The 4th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Adressing Ischemic Cardiomyopathy in Heart Failure

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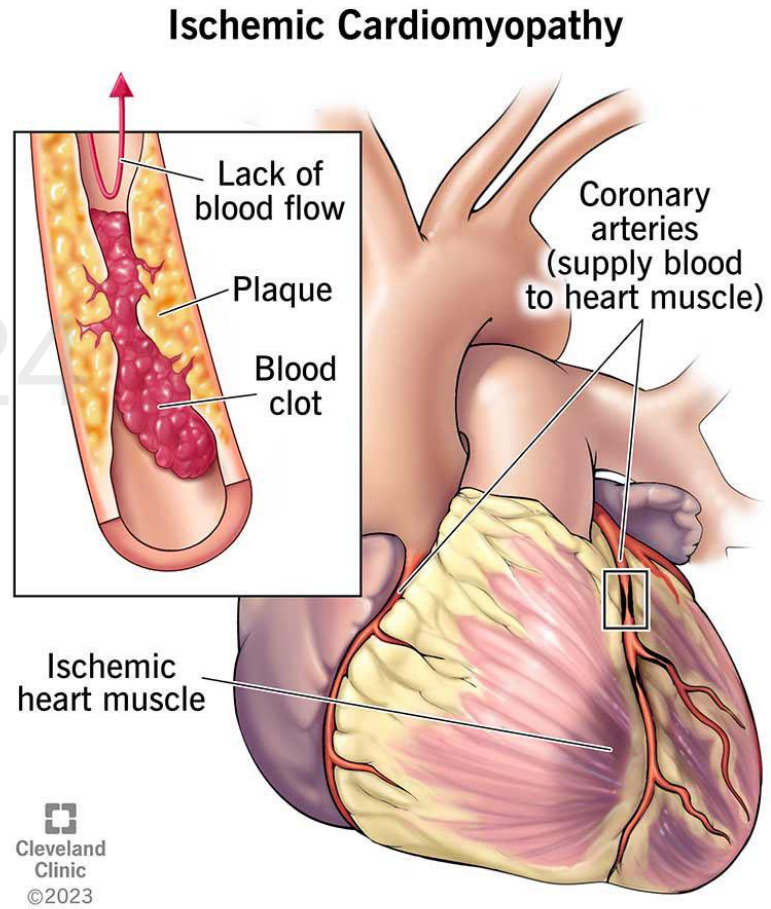
Ischemic Cardiomyopathy

State of left ventricular systolic dysfunction due to coronary artery disease.



Latest definition (introduced in STITCH trial to specify ICM definition in research fields):

Left ventricular dysfunction in the presence of severe coronary artery disease meeting **at least one of the following** conditions:

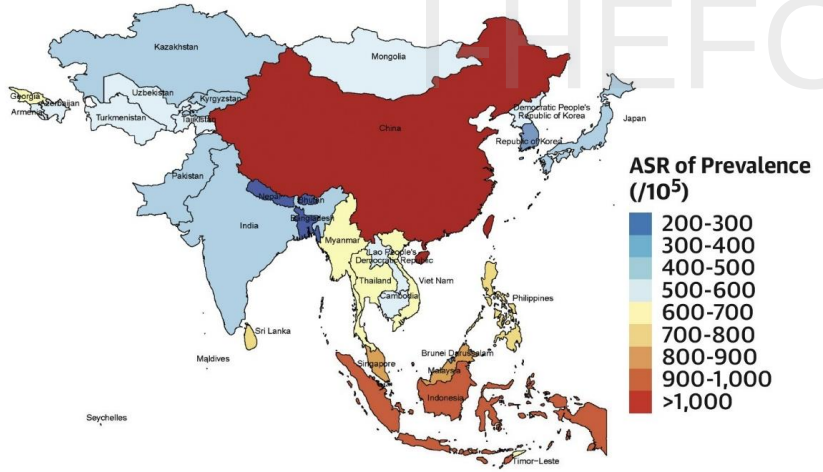
1. History of revascularization or acute myocardial ischemia;
2. Stenosis >75% in the left main (LM) or left anterior descending (LAD) vessel branch;
3. Presence of two or more coronary vessels with luminal stenosis >75%

Felker, G. M., Shaw, L. K. & O'Connor, C. M. A standardized definition of ischemic cardiomyopathy for use in clinical research. *J. Am. Coll. Cardiol.* (2002) doi:10.1016/S0735-1097(01)01738-7.

Epidemiology

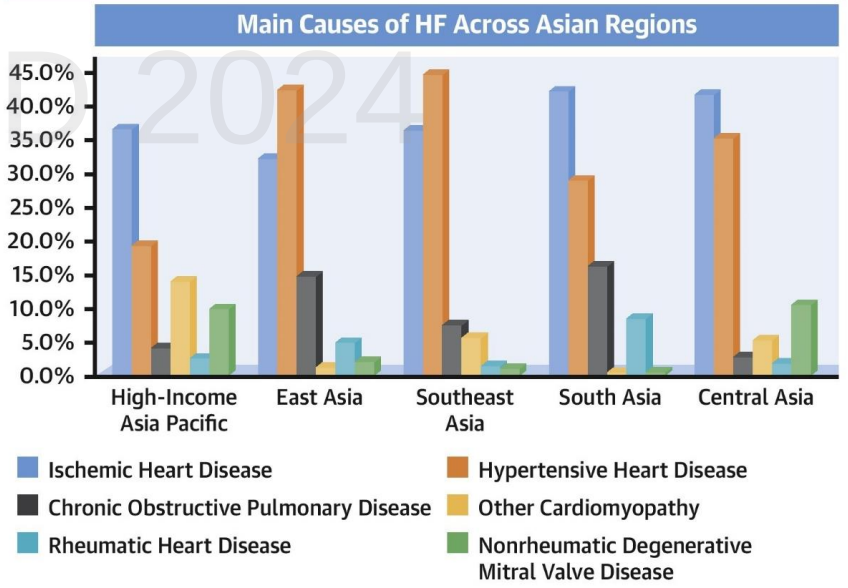
There's still lack of exact number of ICM cases because the use of overlapping multiple terminology in studies, but the presence of IHD as main cause of Heart Failure portrays the possible big number of ICM cases hidden beneath.

The Prevalence of HF in Asia is High: China, Indonesia, and Malaysia Are the 3 Highest Nations in Terms of Age-Standardized Prevalence



Indonesia as the 3rd country with the highest prevalence of heart failure cases in Southeast Asia

The Leading Causes of HF Worldwide and in Asia Are Ischemic Heart Disease and Hypertensive Heart Disease



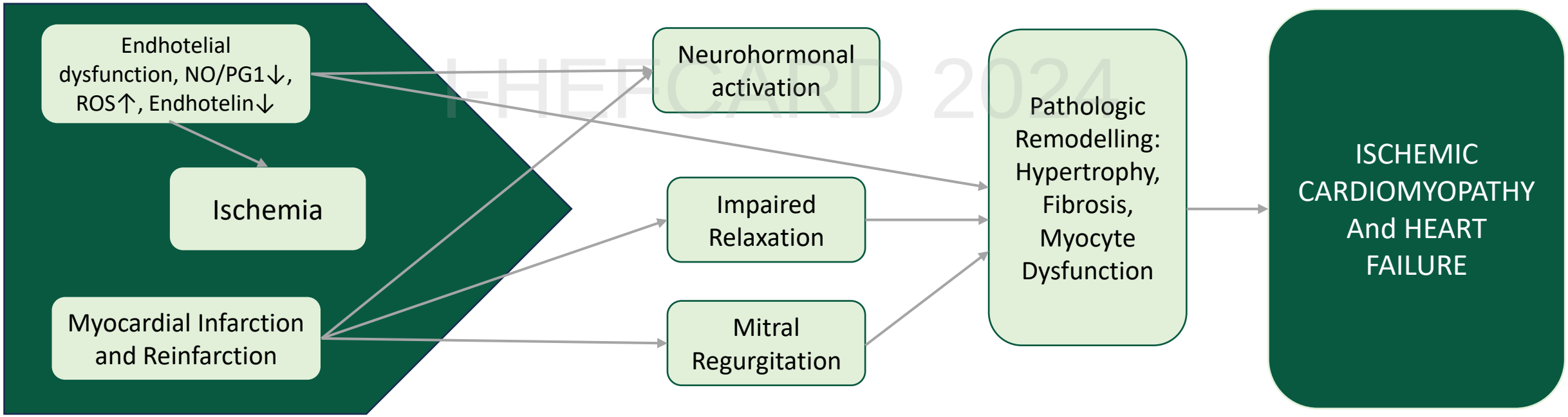
IHD as the 1st leading cause of Heart Failure Worldwide

Feng, J., Zhang, Y. and Zhang, J. (2024) 'Epidemiology and burden of heart failure in Asia', JACC: Asia, 4(4), pp. 249–264. doi:10.1016/j.jacasi.2024.01.013.

Pathophysiology

The main cause → **ISCHEMIA**

Impacts on perfusion of myocardium and its contractility that leads to pathological remodelling and further generate HF sign and symptoms.



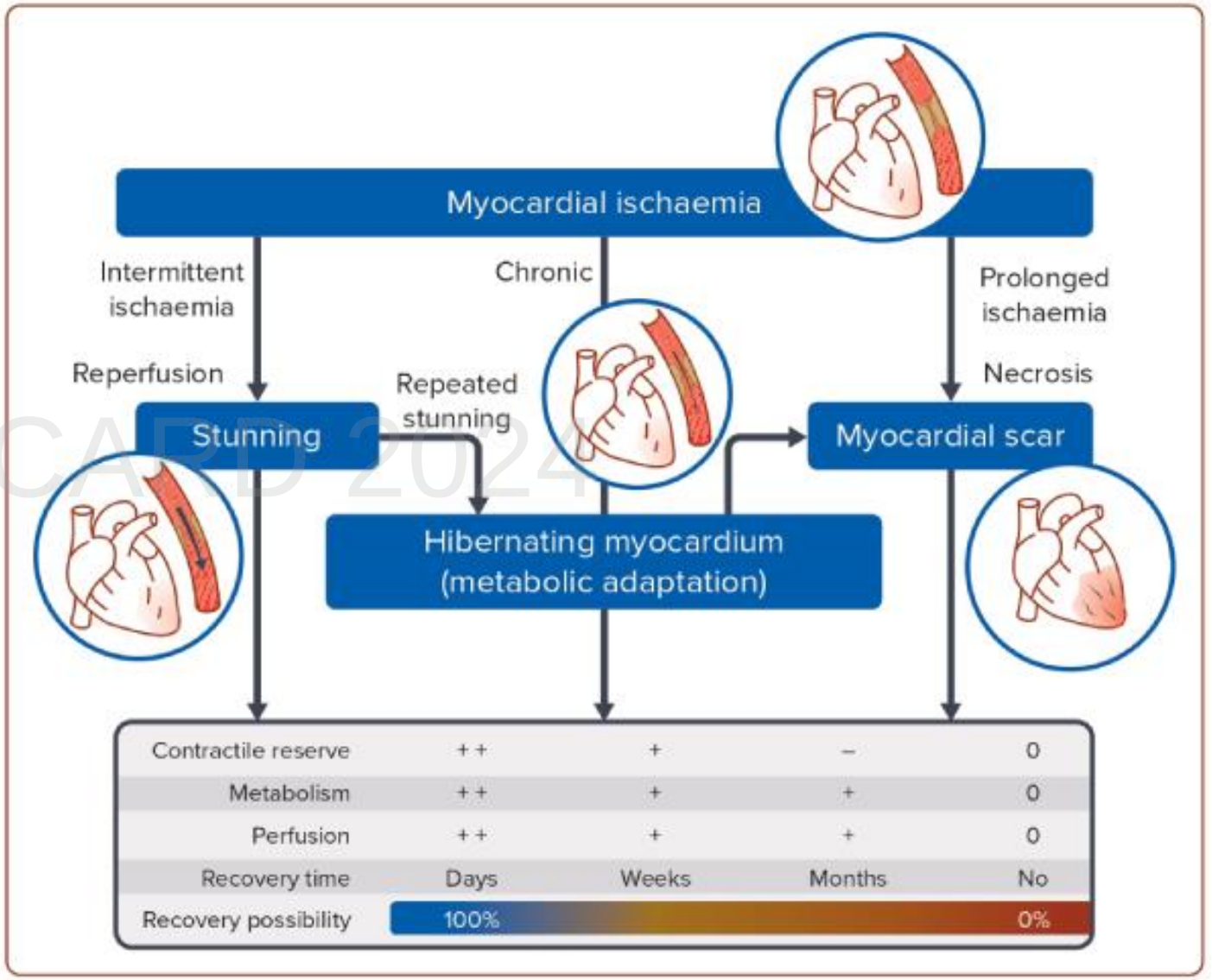
Pathobiology of Ischemic cardiomyopathy and heart failure. (NO : nitric oxide; PG : prostaglandin; ROS : reactive oxygen species).

Schwinger RHG. Pathophysiology of heart failure. Cardiovasc Diagn Ther. 2021 Feb;11(1):263-276. doi: 10.21037/cdt-20-302. PMID: 33708498; PMCID: PMC7944197.

Pathophysiology

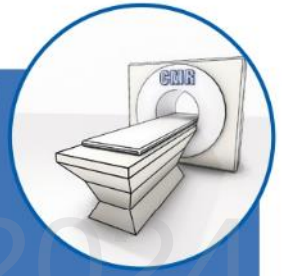
3 main mechanism of Ischemic Cardiomyopathy :

a. **Myocardial Stunning**
b. **Hibernating Myocardium**
c. **Myocardial Scar**



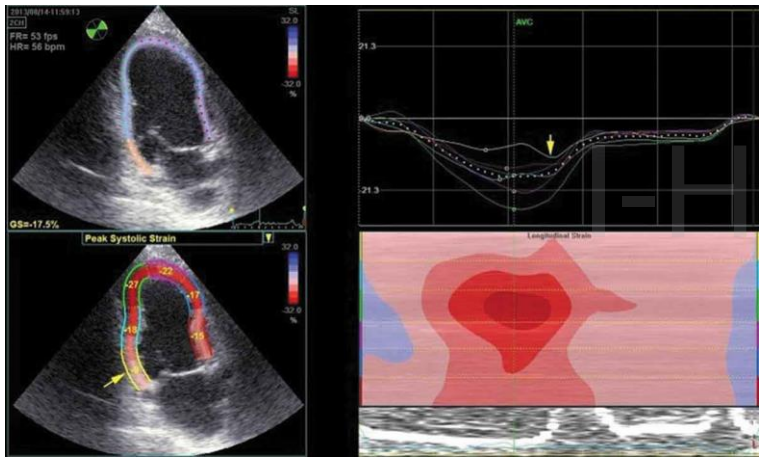
Bernhard Haring, Michael Böhm, Coronary Revascularisation in Heart Failure with Reduced Ejection Fraction, Journal of Asian Pacific Society of Cardiology 2024;3:e14

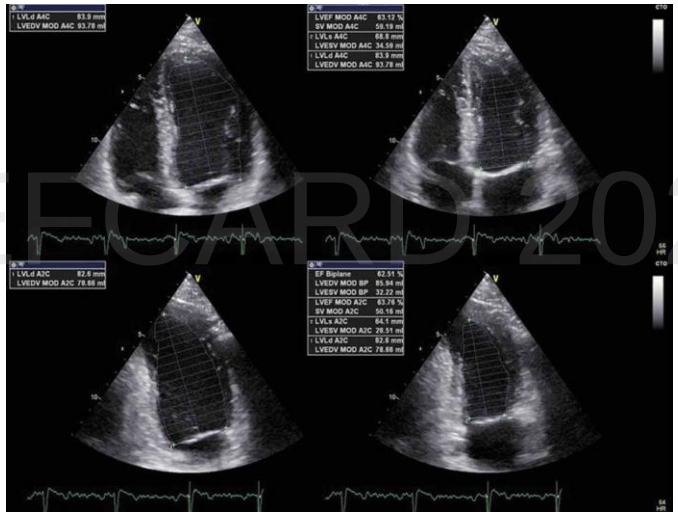
Diagnostic Modalities to assess Myocardial Viability in patients with Ischemic Cardiomyopathy

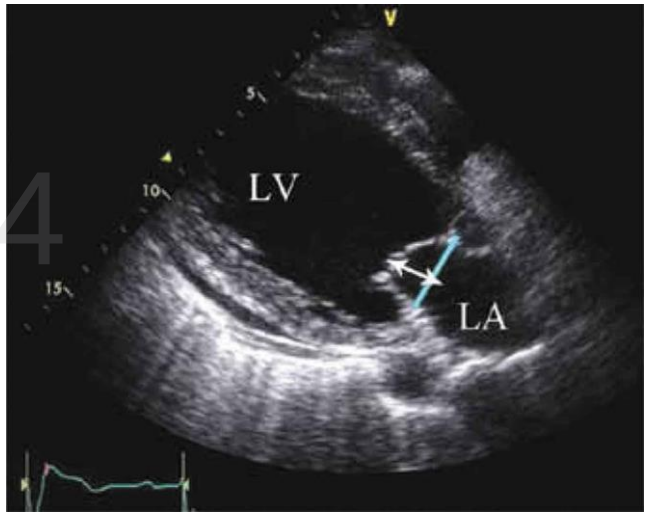
Imaging modality	Transthoracic echo-cardiogram	Single-photon emission computerised tomography	Cardiac MRI	PET
				
Advantages/ disadvantages	• Readily available and cheap • Assessment of ischaemia and viability • Assessment of wall motion abnormalities and wall thickness reduction; LV ejection fraction and valve function • Operator variability	• Readily and widely available • Assessment of ischaemia and viability • Robust semi-qualification • Suitable for almost all patients	• Less available • Gold standard to detect myocardial scar • Gold standard for LV volumes and ejection fraction • Implanted devices may limit use and image quality • Application of gadolinium contrast may be problematic in renal failure	• Less available and expensive • Gold standard to assess myocardial perfusion • Absolute blood flow quantification possible • Assessment of metabolism for viability

Bernhard Haring, Michael Böhm, Coronary Revascularisation in Heart Failure with Reduced Ejection Fraction, Journal of Asian Pacific Society of Cardiology 2024;3:e14

Echocardiographic features to look for in ICM







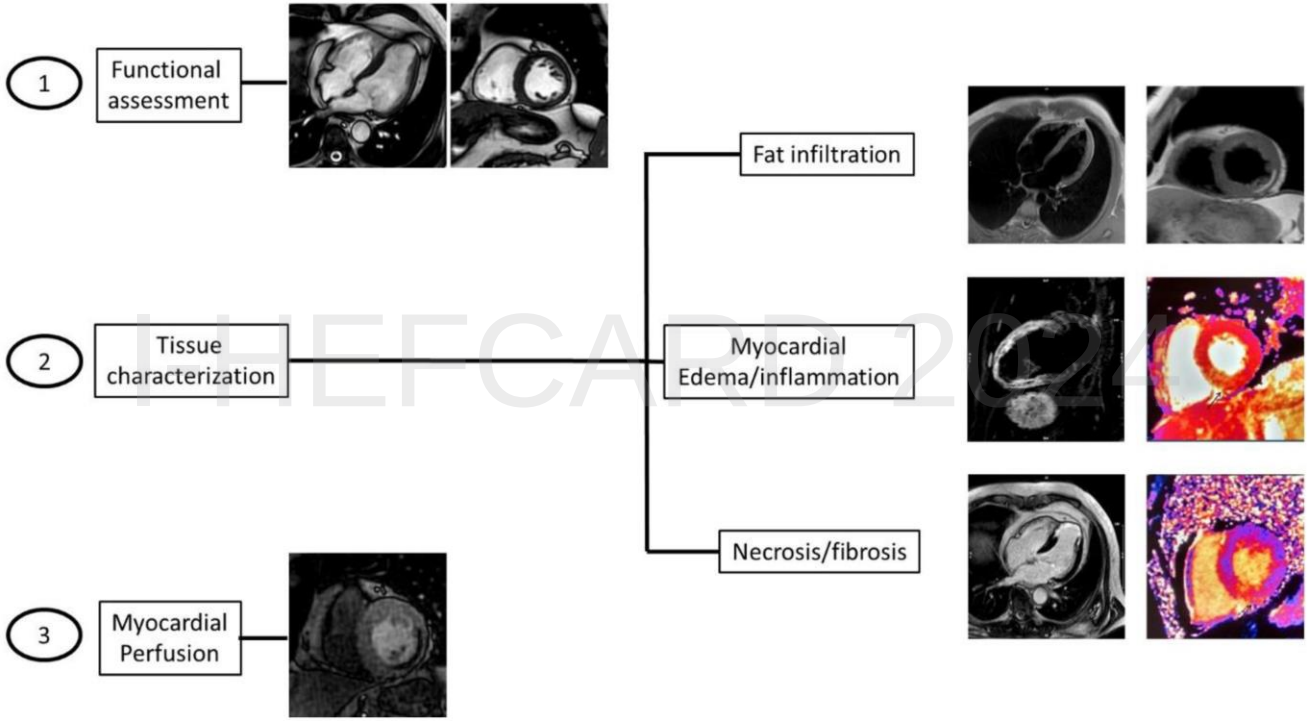
Severe dilatation of the left ventricle is a marker of non-viable myocardium, with higher end-systolic volume indices associated with poor ventricular functional recovery.

The LV wall thickness has been shown to be an important predictor of viable myocardium, as previous studies have shown that end-diastolic wall thickness < 6 mm indicates lack of contractile reserve and functional recovery after revascularization.

Feng, J., Zhang, Y. and Zhang, J. (2024) 'Epidemiology and burden of heart failure in Asia', JACC: Asia, 4(4), pp. 249–264. doi:10.1016/j.jacasi.2024.01.013.

Cabac-Pogorevici, I. et al. (2020) 'Ischaemic cardiomyopathy. Pathophysiological Insights, diagnostic management and the roles of Revascularisation and device treatment. gaps and dilemmas in the era of Advanced Technology', European Journal of Heart Failure, 22(5), pp. 789–799. doi:10.1002/ejhf.1747.

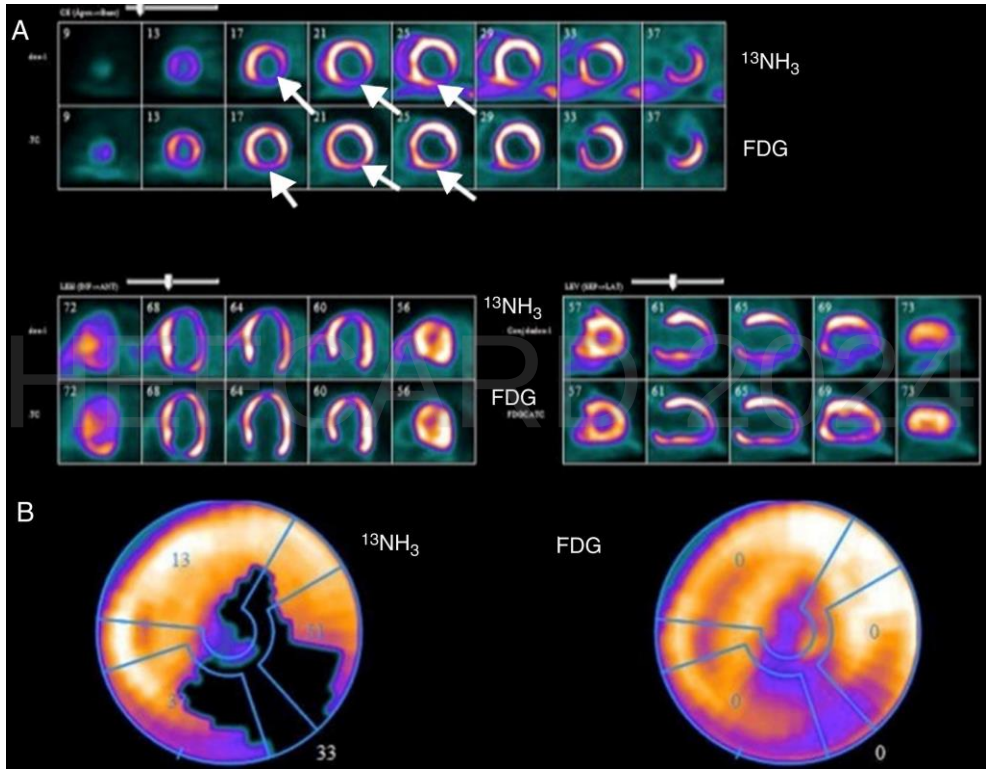
Cardiac MRI features to look for in ICM



CMR provides information regarding cardiac structure and function including shape, size, wall thickness, derivation of cardiac volumes and mass and assessment of global and regional wall motion abnormalities. In conjunction with dobutamine stress and gadolinium-chelated contrast enhancement (LGE), it can provide information regarding myocardial viability with contractile reserve and extent of non-viable myocardial scar tissue, respectively.

Baritussio A, Scatteia A, Bucciarelli-Ducci C. Role of cardiovascular magnetic resonance in acute and chronic ischemic heart disease. Int J Cardiovasc Imaging. 2018 Jan;34(1):67-80. doi: 10.1007/s10554-017-1116-0. Epub 2017 Mar 18. PMID: 28315985; PMCID: PMC5797568.

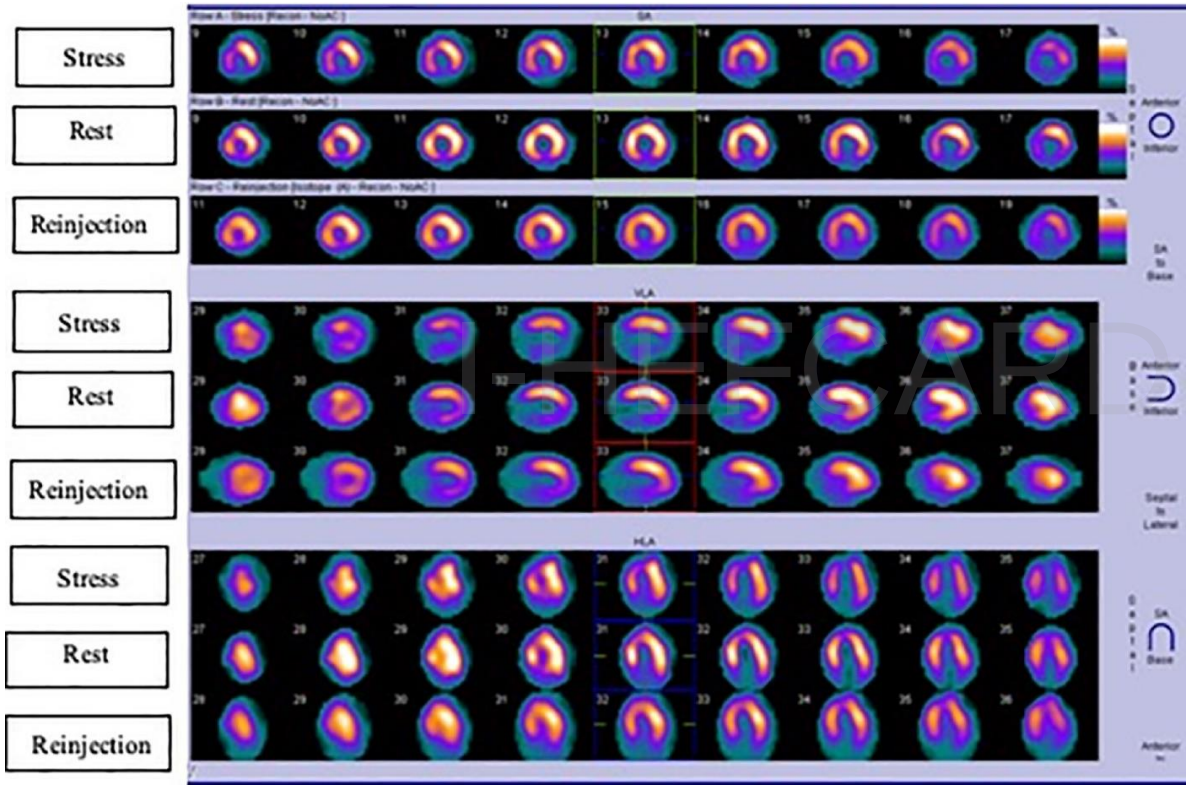
PET SCAN features to look for in ICM



The most specific pattern predicting myocardial viability and functional recovery in PET SCAN, which reflects hibernating myocardium, is referred to myocardial areas of myocardial perfusion/metabolism mismatch with reduced perfusion and hypocontractility but preserved metabolism

Cabac-Pogorevici, I., Muk, B., Rustamova, Y., Kalogeropoulos, A., Tzeis, S. and Vardas, P. (2020), Ischaemic cardiomyopathy. Pathophysiological insights, diagnostic management and the roles of revascularisation and device treatment. Gaps and dilemmas in the era of advanced technology. Eur J Heart Fail, 22: 789-799. https://doi.org/10.1002/ejhf.1747

SPECT features to look for in ICM



Single-photon emission computed tomography stress myocardial perfusion imaging study with thallium-201 and reinjection to assess thallium redistribution in a 68-year-old male patient with heart failure symptoms and left ventricular ejection fraction of 35%. Coronary angiography showed occluded right coronary artery. Images were taken after pharmacological stress with intravenous administration of dipyridamole (0.56 mg/kg), 3 h later at rest and after reinjection of 1 mCi thallium-201. There is a fixed reduced radiotracer uptake involving the basal inferior wall, which does not improve at rest and after reinjection of the radiotracer indicating non-viable myocardium with scar tissue of the basal inferior wall segments. In the remaining inferior wall segments, there is good redistribution of the radiotracer indicating viable myocardium.

Provides an estimation of resting perfusion, stress-induced ischaemia, scar tissue and cardiac systolic function.

Cabac-Pogorevici, I., Muk, B., Rustamova, Y., Kalogeropoulos, A., Tzeis, S. and Vardas, P. (2020), Ischaemic cardiomyopathy. Pathophysiological insights, diagnostic management and the roles of revascularisation and device treatment. Gaps and dilemmas in the era of advanced technology. Eur J Heart Fail, 22: 789-799. https://doi.org/10.1002/ejhf.1747

PROBLEMS IN ICM

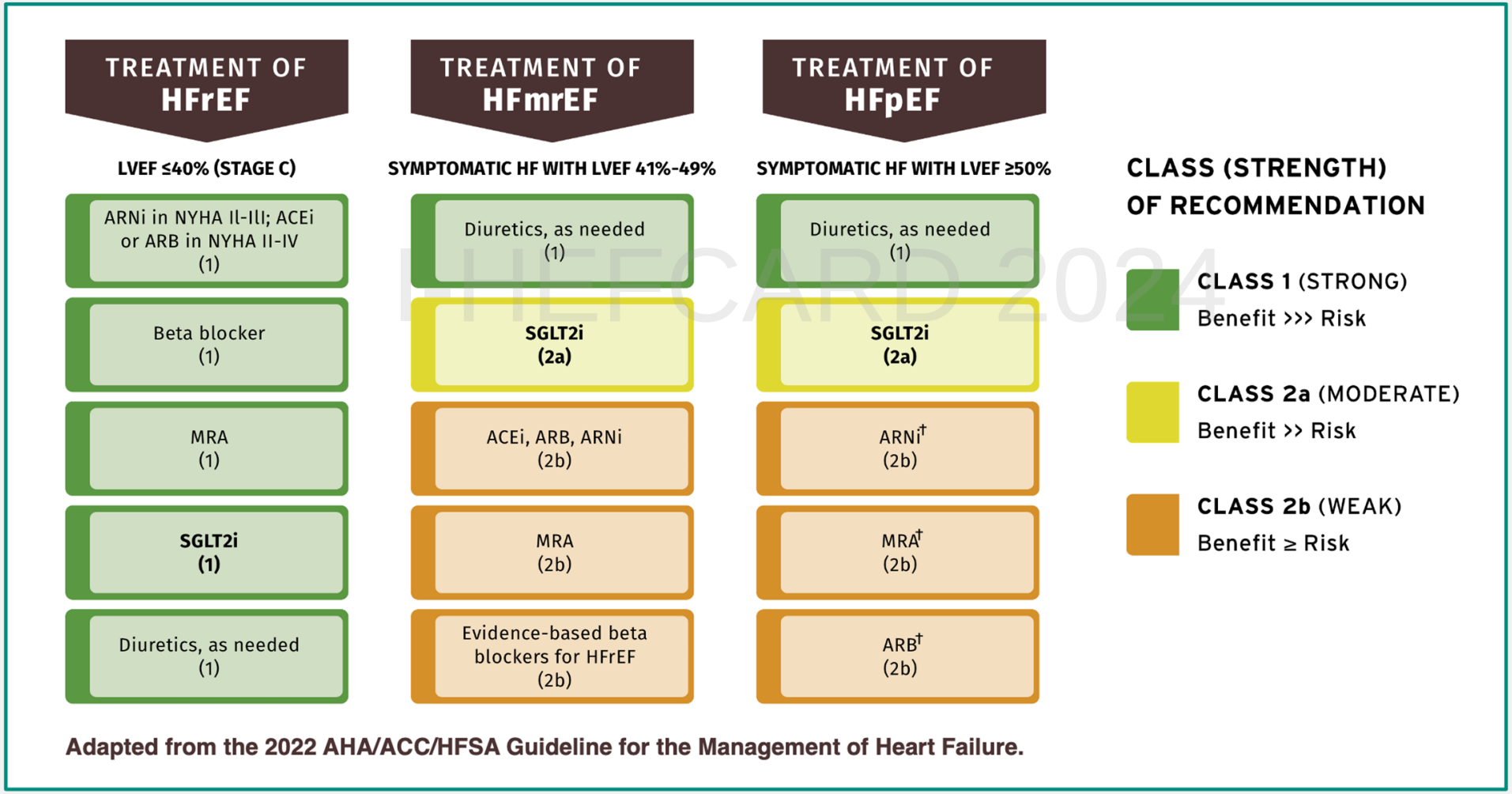
HF

Angina

Arrhytmia

Device

Pharmacological Treatment of HF



The 4th Indonesian Symposium on Heart Failure and Cardiometabolic Disease

Review Article OPEN ACCESS

In-hospital Initiation and Up-titration of Guideline-directed Medical Therapies for Heart Failure with Reduced Ejection Fraction

Zachary L Cox, Shuktika Nandkeolyar, Andrew J Johnson, JoAnn Lindenfeld, Aniket S Rali

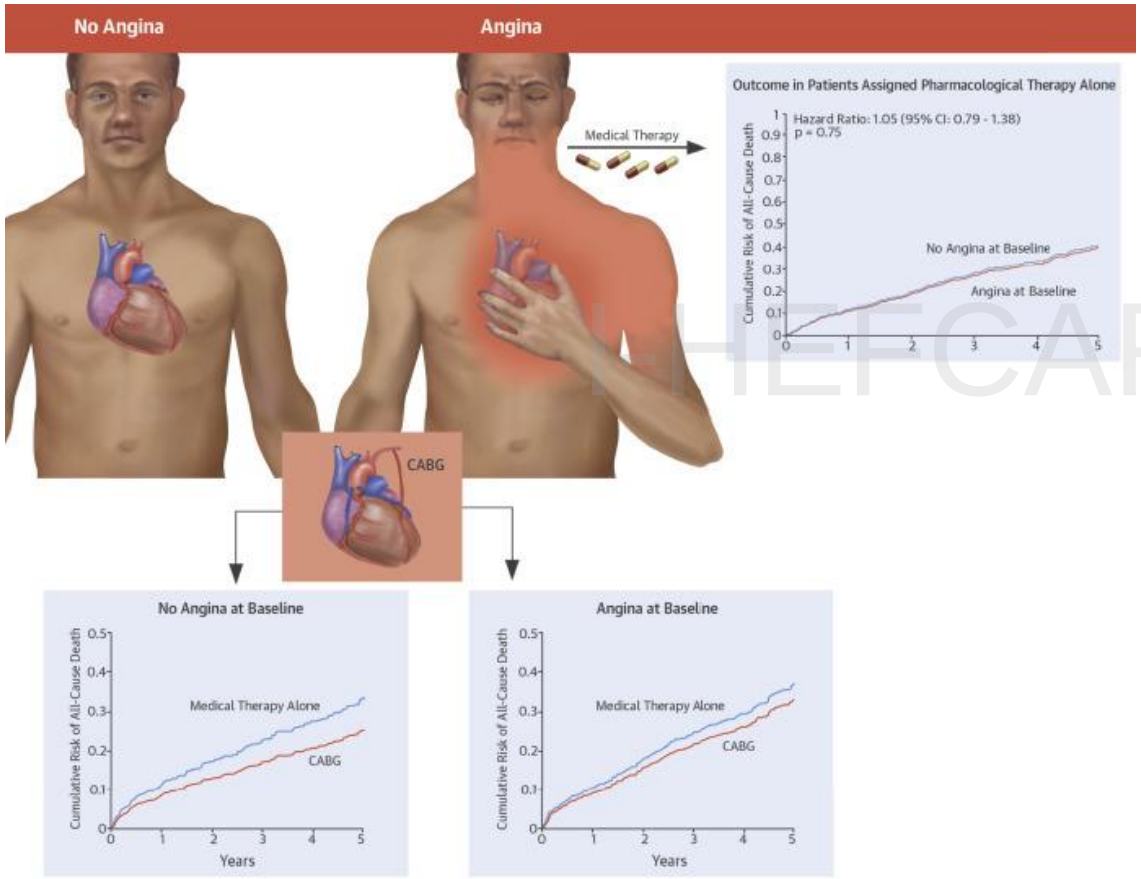
Table 1: Common Initiation and Goal Doses of Guideline-directed Medical Therapy

Medication	Initial Dose	Goal Dose	Titration Comments*	All-cause Mortality, HR [95% CI]†	Mortality Relative Risk Reduction[81]
Angiotensin-Converting Enzyme Inhibitors					
Captopril	6.25 mg 3 times daily	50 mg 3 times daily	Titrate every few days in-hospital and weekly as an outpatient	0.89 [0.82–0.96]	17%
Enalapril	2.5 mg twice daily	10 mg twice daily			
Lisinopril	2.5 mg daily	40 mg daily			
Ramipril	1.25 mg daily	10 mg daily			
Angiotensin Receptor Blocker					
Candesartan	4 mg daily	32 mg daily	Titrate every few days in-hospital and weekly as an outpatient	0.95 [0.88–1.02]	17%
Losartan	25 mg daily	150 mg daily			
Valsartan	40 mg twice daily	160 mg twice daily			
Angiotensin Receptor–Neprilysin Inhibitor					
Sacubitril/valsartan	24/26 mg–49/51 mg twice daily	97/103 mg twice daily	Titrate every week	0.75 [0.66–0.85]	16%‡
β-blockers					
Bisoprolol	1.25–2.5 mg daily	10 mg daily	Titrate every 2 weeks	0.78 [0.72–0.84]	35%
Carvedilol	3.125 mg twice daily	25–50 mg twice daily			
Metoprolol XL	25 mg daily	200 mg daily			
Mineralocorticoid Receptor Antagonists					
Spironolactone	12.5–25 mg daily	25–50 mg daily	Titration often not required	0.76 [0.67–0.85]	30%
Eplerenone	25 mg daily	25–50 mg daily			
Sodium–Glucose Cotransporter 2 Inhibitors					
Empagliflozin	10 mg daily	10 mg daily	Titration not required	0.88 [0.78–0.99]	17%
Dapagliflozin	10 mg daily	10 mg daily			
ARNI + BB + MRA + SGLT2I Quadruple Therapy					
ARNI + BB + MRA + SGLT2I				0.39 [0.31–0.49]	74%

*Titration should be as tolerated and guided by clinical parameters. †HR for all-cause mortality relative risk reduction compared with placebo from source: Tromp et al.[82] ‡Replacing ACEI/ARB.

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor–neprilysin inhibitor; BB = β-blocker; MRA = mineralocorticoid receptor antagonist; SGLT2I = sodium–glucose cotransporter 2 inhibitor.

Is Angina a Significant Problem?

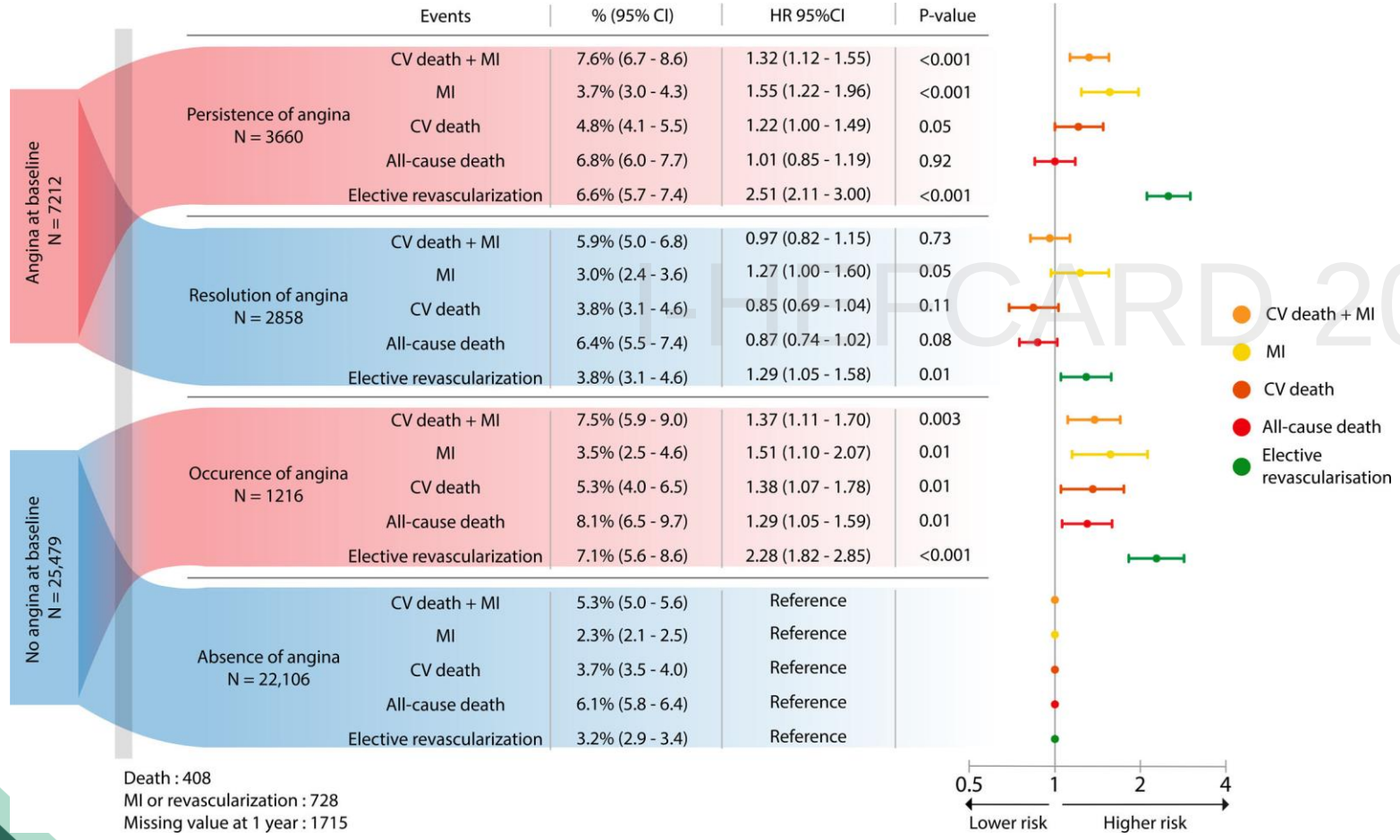


Angina does not predict all-cause mortality in medically treated patients with LV systolic dysfunction and CAD, nor does it identify patients who have a greater survival benefit from revascularization (CABG).

Jolicœur, E.M. et al. J Am Coll Cardiol. 2015; 66(19):2092-100.

E. Marc Jolicœur, Allison Dunning, Serenella Castelvecchio, Rafal Dabrowski, Myron A. Waclawiw, Mark C. Petrie, Ralph Stewart, Pardeep S. Jhund, Patrice Desvigne-Nickens, Julio A. Panza, Robert O. Bonow, Benjamin Sun, Tan Ru San, Hussein R. Al-Khalidi, Jean L. Rouleau, Eric J. Velazquez, John G.F. Cleland,. Importance of Angina in Patients With Coronary Disease, Heart Failure, and Left Ventricular Systolic Dysfunction: Insights From STICH. Journal of the American College of Cardiology 66:19. 2015. https://doi.org/10.1016/j.jacc.2015.08.882.

Is Angina a Significant Problem?



Angina affects almost one-quarter of patients with stable coronary artery disease but resolves without events or coronary revascularization in most patients. Resolution of angina within 1 year with conservative management predicted outcomes similar to lack of angina, whereas persistence or occurrence was associated with worse outcomes (cardiovascular death or myocardial infarction)

Mesnier, J. et al. (2021) 'International observational analysis of evolution and outcomes of chronic stable angina: The multinational clarify study', Circulation, 144(7), pp. 512–523. doi:10.1161/circulationaha.121.054567.

Ant gina

Ranolazine Haemodynamic Effect

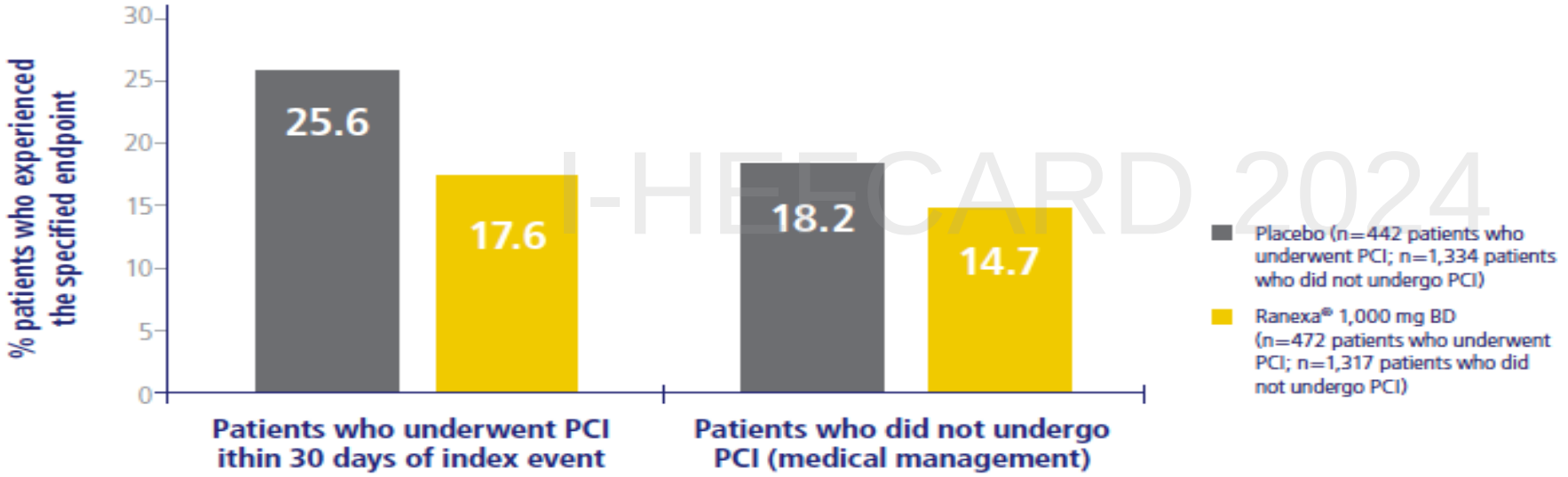
Anti-angina effect of Ranolazine do not depend upon changes on heart rate, blood pressure or vasodilation

* normal ejection fraction; ** heart rate > 70 bpm
BB = beta blocker; CCB = calcium channel blocker; DHP = dihydropyridine; SBP = systolic blood pressure

Manolis AJ, Poulimenos LE, Ambrosio G, Kallistratos MS, Lopez-Sendon J, Dechend R, Mancia G, Camm AJ. Medical treatment of stable angina: A tailored therapeutic approach. Int J Cardiol. 2016 Oct 1;220:445-53.

MERLIN-TIMI 36: adding ranolazine reduced the risk of recurrent ischemia with or without PCI

Patients experiencing recurrent ischemia with or without PCI



HR	0.69	0.81
95% CI	0.51–0.92	0.66–0.99
p=value	0.01	0.03

There was no evidence for heterogeneity in the benefit of adding ranolazine between patients who did, and who did not undergo PCI (p interaction=0.39).

Ranolazine significantly reduced the risk of recurrent ischemia with or without PCI vs placebo in patients with ACS who had prior chronic angina[1]

1. Modified from Gutiérrez JA et al. Clin Cardiol 2015;38:469–75 (from figure 2).

Angina..

PCI or CABG?

When is 'appropriate' for PCI Revascularization in Angina?

FIGURE 2 Appropriateness Criteria for PCI in Patients With Intermediate- and High-Risk Noninvasive Testing

Intermediate-Risk and High-Risk Noninvasive Risk Stratification includes resting mild/moderate LVSD (LVEF 35%-49%) and severe LVSD (LVEF <35%) respectively not readily explained by noncoronary causes

Angiographic Presentation	No Symptoms	Symptoms (0 AA Drugs)	Symptoms (1 AA Drug)	Symptoms (≥2 AA Drugs)
1-vessel disease	M	M	M	A
2-vessel disease (no proximal LAD)	M	M	A	A
2-vessel disease with proximal LAD (regardless of diabetes)	M	A	A	A
3-vessel disease of low complexity (i.e., SYNTAX ≤22) and no diabetes	M	A	A	A
3-vessel disease of low complexity (i.e., SYNTAX ≤22) and diabetes	M	M	A	A
3-vessel disease of high complexity (i.e., SYNTAX >22) (regardless of diabetes)	M	M	M	M

The 2017 appropriateness criteria for revascularization do not provide a recommendation for PCI in patients with LVSD due to insufficient data. Nonetheless, resting LVEF <35% and LVEF 35% to 49% not readily explained by noncoronary causes are deemed high- and intermediate-risk findings respectively on noninvasive study. PCI in these settings has been deemed "appropriate" or "maybe appropriate" depending on symptoms, antianginal therapy, presence of diabetes mellitus, and angiographic presentation. Adapted from Patel et al. (49). A = appropriate; AA = antianginal; CAD = coronary artery disease; LAD = left anterior descending artery; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; M = maybe appropriate; PCI = percutaneous coronary intervention.

Parikh, P.B. et al. (2021) 'Impact of percutaneous coronary intervention on outcomes in patients with heart failure', Journal of the American College of Cardiology, 77(19), pp. 2432–2447. doi:10.1016/j.jacc.2021.03.310.

Recent Study Summary of Revascularization as part of ICM Management

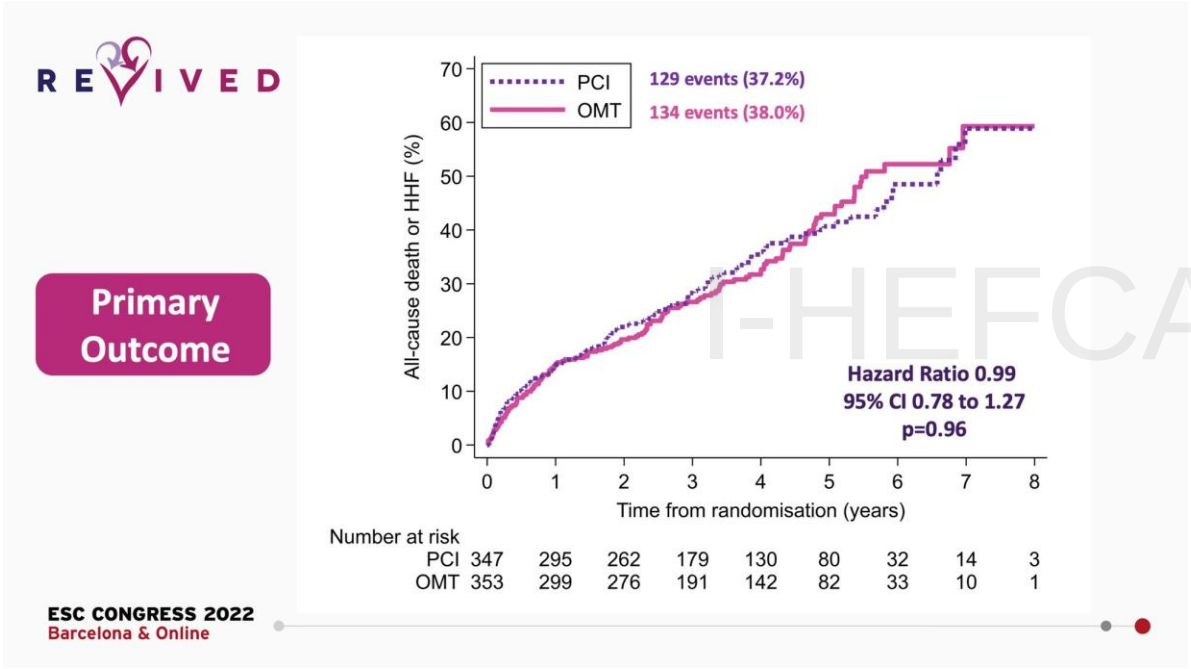
Table 1: Randomised Controlled Trials on Revascularisation in Heart Failure with Reduced Ejection Fraction Patients with Ischaemic Cardiomyopathy

	HEART[9]	PARR-2[10,11]	STICH[12,13]	REVIVED-BCIS2[14]
Number of enrolled patients	138	430	1,212	700
Primary outcome	All-cause mortality	Cardiac death, MI or hospitalisation for cardiac cause	All-cause mortality	All-cause mortality, hospitalisation for HF
LVEF at enrolment	24%	27%	28%	27%
Revascularisation method	CABG and PCI	CABG and PCI	CABG	PCI
Follow-up (median)	59 months	5 years	4.7 years[12] 9.8 years[13]	41 months
Outcome	No significant benefit of revascularisation over OMT	No significant difference between PET-guided and standard strategies	No benefit of CABG over OMT at 5 years After 10 years CABG was associated with a lower all-cause mortality than OMT (0.72; 95% CI [0.64–0.82]; p<0.001)	No significant benefit of revascularisation over OMT

CABG = coronary artery bypass graft; LVEF = left ventricular ejection fraction; OMT = optimal medical therapy; PCI = percutaneous coronary intervention.

Bernhard Haring, Michael Böhm, Coronary Revascularisation in Heart Failure with Reduced Ejection Fraction, Journal of Asian Pacific Society of Cardiology 2024;3:e14

REVIVED trial



Author conclusion: "Compared with OMT alone, PCI neither reduced the occurrence of death or hospitalization for heart failure nor influenced the degree of left ventricular recovery in patients with severe ischemic left ventricular dysfunction"

STICH trial

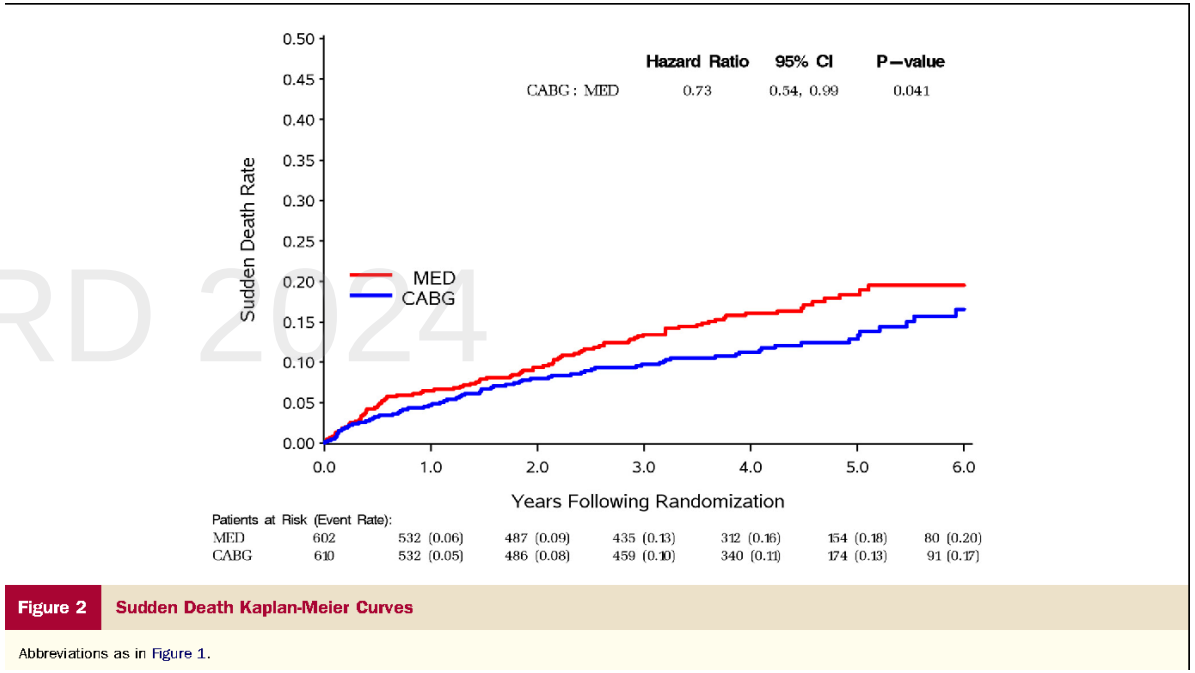


Figure 2 Sudden Death Kaplan-Meier Curves

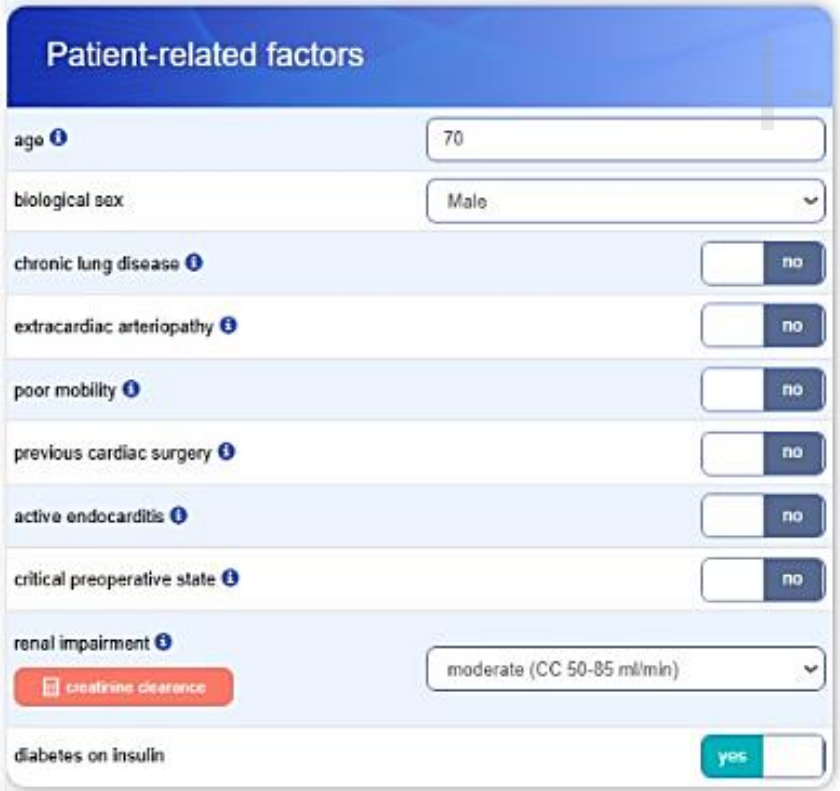
Abbreviations as in Figure 1.

Author conclusion: "The STICH trial showed that in patients with ischemic cardiomyopathy, coronary artery bypass grafting (CABG) + medical therapy resulted in higher mortality at 30 days, but with a significant improvement in long-term mortality (out to 10 years) compared with medical therapy alone."

Perera, D. *et al.* (2023d) 'Arrhythmia and death following percutaneous revascularization in ischemic left ventricular dysfunction: Prespecified analyses from the revived-BCIS2 trial', *Circulation*, 148(11), pp. 862–871. doi:10.1161/circulationaha.123.065300.
Velazquez EJ, Lee KL, Jones RH, Al-Khalidi HR, Hill JA, Panza JA, Michler RE, Bonow RO, Doenst T, Petrie MC, Oh JK, She L, Moore VL, Desvigne-Nickens P, Sopko G, Rouleau JL; STICHES Investigators. Coronary-Artery Bypass Surgery in Patients with Ischemic Cardiomyopathy. N Engl J Med. 2016 Apr 21;374(16):1511-20. doi: 10.1056/NEJMoa1602001. Epub 2016 Apr 3. PMID: 27040723; PMCID: PMC4938005.

EURO SCORE - II

- The European System for Cardiac Operative Risk Evaluation **(EuroSCORE),** which have been tested specifically in STICH patients, is a **cardiac risk model that would appear suitable to predict the 30-day postoperative mortality after cardiac surgery.** It was first introduced in 1999 and renewed recently in 2012.



<4 % : low surgical risk
>4% : high surgical risk

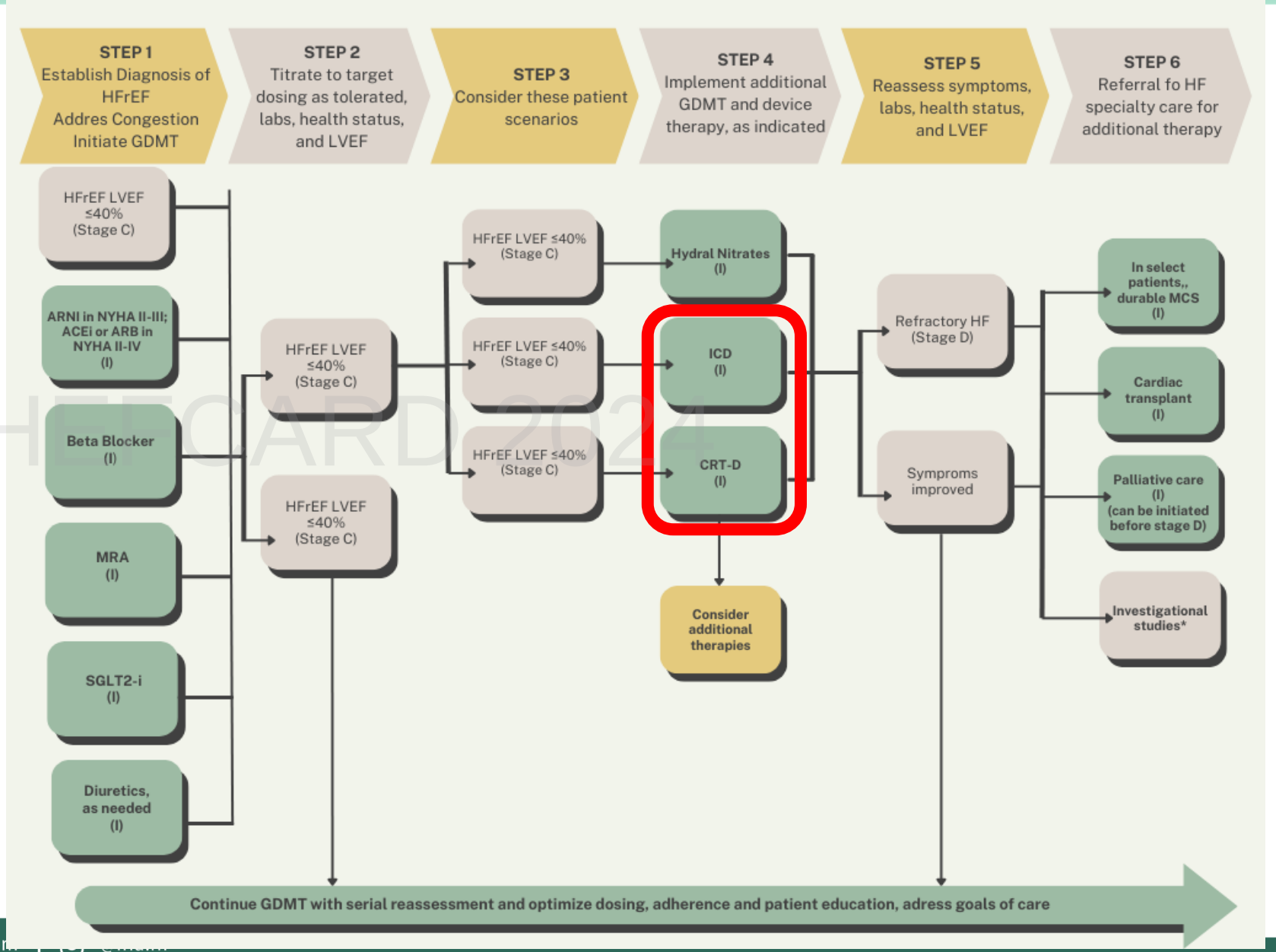
Prevention of IHD as the basis of ICM Prevention

Mesnier, J. et al. (2021) 'International observational analysis of evolution and outcomes of chronic stable angina: The multinational clarify study', Circulation, 144(7), pp. 512–523. doi:10.1161/circulationaha.121.054567.

Device Therapy Recommendation on HF following CAD

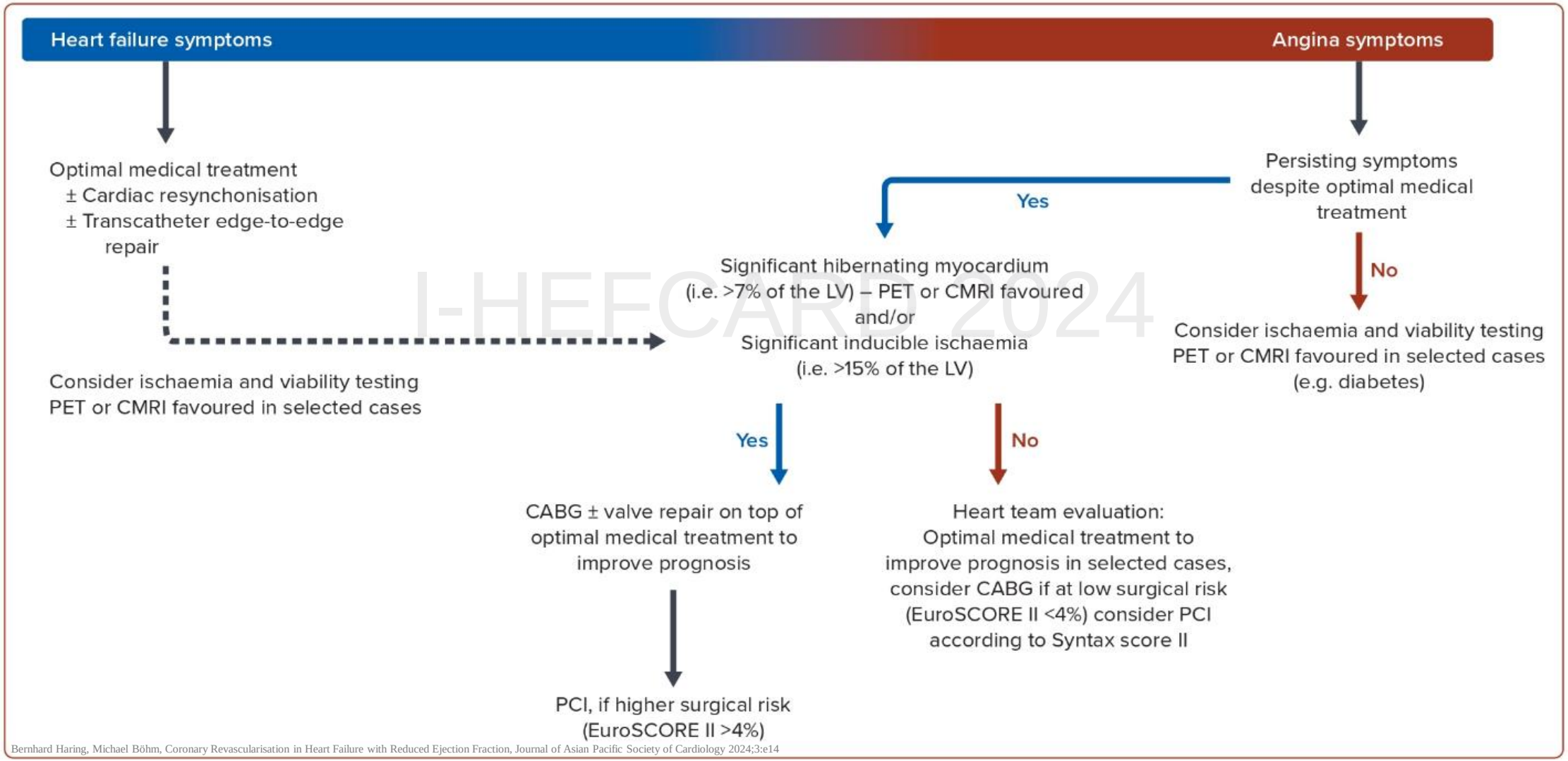
Device Therapy: Additional treatment for HF Patients

(refractory to maximally tolerated medical therapy)



Yancy CW, Jessup M, Bozkurt B, Butler J, Casey DE Jr, Colvin MM, Drazner MH, Filippatos GS, Fonarow GC, Givertz MM, Hollenberg SM, Lindenfeld J, Masoudi FA, McBride PE, Peterson PN, Stevenson LW, Westlake C. 2017 ACC/AHA/HFSA Focused Update of the 2013 ACCF/AHA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Failure Society of America. Circulation. 2017 Aug 8;136(6):e137-e161. doi: 10.1161/CIR.0000000000000509. Epub 2017 Apr 28. PMID: 28455343.

Summary of 'proposed algorithm' on Managing ICM



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CABG = coronary artery bypass graft; CMRI = cardiac MRI; LV = left ventricle; PCI = percutaneous coronary intervention.

TAKE HOME MESSAGE

- ICM represents an interesting clinical puzzle, relating to the vast spectrum of the underlying pathophysiological entities and clinical manifestations
- Both diagnosis and treatment remain a challenge
- Major problems : HF, angina, device
- HF treatment : 4 pillars
- Angina treatment : Beta blocker , Ranolazine
- Anti-angina effect of Ranolazine do not depend upon changes on heart rate, blood pressure or vasodilation
- Individualised approach should be implemented by the HEART TEAM → in the decision making process : PCI –CABG – ICD -CRT

THANK YOU