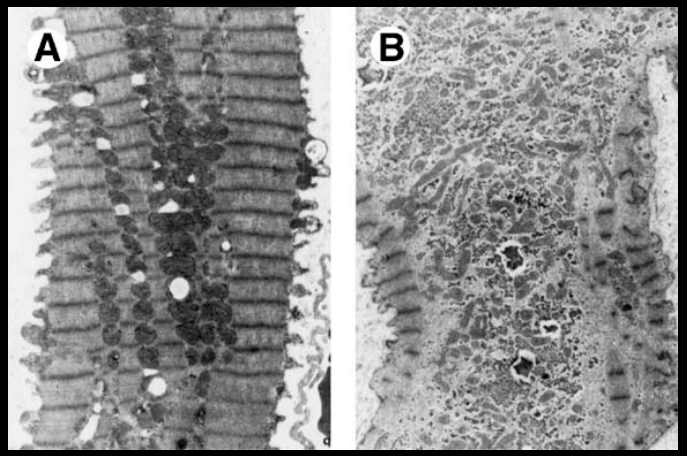
Courtesy of Prof S. Neubauer

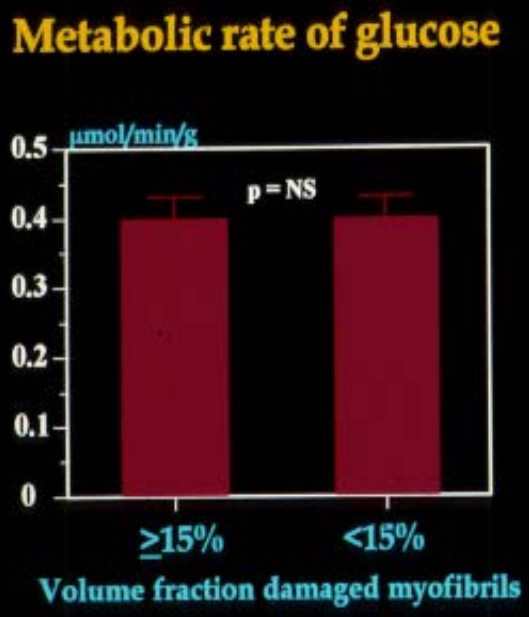
Factors determining the accuracy of hibernation assessment

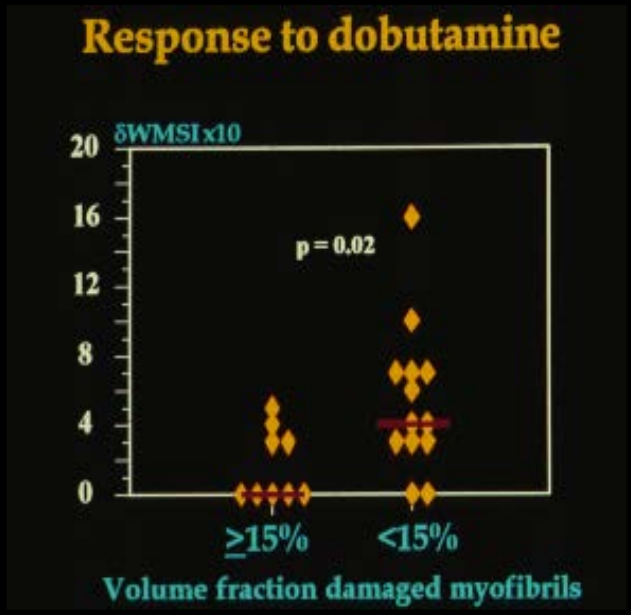
- Severity of LV impairment
- Tissue ultrastructure
- Time of LV assessment after revascularisation
- Co-morbidities

These issues have a major impact according to the mechanism of action of the technique employed and are generally not taken into account in meta-analysis

The response to dobutamine, but NOT that of FDG depends on the volume of irreversibly damaged myocardium



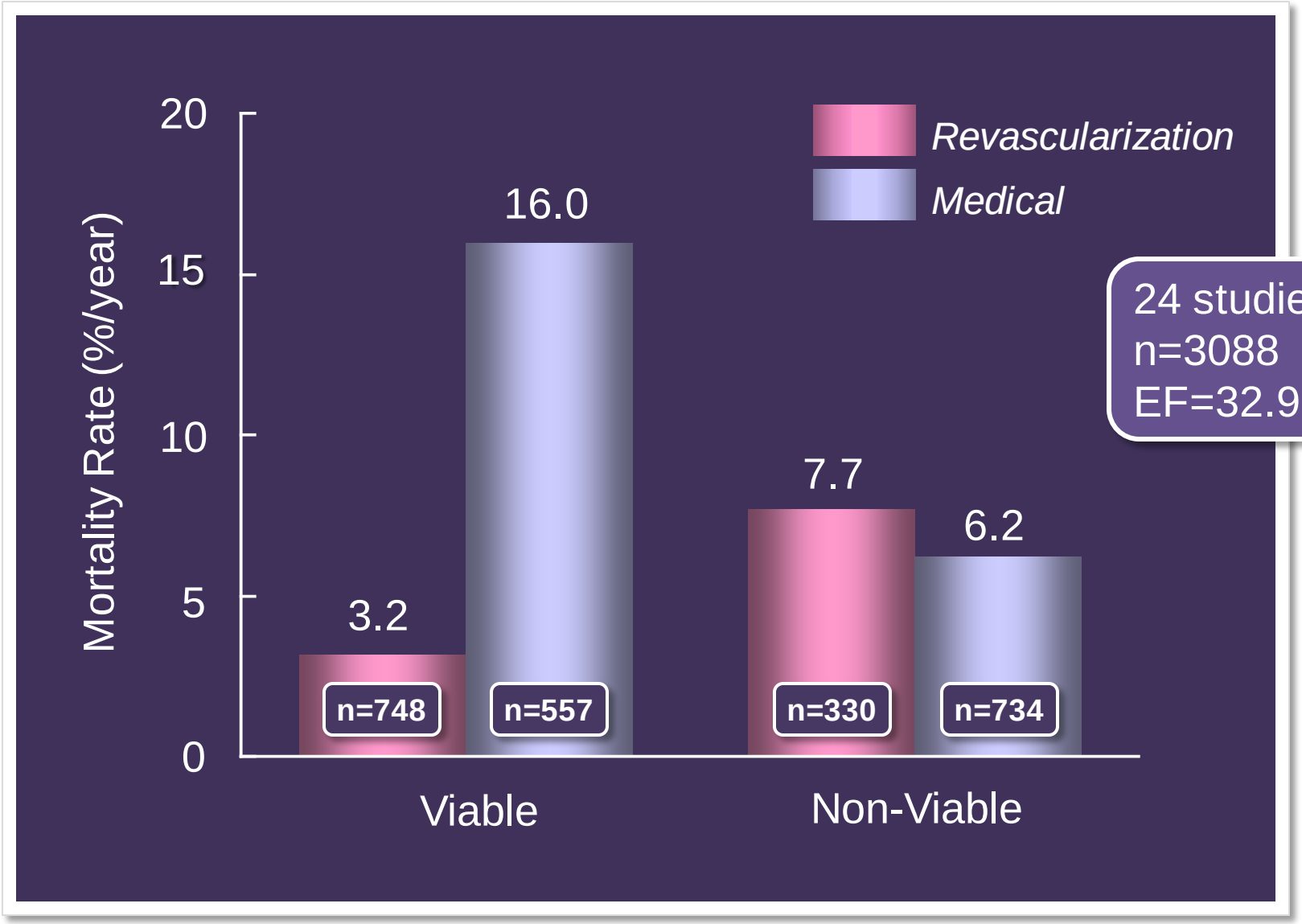




Heart 1999; 82 684-688

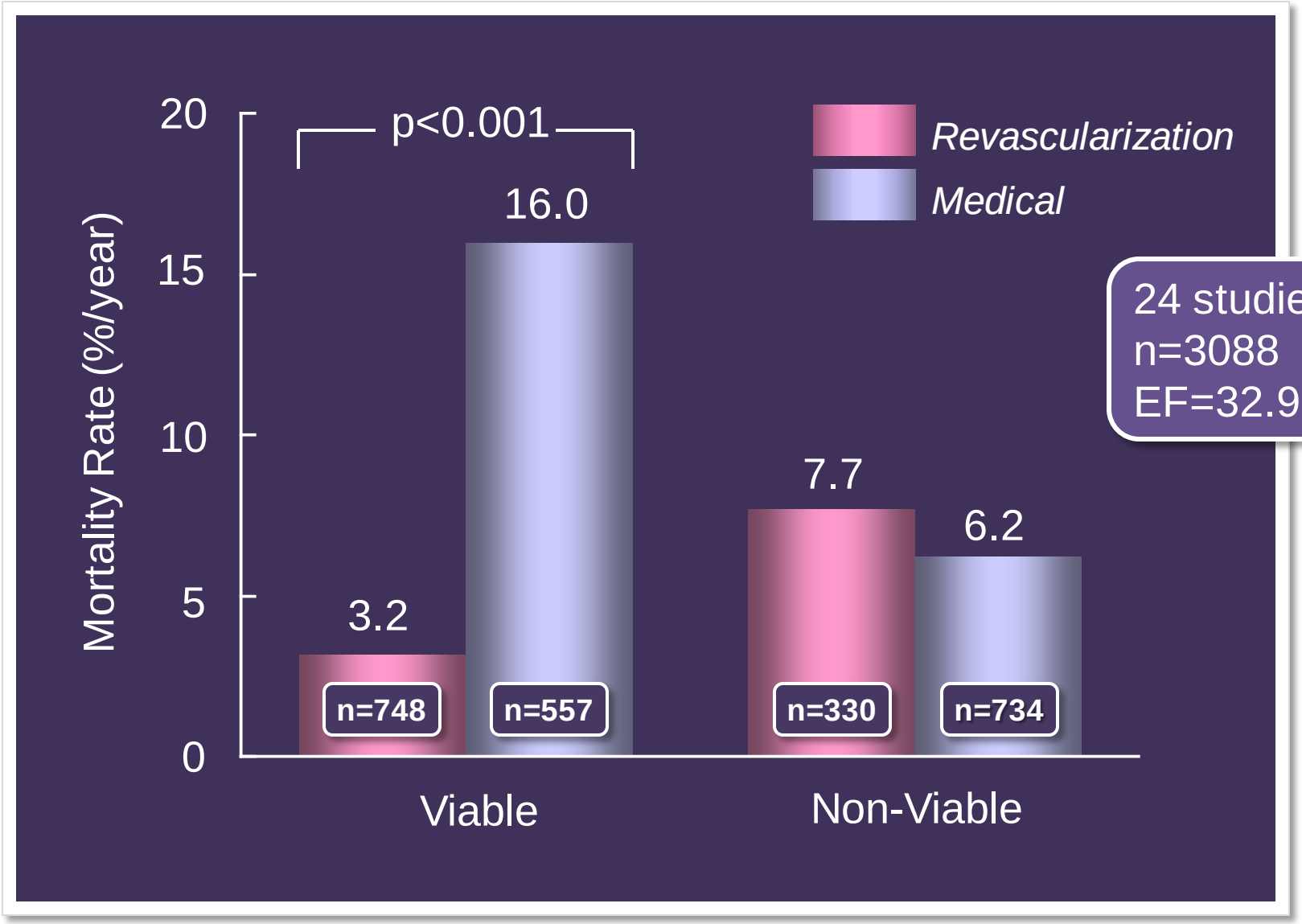
- LV dysfunction in patients with CAD is not always an irreversible process, as LV function may improve substantially after CABG
- Assessment of myocardial viability is often used to predict improvement in LV function after CABG and thus select patients for CABG
- Numerous studies have suggested that identification of viable myocardium also predicts ***improved survival*** after CABG

Myocardial Viability and Improved Survival



Allman et al, *J Am Coll Cardiol* 2002;39:1151-1158

Myocardial Viability and Improved Survival



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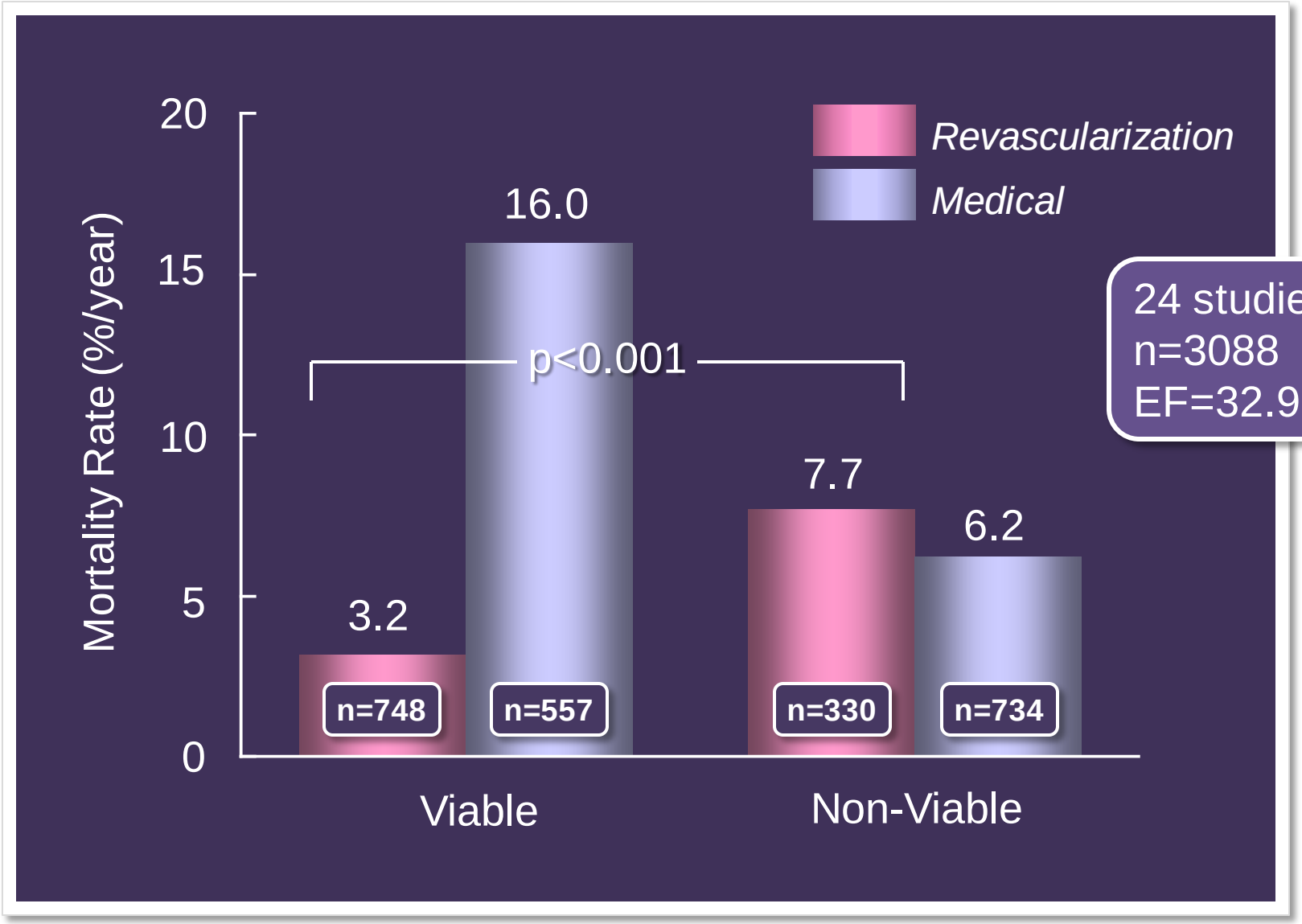

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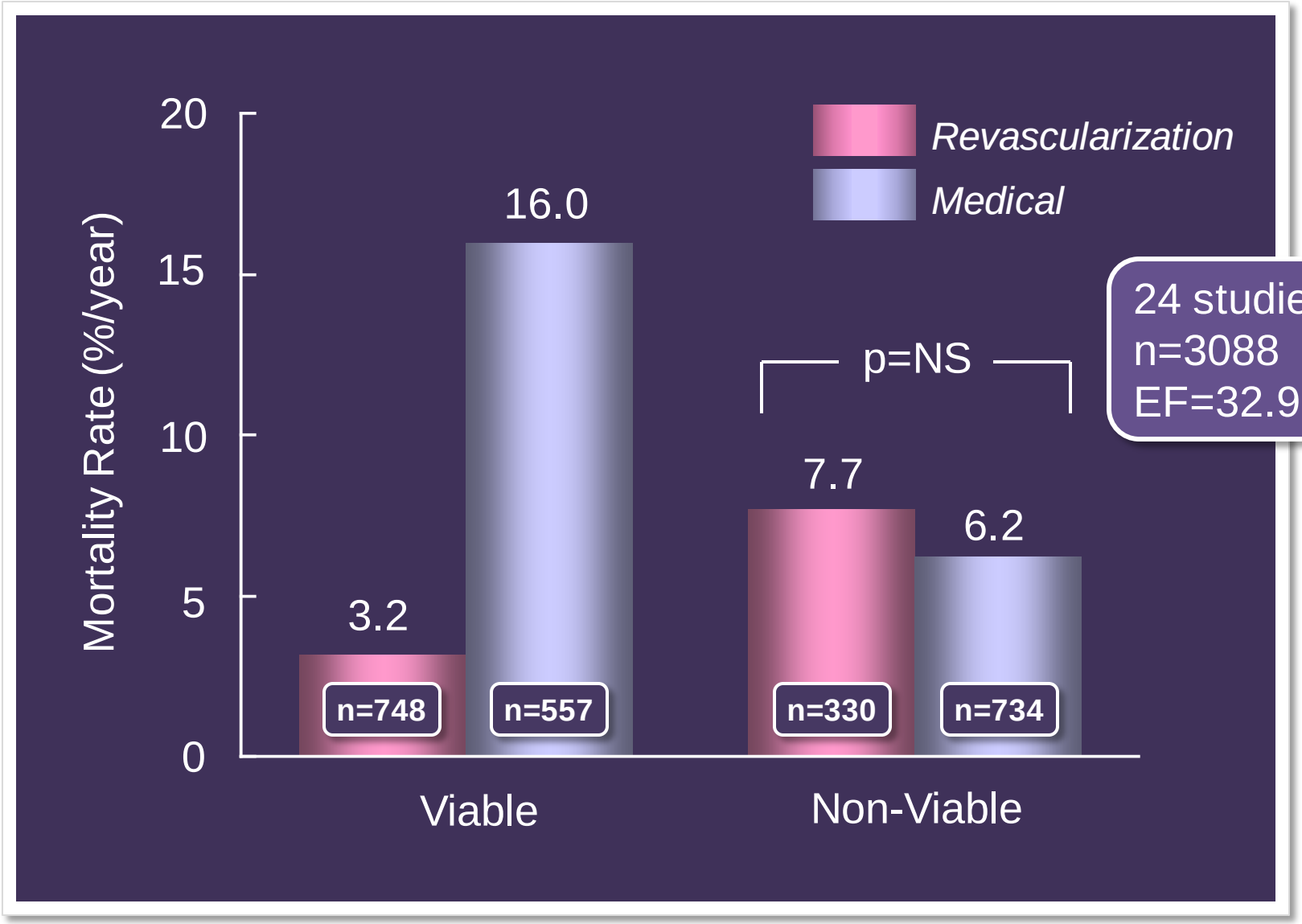

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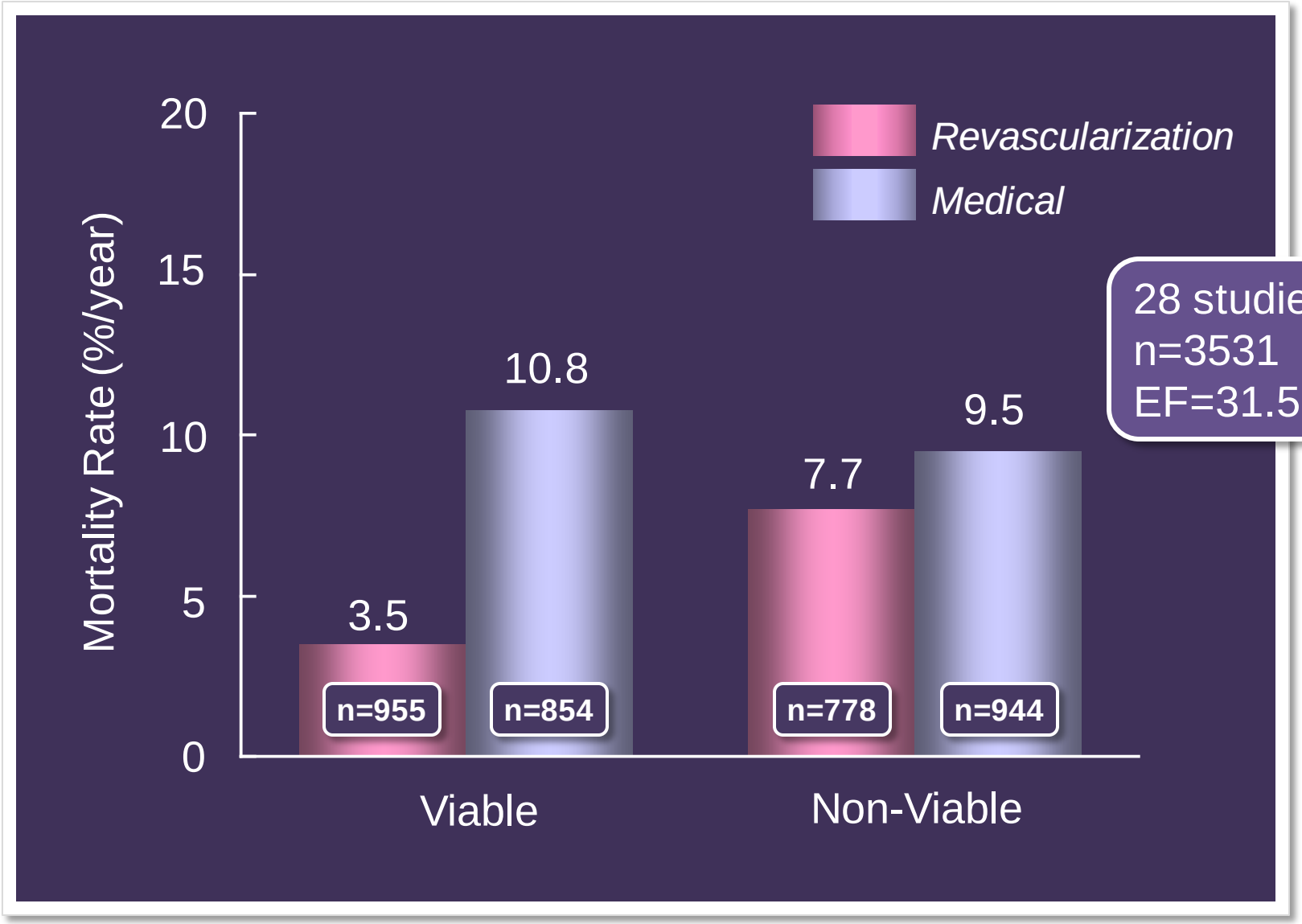

from Schinkel et al, *Curr Prob Cardiol* 2007;32:375-410

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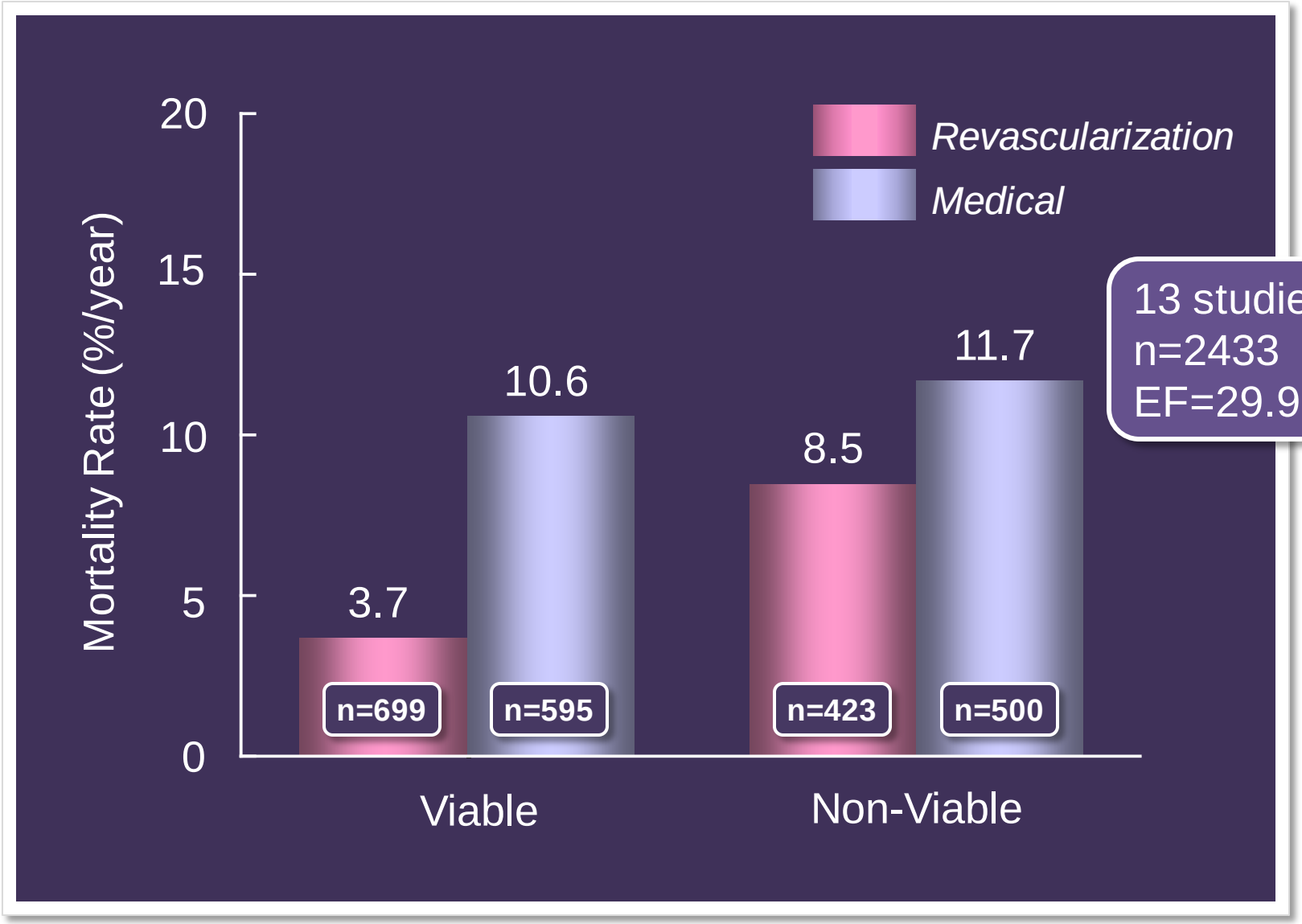

from Camici et al, *Circulation* 2008;117:103-114

Limitations of Cohort Studies

- Retrospective
- Decision for CABG may have been influenced by viability status
- No (or inadequate) adjustment for key baseline variables (age, comorbidities)
- Cohort studies carried out before modern aggressive medical therapy

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- Cohort studies carried out before modern aggressive medical therapy

Medical therapy also improves LV function in patients with hibernating myocardium … especially beta-blocker therapy

- Cleland et al. Lancet 2003:362:14-21
- Bello et al. Circulation 2003;108:1945-1953
- Seghatol et al. Am J Cardiol 2004;93:854-859

ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2008‡

Revascularization in patients with heart failure

Key evidence

There are no data from multicentre trials assessing the value of revascularization procedures for the relief of HF symptoms. However, single-centre, observational studies on HF of ischaemic origin suggest that revascularization may lead to symptomatic improvement and potentially improve cardiac function. Clinical trials are ongoing that address the effect of intervention on clinical outcomes.[134]

Surgical Treatment of Ischemic Heart Failure

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction

Eric J. Velazquez, M.D., Kerry L. Lee, Ph.D., Marek A. Deja, M.D., Ph.D., Anil Jain, M.D., George Sopko, M.D., M.P.H., Andrey Marchenko, M.D., Ph.D., Imtiaz S. Ali, M.D., Gerald Pohost, M.D., Sinisa Gradinac, M.D., Ph.D., William T. Abraham, M.D., Michael Yii, M.S., F.R.C.S., F.R.A.C.S., Dorairaj Prabhakaran, M.D., D.M., Hanna Szwed, M.D., Paolo Ferrazzi, M.D., Mark C. Petrie, M.D., Christopher M. O'Connor, M.D., Pradit Panchavinnin, M.D., Lilin She, Ph.D., Robert O. Bonow, M.D., Gena Roush Rankin, M.P.H., R.D., Robert H. Jones, M.D., and Jean-Lucien Rouleau, M.D., for the STICH Investigators*

N Engl J Med 2011;364:1607-16.

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N Engl J Med 2011;364:1617-25.

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This article (10.1056/NEJMoa1100356) was published on April 4, 2011, at NEJM.org.

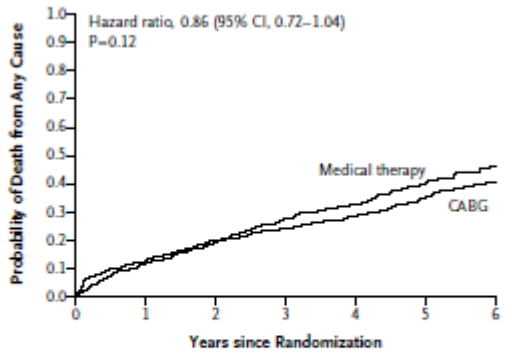

Figure 1. Kaplan–Meier Curves for the Probability of Death from Any Cause.
CABG denotes coronary-artery bypass grafting.

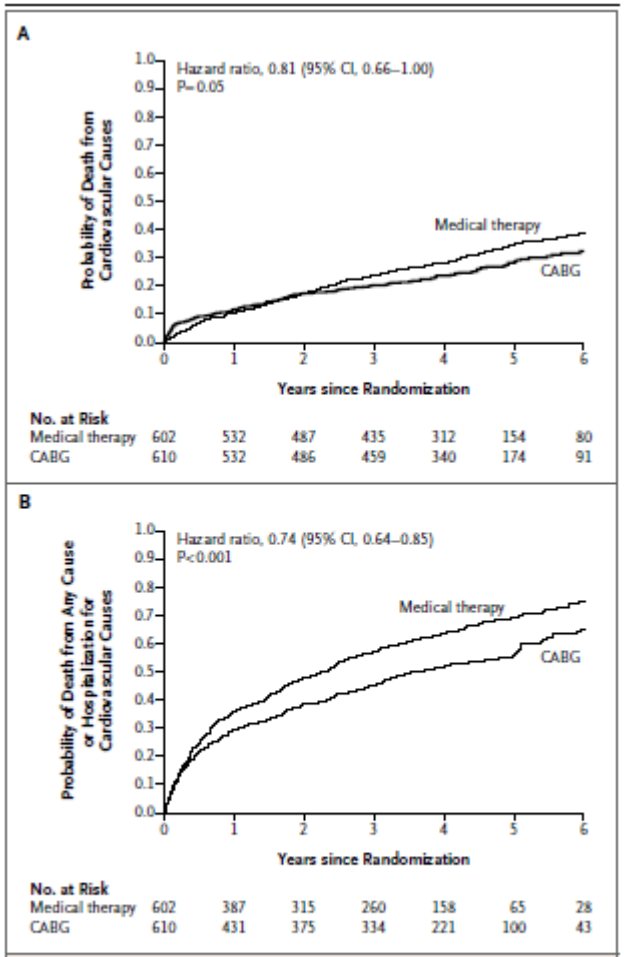

Figure 2. Kaplan–Meier Curves for the Probability of Death from Cardiovascular Causes and of Death from Any Cause or Hospitalization for Cardiovascular Causes.
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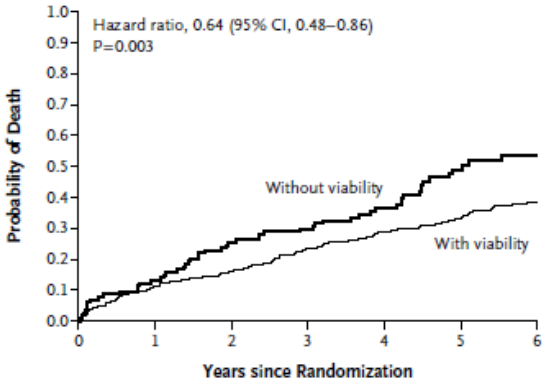

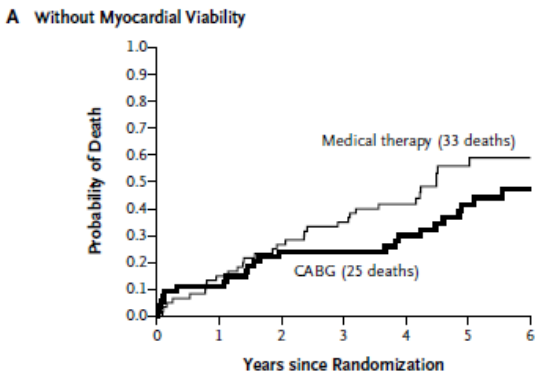

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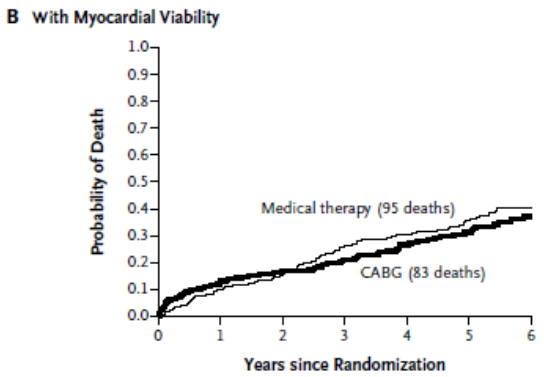

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Bonow et al.N Engl J Med 2011

Limits of STICH viability

- The authors note: "*Conclusions that can be draw from our results are limited by a number of factors*"

  - First, viability data were not available for all the patients .... The study patients represent slightly less than 50% of the randomized group. Furthermore, viability testing was not performed on a randomly selected subgroup;
  - Second, only 114 of 601 patients (19%) were deemed not to have viable myocardium. This small number limited the power of our analysis to detect a differential effect of CABG.....
  - Third, we cannot exclude the possibility that results of viability testing could have influenced subsequent clinical decision making.
  - Fourth, our analysis was based on SPECT and dobutamine echocardiography. We did not incorporate other approaches, such as positron-emission tomography (PET) or contrast-enhanced magnetic resonance imaging (MRI).

Bonow et al.N Engl J Med 2011

Myocardial Viability in Ischemic Left Ventricular Dysfunction

TO THE EDITOR: Bonow et al. (April 28 issue)[1] found that the presence of a substantial amount of viable myocardium was associated with a greater survival benefit in a substudy of 601 patients with ischemic left ventricular dysfunction who were enrolled in the Surgical Treatment for Ischemic Heart Failure trial (STICH; ClinicalTrials.gov number, NCT00023595) (unadjusted P= 0.003).[2] They also reported the counterintuitive finding that the presence of viable myocardium did not identify patients with a differential survival benefit after surgical revascularization, as compared with medical therapy alone (Fig. 2B of the article). Although total left ventricular viability as used by Bonow et al. is a good predictor of outcome, it does not distinguish between normal myocardium and dysfunctional but viable myocardium. On the other hand, the extent of dysfunctional but viable myocardium — more than the total extent of viability (normal plus dysfunctional) — is the likely predictor of functional recovery underpinning the survival benefit after revascularization.[3-5] Finally, if one is to expect an incremental survival benefit from revascularization in these patients, we believe that spatial coherence between the region of dysfunctional but viable myocardium and the site of the coronary-artery lesion must be demonstrated.

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No potential conflict of interest relevant to this letter was reported.

1. Bonow RO, Maurer G, Lee KL, et al. Myocardial viability and survival in ischemic left ventricular dysfunction. N Engl J Med 2011;364:1617-25.
2. Velazquez EJ, Lee KL, Deja MA, et al. Coronary-artery bypass surgery in patients with left ventricular dysfunction. N Engl J Med 2011;364:1607-16.
3. Wijns W, Vatner SF, Camici PG. Hibernating myocardium. N Engl J Med 1998;339:173-81.
4. Camici PG, Prasad SK, Rimoldi OE. Stunning, hibernation, and assessment of myocardial viability. Circulation 2008;117:103-14.
5. D'Egidio G, Nichol G, Williams KA, et al. Increasing benefit from revascularization is associated with increasing amounts of myocardial hibernation: a substudy of the PARR-2 trial. JACC Cardiovasc Imaging 2009;2:1060-8.

TO THE EDITOR: In the viability substudy of the STICH trial, Bonow et al. conclude that viability assessment does not identify patients with a survival benefit from coronary-artery bypass grafting (CABG) versus medical therapy. Important limitations of this study should be considered before adopting a blanket policy of withholding viability assessment in patients with coronary artery disease and left ventricular dysfunction. Despite the goal of uniform testing in this trial,

REMEDYS

Revascularization versus
Medical Treatment for Ischemic Ventricular **Dys**function

TRIAL and REGISTRY

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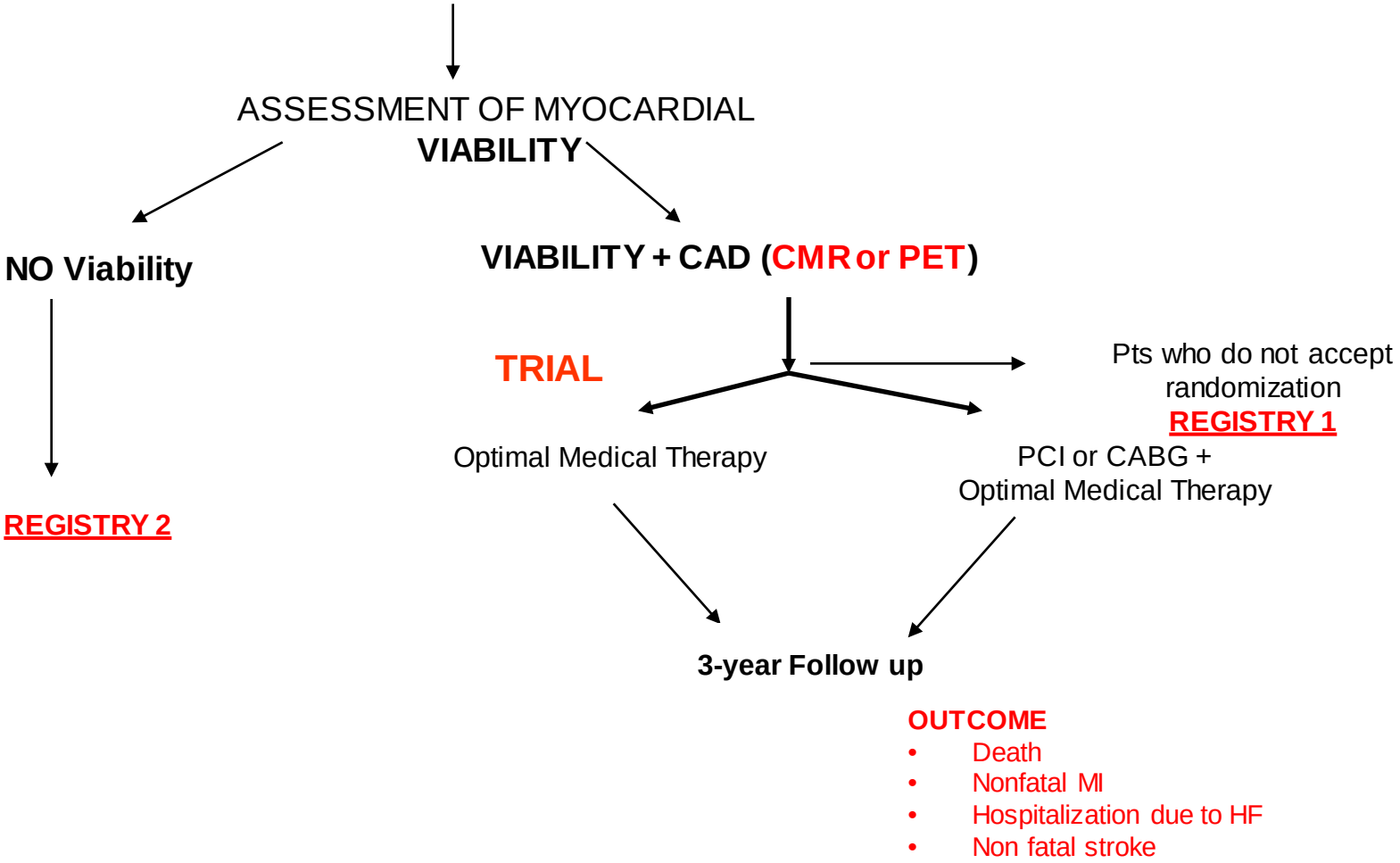

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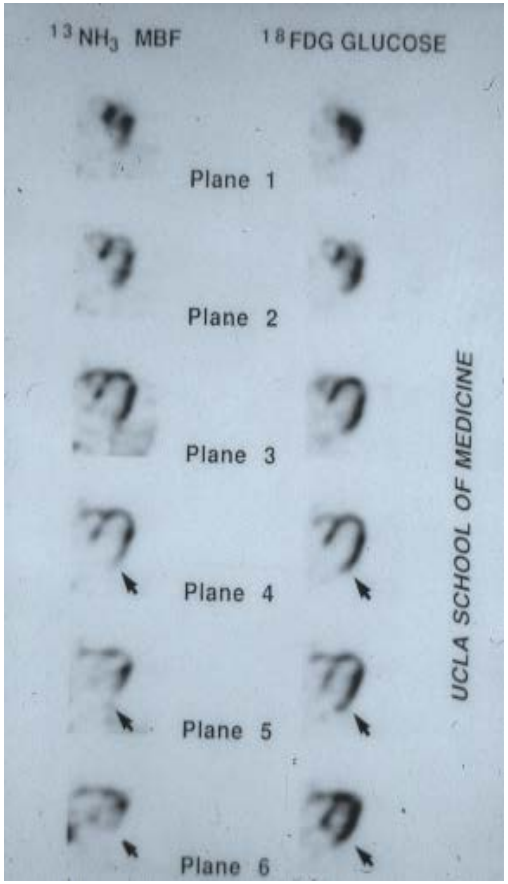
Acknowledgements

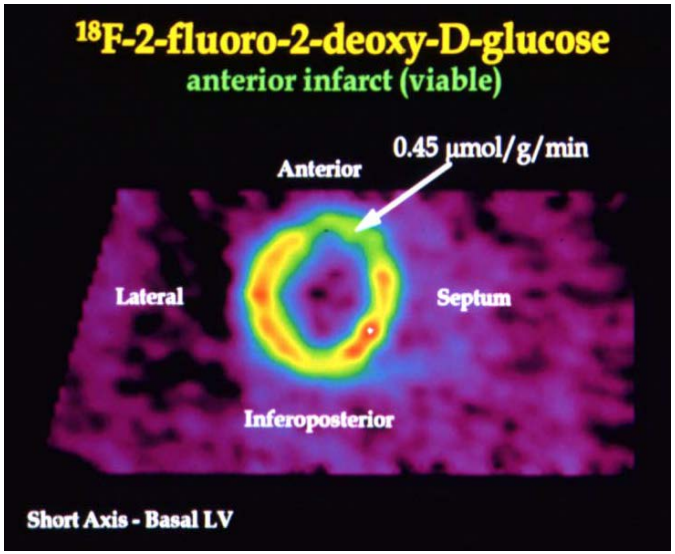
Terry Jones
Adriaan Lammertsma
Robert Bonser
Domenico Pagano
Enrico Ammirati
Maria Frigerio
Stefan Neubauer
Robert Bonow
Ottavio Alfieri
Antonio Colombo
Aldo Maggioni
Ornella Rimoldi

Image quality with FDG-PET depends on co-morbidities such as diabetes: importance of acquisition protocol

Traditional (UCLA) flow/metabolism match-mismatch following oral glucose load

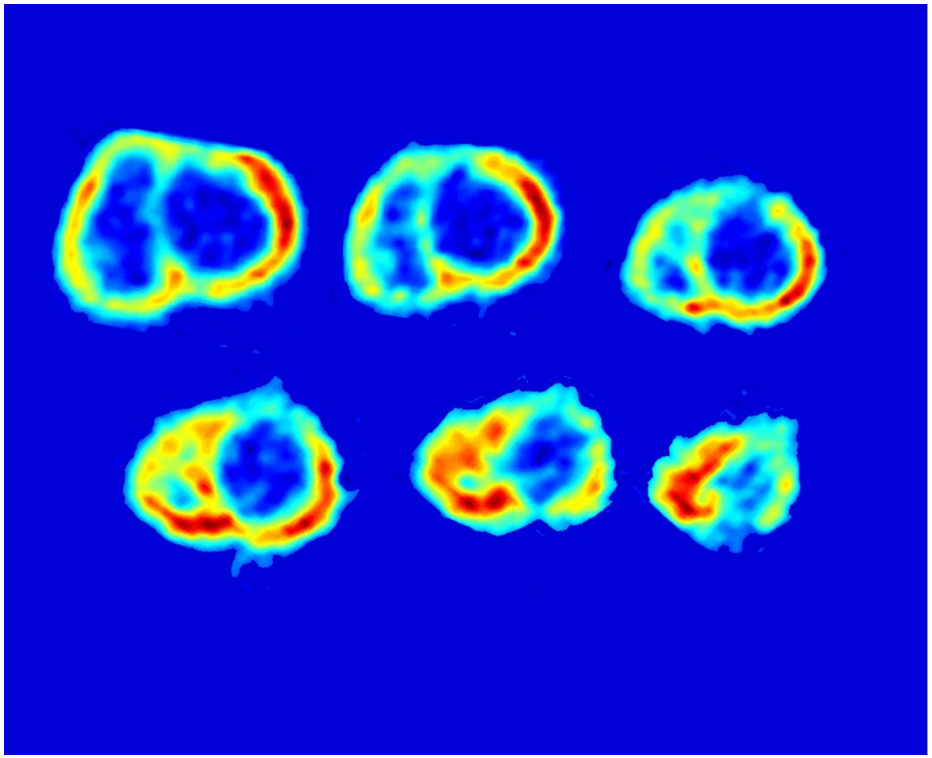


Measurement of FDG uptake during glucose clamp (Hammersmith)

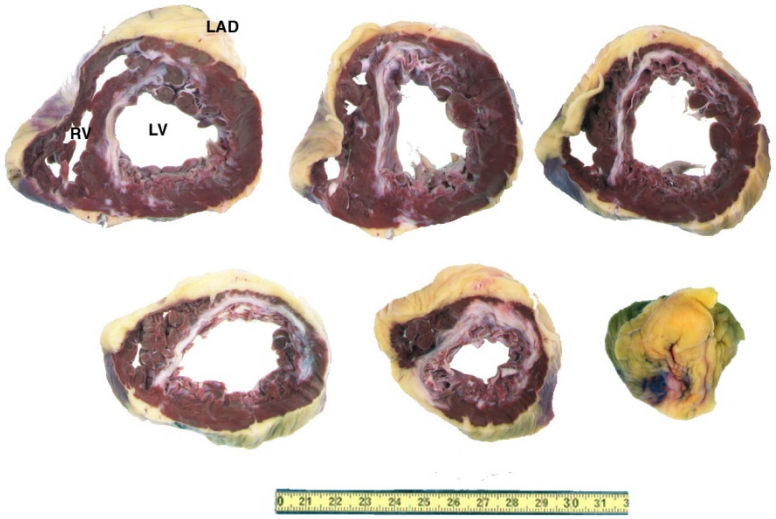


Circulation 1996; 93: 737-744
J Clin Invest 1996; 98: 2094-2099

Validation of PET-infarct size in pigs and patients undergoing transplant



Patient # 6143 K.B.



Rimoldi et al. Eur J Nucl Med 2002; 29: 203-215

PET viability

- Pros
  - Highest sensitivity (NPV) for detection of hibernation
  - It can be done in pts with implanted devices
  - No need of flow scan if clamp used (no cyclotron on site)
  - Technique of choice for pts with lowest EF
  - Concomitant infarct size
  - Inter-patients and inter-centres data comparability
- Cons
  - Limited information on endocardium vs epicardium compared to CMR
  - Extra time for clamp
  - Costs

How myocardial viability affects survival

Patients (n=35) with E.F. ≤25%

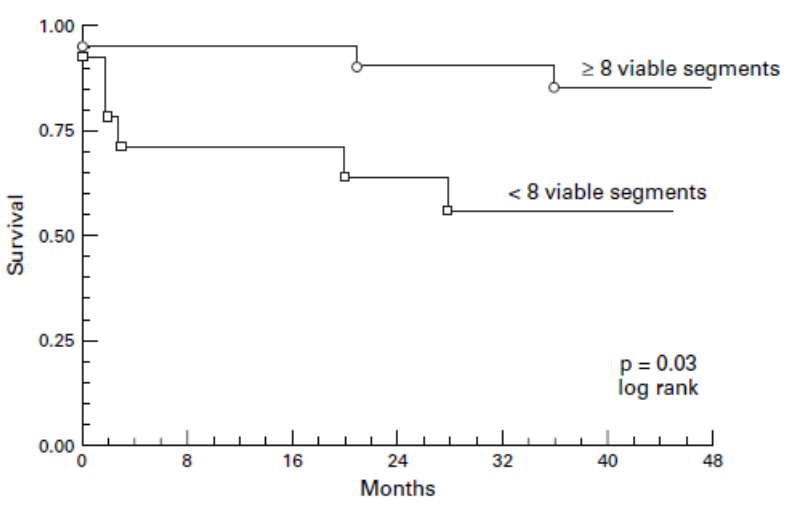


Figure 1 Kaplan-Meier curves showing estimated cardiac event free survival for patients in group 1 (≥ 8 viable segments) and group 2 (< 8 viable segments).

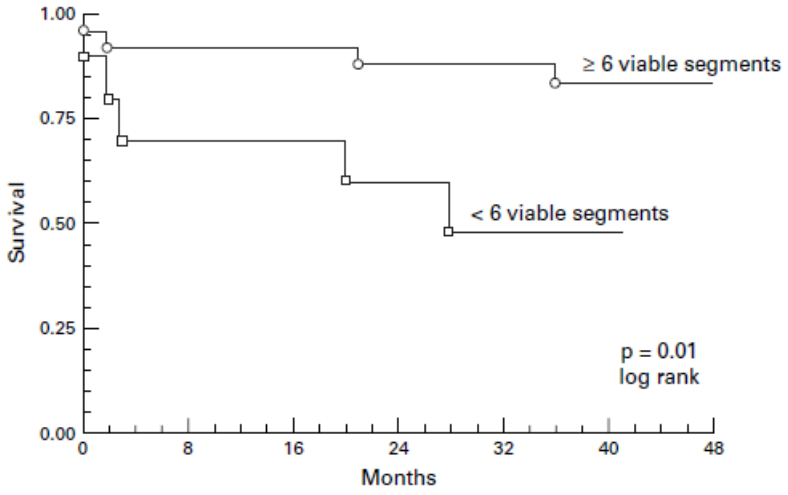


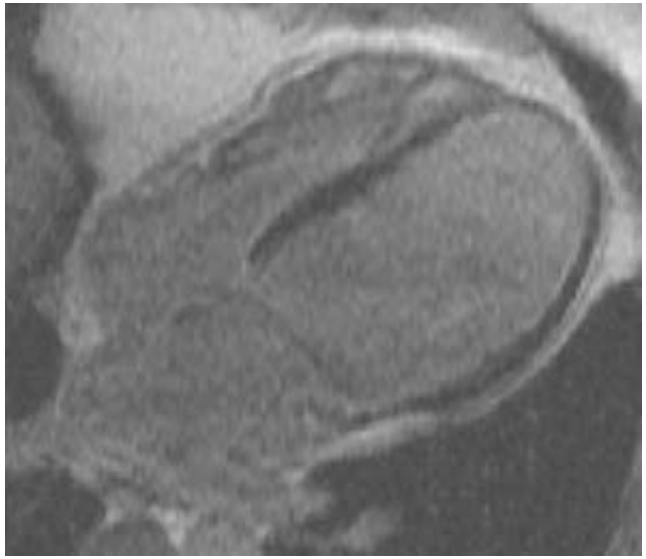
Figure 2 Kaplan-Meier curves showing estimated cardiac event free survival for patients with ≥ 6 viable segments and patients with < 6 viable segments.

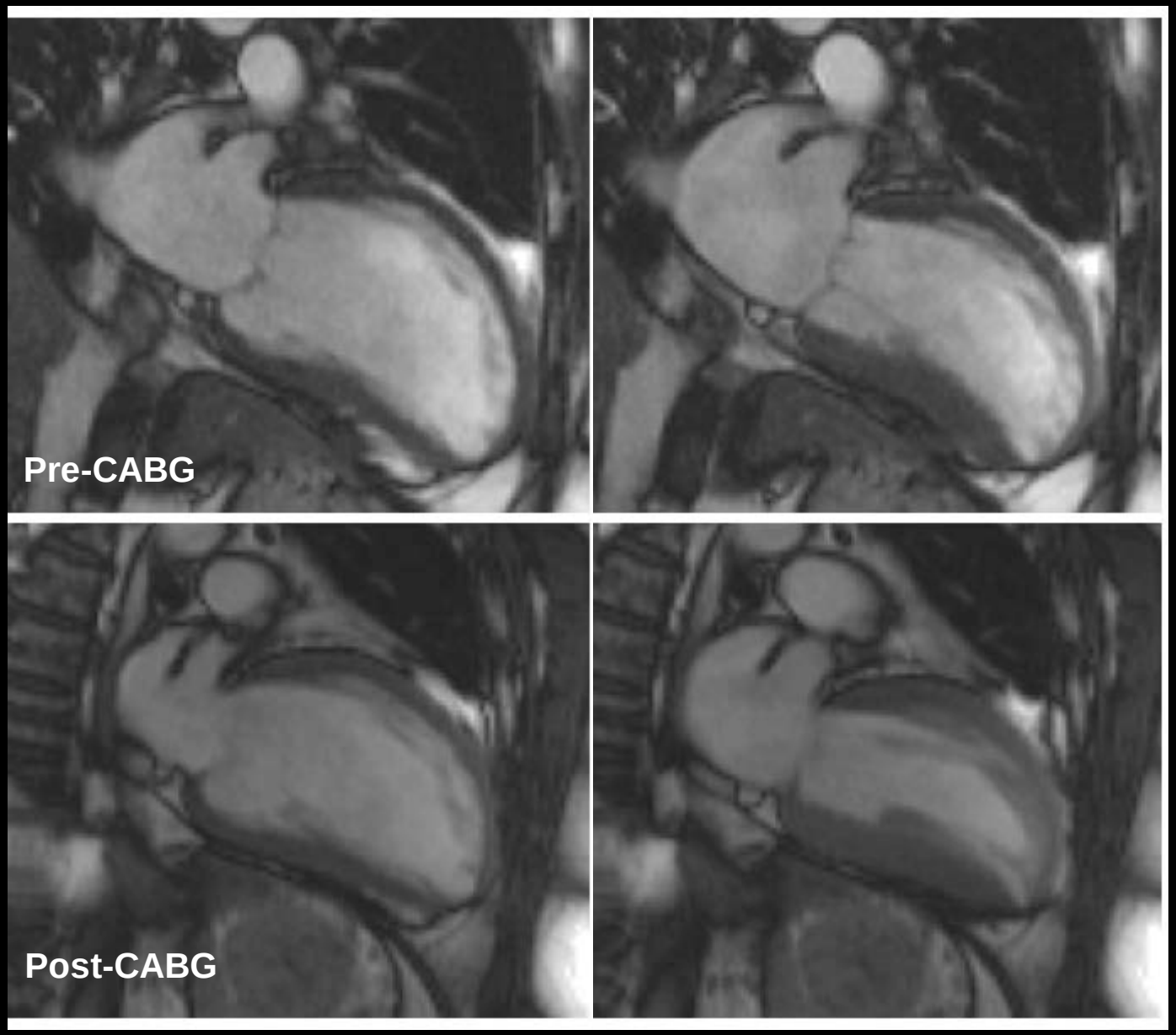
Pagano et a. Heart 2000; 83: 456-461

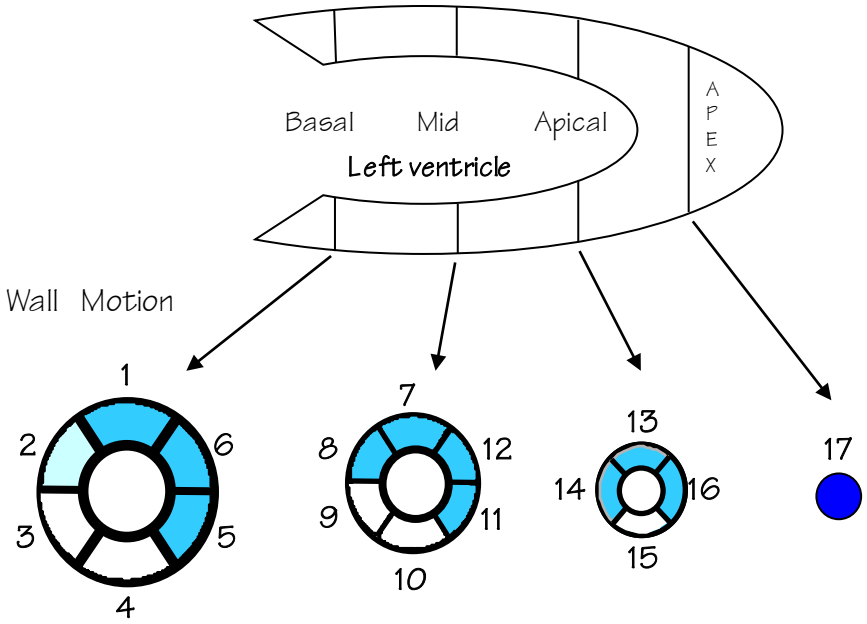
Case

- 48 y. o. male with new onset heart failure
- Angiogram showed LMS stenosis and proximal LAD/LCx disease.
- **CMR Report**:
  - Dilated LV with severe impairment of systolic function. **LVEF 28%.**
  - Subendocardial anteroseptal infarction.
  - "All 17 segments are viable, and of these 11 segments are hibernating. Following revascularization, a significant improvement in ventricular function would be expected. "
  - **Follow-up CMR scan 12 months post-CABG**:
    - "Significantly improved LV function and dimensions with reverse remodelling compared to pre-op scan." **LVEF 47%.**


Limited MI



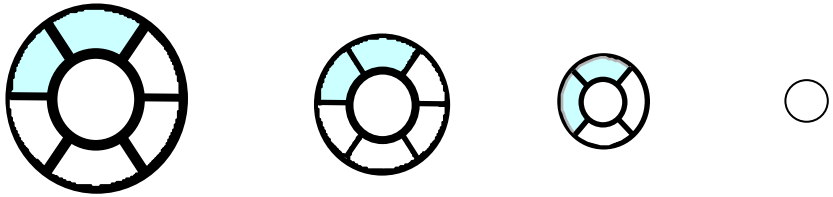

End-diastole
End-systole
Pre-CABG
Post-CABG



CMR Viability Assessment

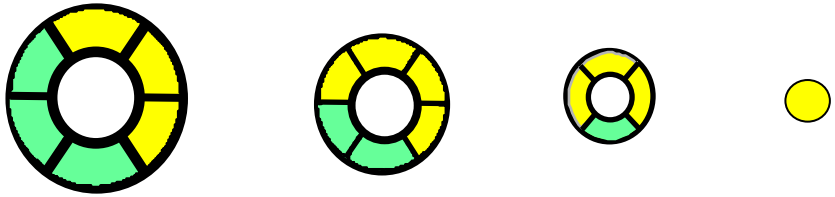
- Normal
- Mildly Hypokinetic
- Severely hypokinetic
- Akinetic

Gadolinium Enhancement



- Normal (no MI)
- <25% (subendocardial MI)
- 25-50% (Intermediate MI)
- >50% (Near Transmural MI)

Viability Assessment



- Non-viable
- Viable & Hibernating
- Viable

Cardiovascular Magnetic Resonance Unit, Royal Brompton Hospital

ORIGINAL ARTICLE

Coronary-Artery Bypass Surgery in Patients with Left Ventricular Dysfunction

Eric J. Velazquez, M.D., Kerry L. Lee, Ph.D., Marek A. Deja, M.D., Ph.D., Anil Jain, M.D., George Sopko, M.D., M.P.H., Andrey Marchenko, M.D., Ph.D., Imtiaz S. Ali, M.D., Gerald Pohost, M.D., Sinisa Gradinac, M.D., Ph.D., William T. Abraham, M.D., Michael Yii, M.S., F.R.C.S., F.R.A.C.S., Dorairaj Prabhakaran, M.D., D.M., Hanna Szwed, M.D., Paolo Ferrazzi, M.D., Mark C. Petrie, M.D., Christopher M. O'Connor, M.D., Pradit Panchavinnin, M.D., Lilin She, Ph.D., Robert O. Bonow, M.D., Gena Roush Rankin, M.P.H., R.D., Robert H. Jones, M.D., and Jean-Lucien Rouleau, M.D., for the STICH Investigators*

This article (10.1056/NEJMoa1100356) was published on April 4, 2011, at NEJM.org.

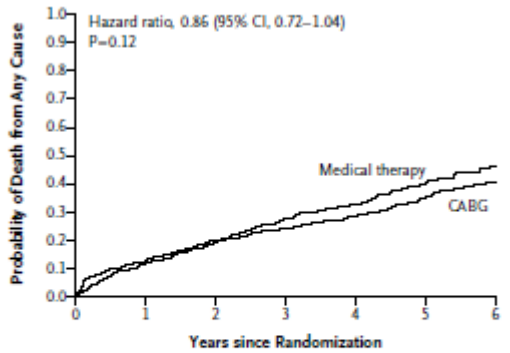


Figure 1. Kaplan–Meier Curves for the Probability of Death from Any Cause.
CABG denotes coronary-artery bypass grafting.

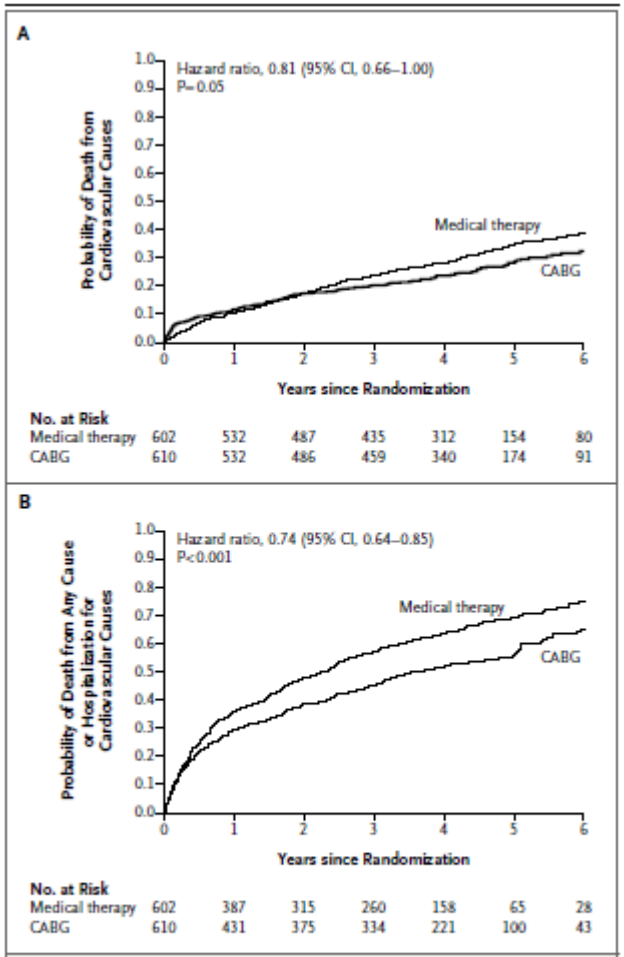


Figure 2. Kaplan–Meier Curves for the Probability of Death from Cardiovascular Causes and of Death from Any Cause or Hospitalization for Cardiovascular Causes.
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The NEW ENGLAND JOURNAL of MEDICINE

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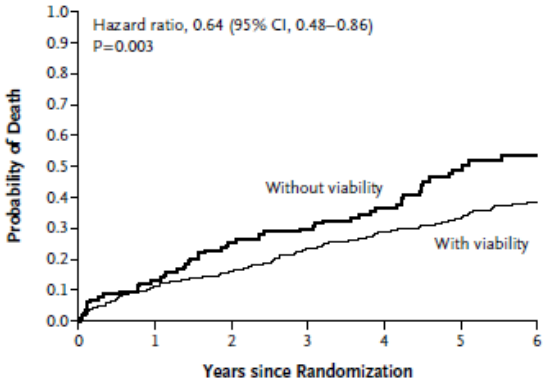

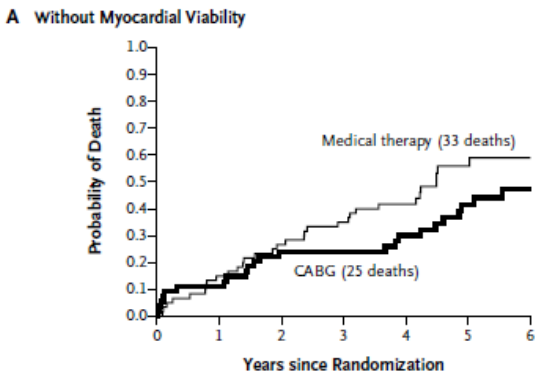

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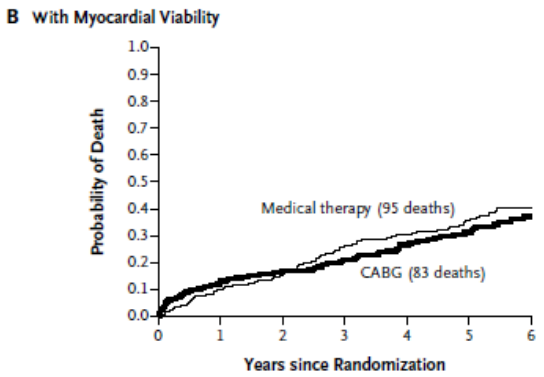

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Bonow et al.N Engl J Med 2011

Our comments to STICH viability

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Ammirati, Rimoldi, Camici NEJM 2011

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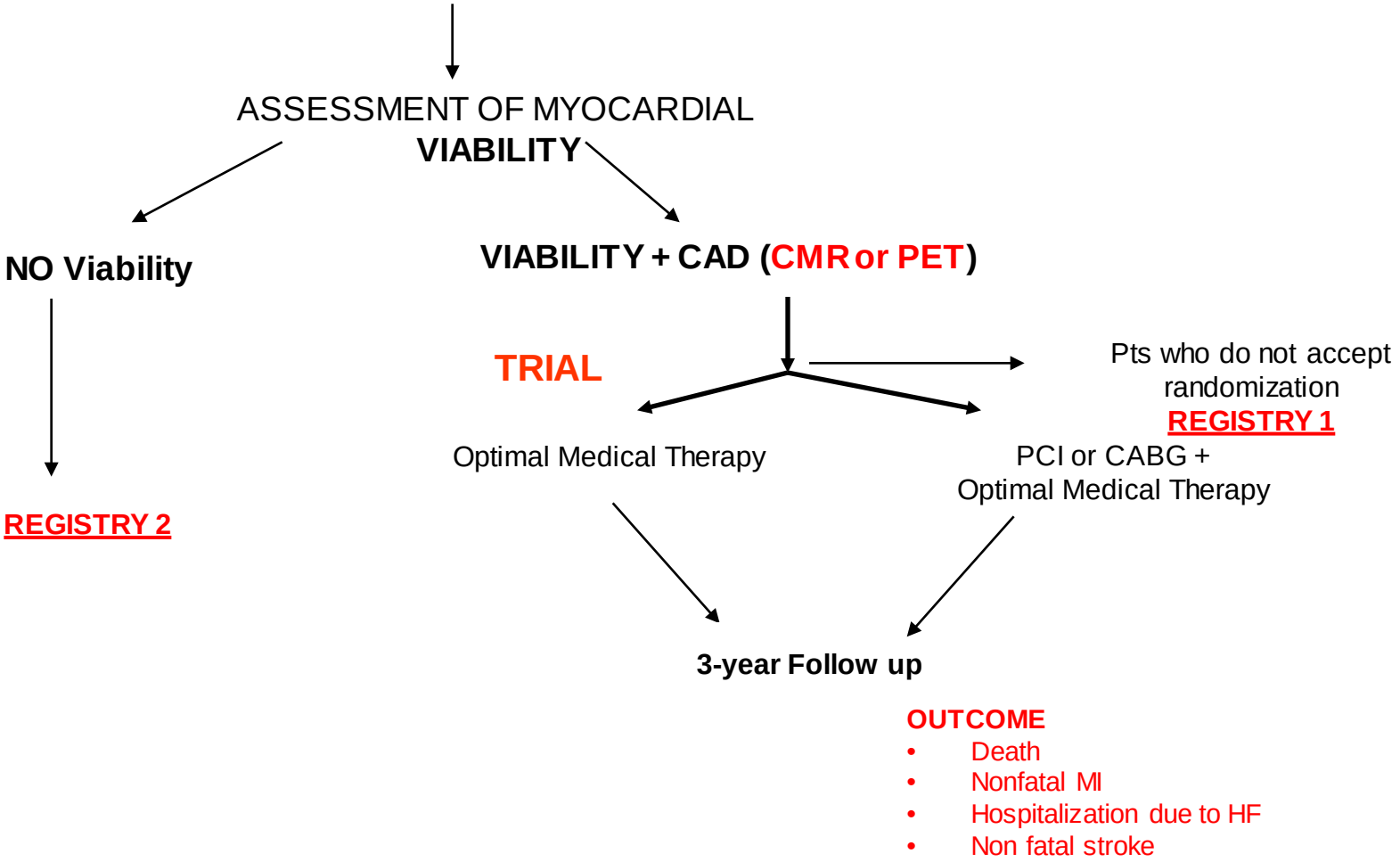

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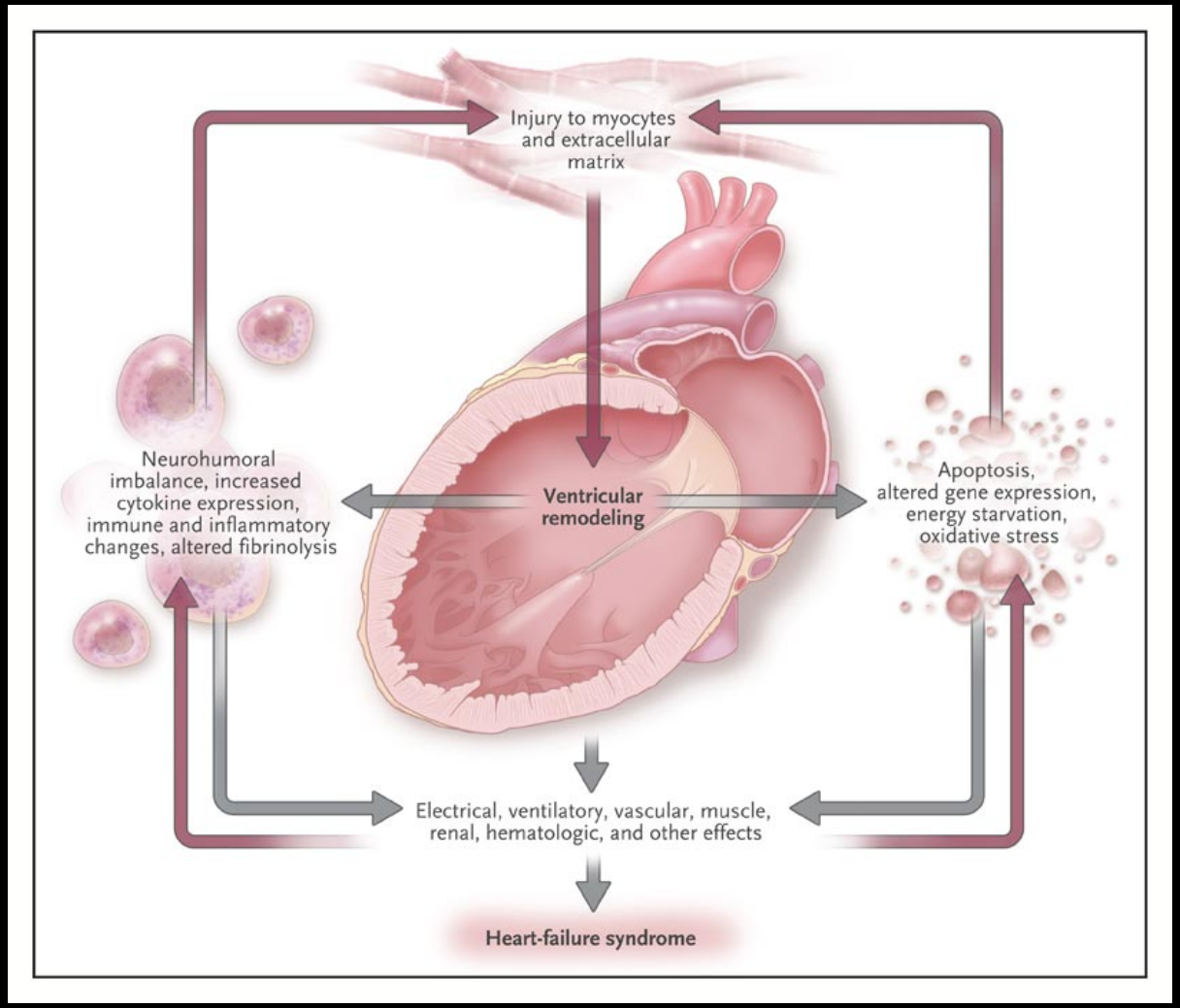
Pathophysiology of Systolic Heart Failure



McMurray J. N Engl J Med 2010;362:228-238