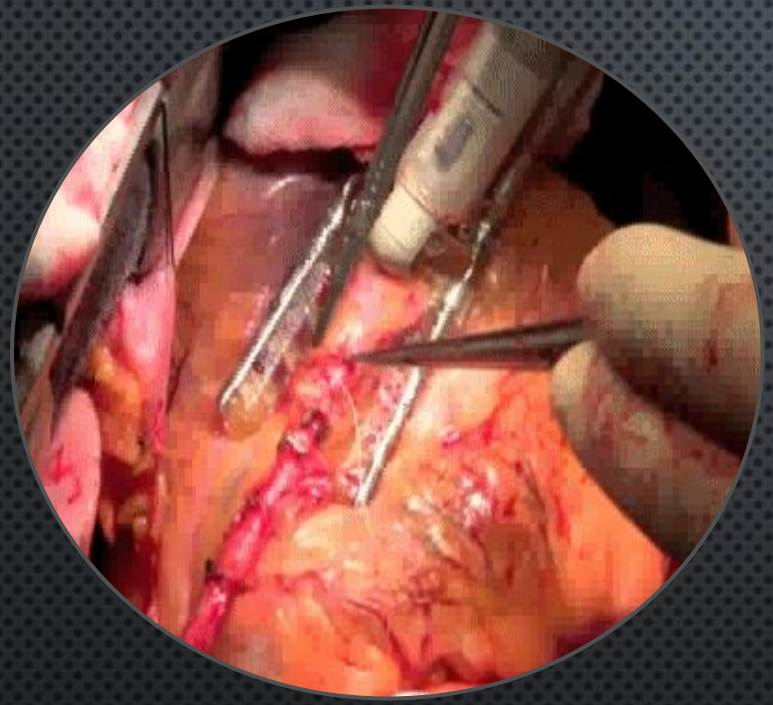
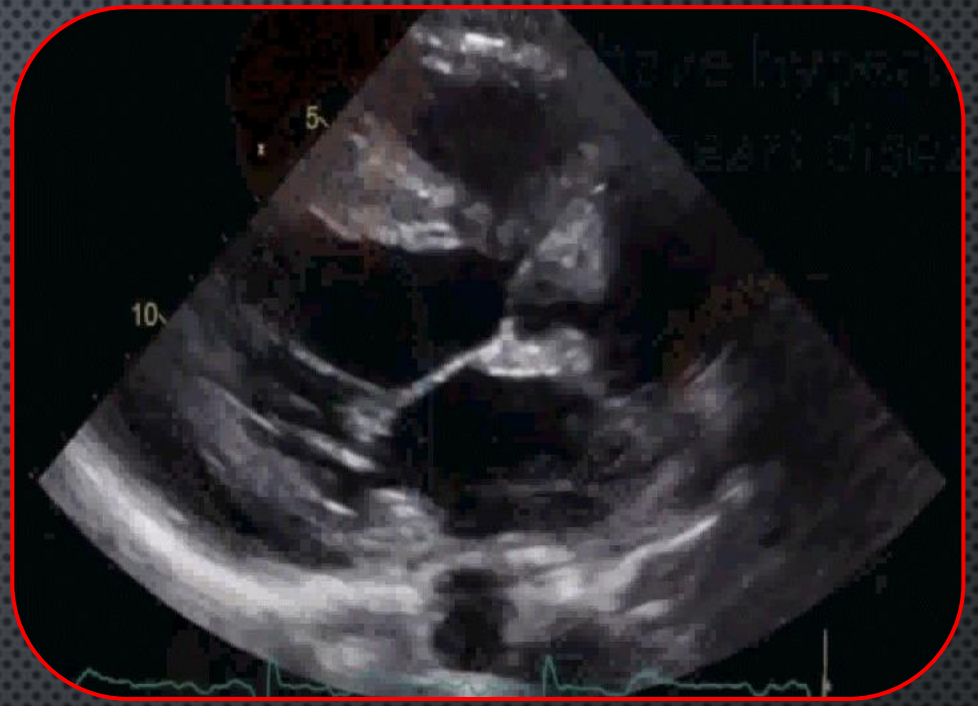
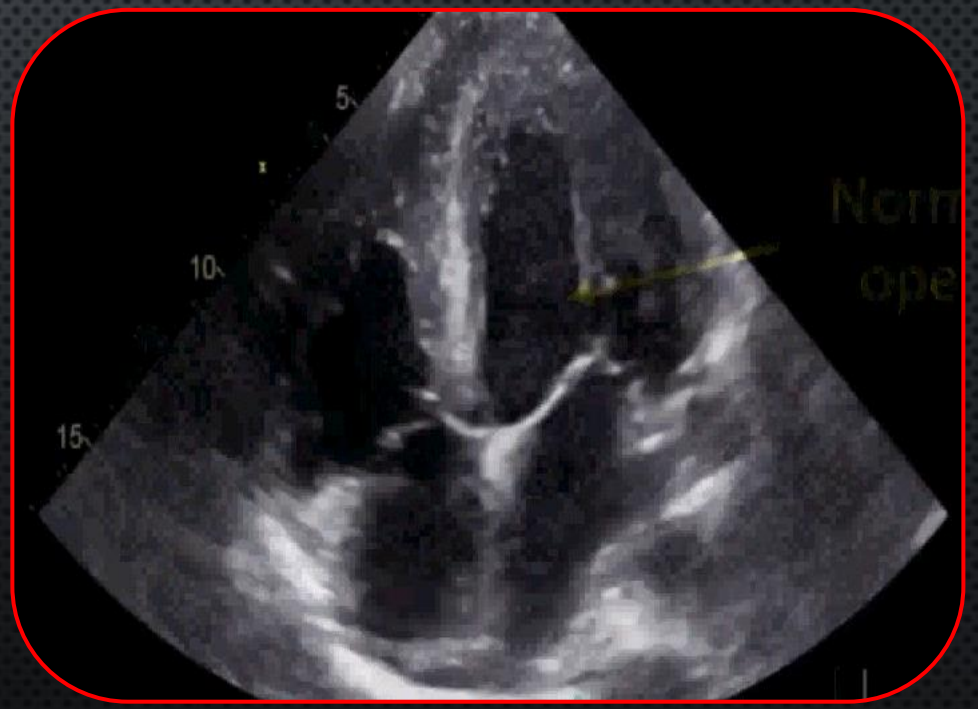
SGLT2 inhibition and heart failure



What is the most common





Robert Chilton, DO, FACC, FAHA, MACOI
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Introduction

Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes in the Collaborative Atorvastatin Diabetes Study (CARDS): multicentre randomised placebo-controlled trial

Helen M Colhoun, D John Betteridge, Paul N Durrington, Graham A Hitman, H Andrew W Neil, Shona J Livingstone, Margaret J Thomason, Michael I Mackness, Valentine Charlton-Menys, John H Fuller, on behalf of the CARDS investigators*

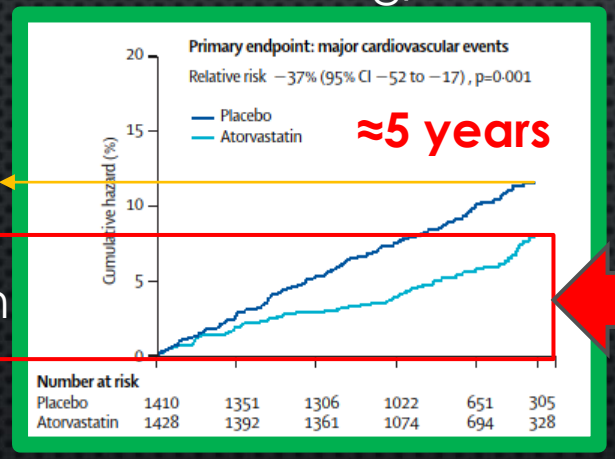
Summary

Background Type 2 diabetes is associated with a substantially increased risk of cardiovascular disease, but the role of lipid-lowering therapy with statins for the primary prevention of cardiovascular disease in diabetes is inadequately defined. We aimed to assess the effectiveness of atorvastatin 10 mg daily for primary prevention of major cardiovascular events in patients with type 2 diabetes without high concentrations of LDL-cholesterol.

Methods 2838 patients aged 40–75 years in 132 centres in the UK and Ireland were randomised to placebo (n=1410) or atorvastatin 10 mg daily (n=1428). Study entrants had no documented previous history of cardiovascular disease, an LDL-cholesterol concentration of 4·14 mmol/L or lower, a fasting triglyceride amount of 6·78 mmol/L or less, and at least one of the following: retinopathy, albuminuria, current smoking, or hypertension. The primary endpoint was time to first occurrence of the following: acute coronary heart disease events, coronary revascularisation, or stroke. Analysis was by intention to treat.

colhoun2004.pdf

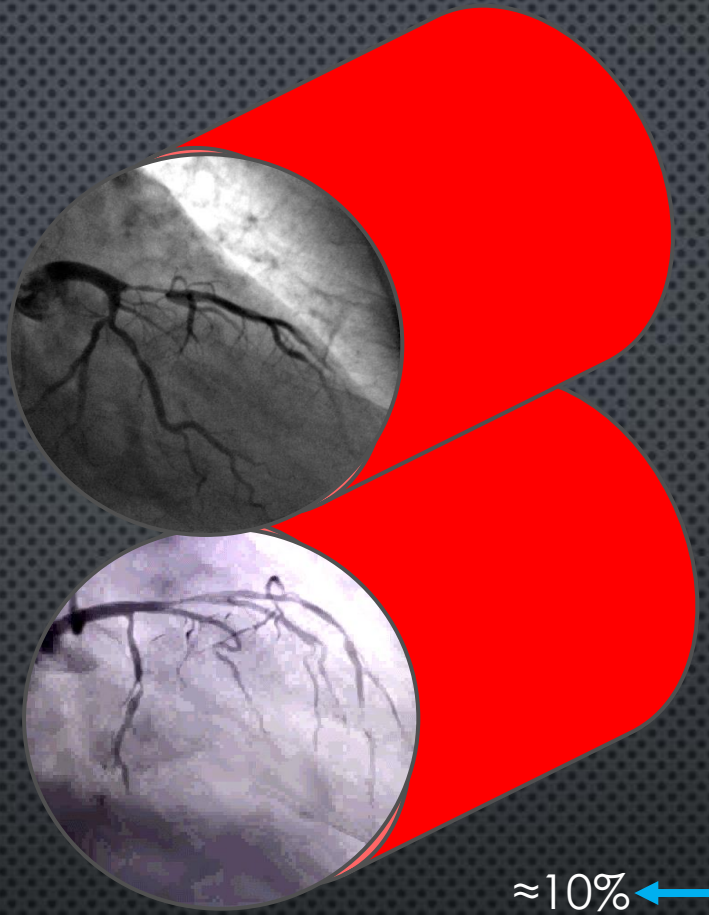
<LDL 160 mg/dl
<TGL 600 mg/dl



Statin

Primary prevention

≈8%



Still had event on statin

≈10%

ORIGINAL ARTICLE

Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease

John C. LaRosa, M.D., Scott M. Grundy, M.D., Ph.D., David D. Waters, M.D., Charles Shear, Ph.D., Philip Barter, M.D., Ph.D., Jean-Charles Fruchart, Pharm.D., Ph.D., Antonio M. Gotto, M.D., D.Phil., Heiner Greten, M.D., John J.P. Kastelein, M.D., James Shepherd, M.D., and Nanette K. Wenger, M.D., for the Treating to New Targets (TNT) Investigators*

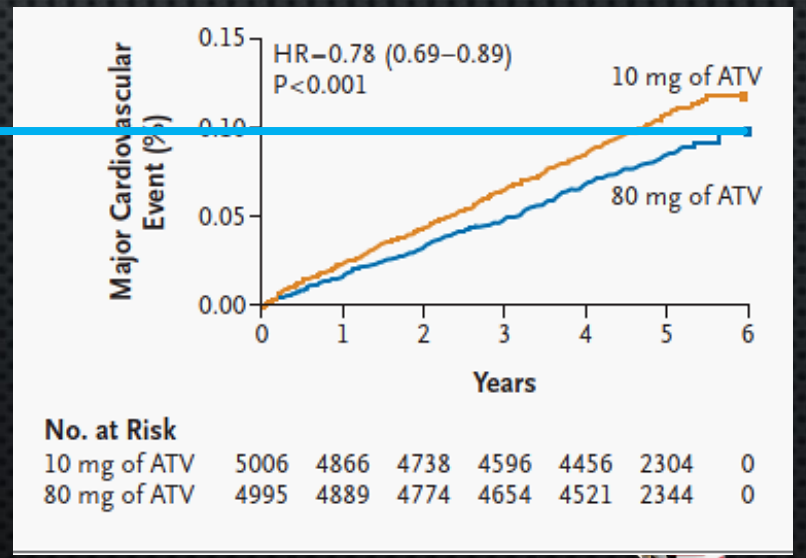
ABSTRACT

BACKGROUND

Previous trials have demonstrated that lowering low-density lipoprotein (LDL) cholesterol levels below currently recommended levels is beneficial in patients with acute coronary syndromes. We prospectively assessed the efficacy and safety of lowering LDL cholesterol levels below 100 mg per deciliter (2.6 mmol per liter) in patients with stable coronary heart disease (CHD).

METHODS

A total of 10,001 patients with clinically evident CHD and LDL cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) were randomly assigned to double-blind therapy and received either 10 mg or 80 mg of atorvastatin per day. Patients were followed for a median of 4.9 years. The primary end point was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non–procedure-relat-

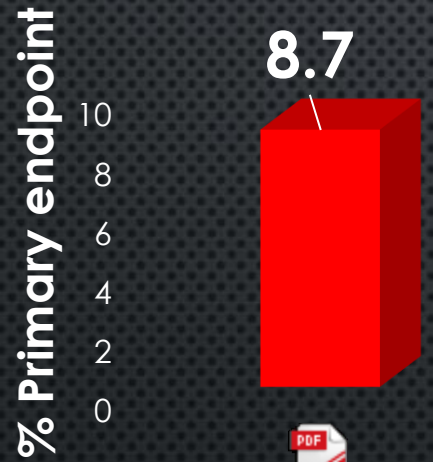


Secondary prevention

larosa2005.pdf

Beyond statins

5 years TNT trial best results secondary prevention A-80

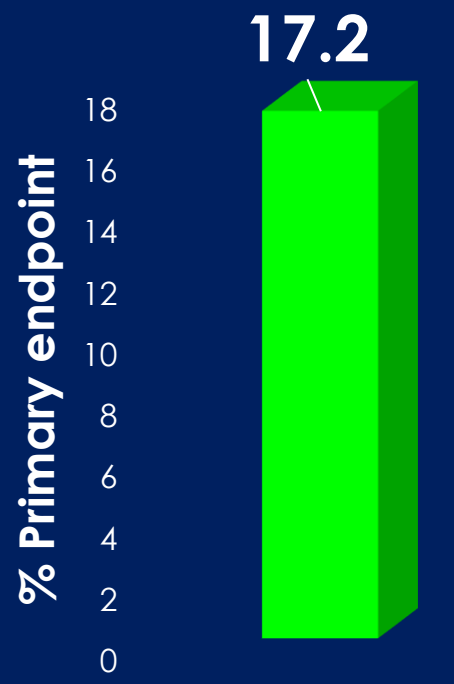


larosa2005.pdf

Death from CHD, **nonfatal non–procedure-related myocardial infarction**, or resuscitation after cardiac arrest

NOT same type of patients

5 years REDUCE IT best results secondary prevention



≈90% statins

Icosapent ethyl 2 gms bid

216 Trig entry

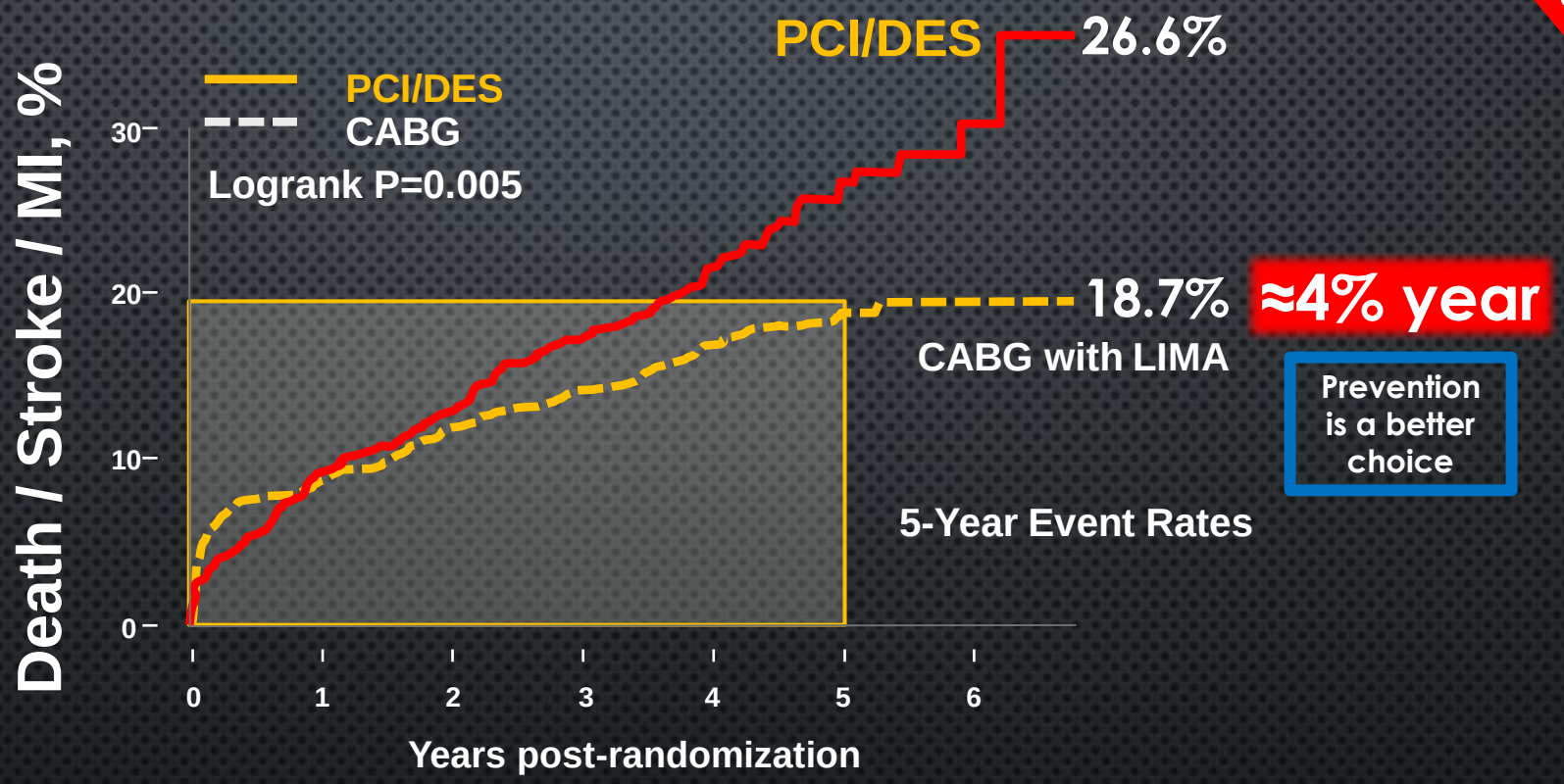
Death from CHD, **nonfatal myocardial infarction**, nonfatal stroke, coronary revascularization, or unstable angina

bhatt2018.pdf

N Engl J Med 2019;380:11-22.
DOI: 10.1056/NEJMoa1812792

PRIMARY OUTCOME – DEATH / STROKE / MI

Diabetes



REVASCULARIZATION

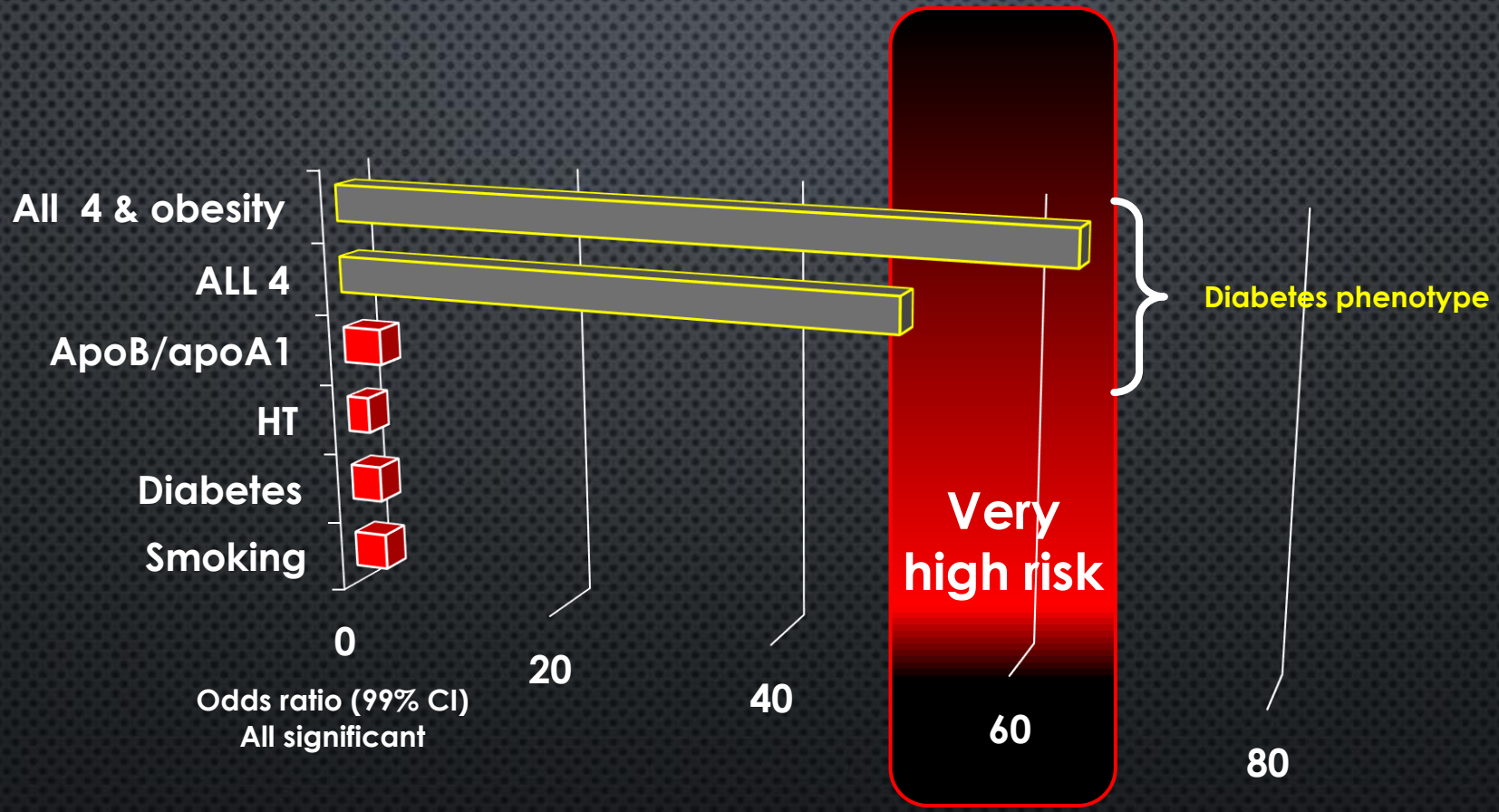
≈4% year

Prevention is a better choice

N Engl J Med 2012; 367:2375-2384

FREEDOM trial

INTERHEART trial: 9 modifiable risk factors account for 90% of myocardial infarctions



Adapted from Lancet 2004; 364: 937–52

Definition

DEFINITION OF HEART FAILURE

Heart failure is not a single pathological diagnosis, but a **clinical syndrome** consisting of

Symptoms
Breathlessness, ankle swelling, and fatigue

Signs
elevated jugular venous pressure, pulmonary crackles, and peripheral edema

Elevated intracardiac pressures and/or inadequate cardiac output

ehab368 (1).pdf

Identification of the etiology of the underlying cardiac dysfunction is mandatory in the diagnosis of HF

Myocardial dysfunction: either systolic, diastolic

Endocardium

Valves (aortic stenosis)

Electrical

Pericardial disease

Others?

Table 3 **Definition of heart failure with reduced ejection fraction, mildly reduced ejection fraction and preserved ejection fraction**

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF ≤40%	LVEF 41–49%[b]	LVEF ≥50%
	3	–	–	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures, including raised natriuretic peptides[c]

Increases with age, renal disease

ehab368 (1).pdf

IMPORTANT

Patients with non-CV disease, e.g. anemia, pulmonary, renal, thyroid, or hepatic disease may have symptoms and signs very similar to those of HF,

but in the absence of cardiac dysfunction, they do **not** fulfil the criteria for HF.

The ESC Long-Term Registry, in the outpatient setting, reports that 60% have HFrEF, 24% have HFmrEF, and 16% have HFpEF. (50% women)

Eur J Heart Fail 2017;19:15741585

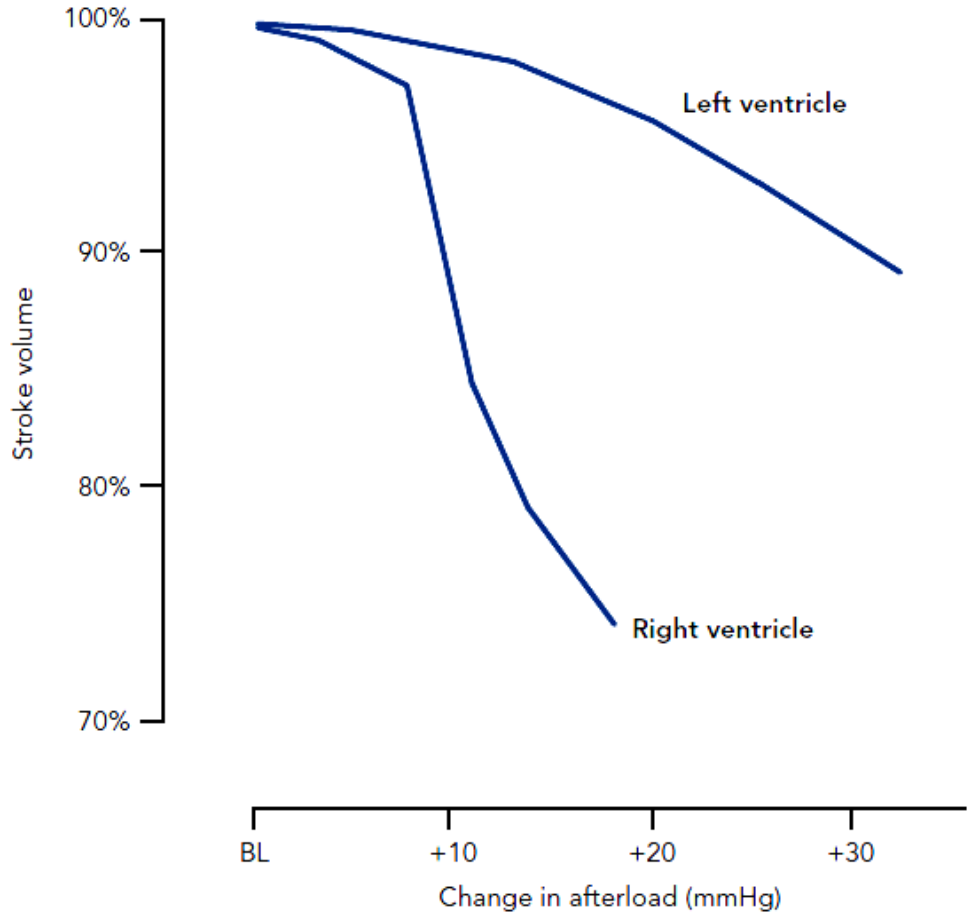
ehab368 (1).pdf

Right ventricular dysfunction

RV mechanics and function are altered in the setting of either **pressure** or **volume overload**

Chronic RV failure is LV dysfunction-induced pulmonary hypertension

Figure 1: Effect of Increasing Afterload on Stroke Volume of the Right and Left Ventricles



Right ventriclar stroke volume decreases rapidly when afterload is increased, in contrast to left ventricular stroke volume which is maintained against an augmented afterload.
BL = baseline.

DOI:https://doi.org/10.15420/cfr.2019.15.2

Recommended diagnostic tests in all patients with suspected chronic heart failure

Recommendations	Class[a]	Level[b]
BNP/NT-proBNP[c]	I	B
12-lead ECG	I	C
Transthoracic echocardiography	I	C
Chest radiography (X-ray)	I	C
Routine blood tests for comorbidities, including full blood count, urea and electrolytes, thyroid function, fasting glucose and HbA1c, lipids, iron status (TSAT and ferritin)	I	C

BNP = B-type natriuretic peptide; ECG = electrocardiogram; HbA1c = glycated haemoglobin; NT-proBNP = N-terminal pro-B-type natriuretic peptide; TSAT = transferrin saturation.

[a]Class of recommendation.

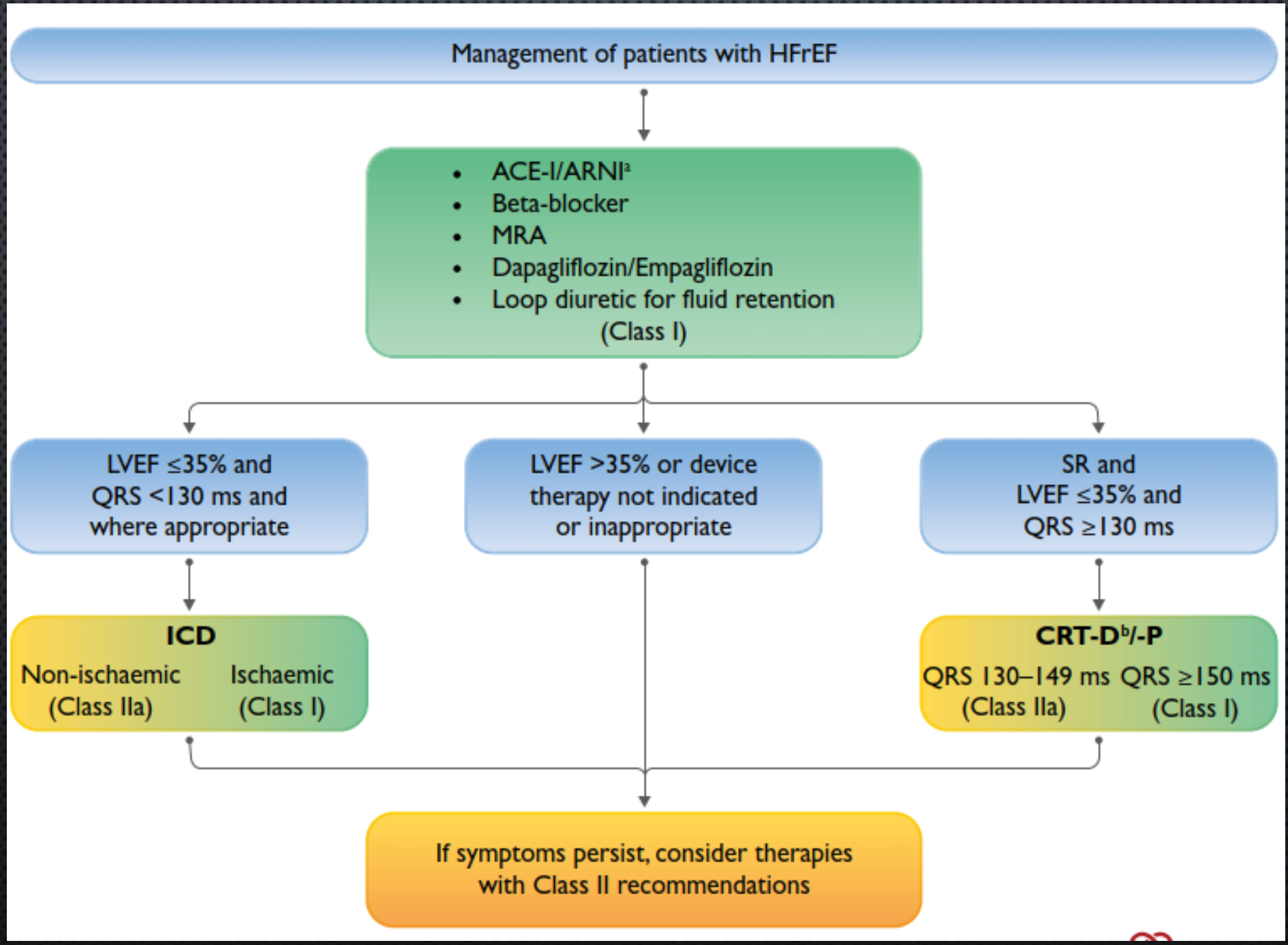
[b]Level of evidence.

[c]References are listed in section 4.2 for this item.

Recommendations for specialized diagnostic tests for selected patients with chronic heart failure to detect reversible/treatable causes of heart failure

Recommendations	Class[a]	Level[b]
CMR		
CMR is recommended for the assessment of myocardial structure and function in those with poor echocardiogram acoustic windows.	I	C
CMR is recommended for the characterization of myocardial tissue in suspected infiltrative disease, Fabry disease, inflammatory disease (myocarditis), LV non-compaction, amyloid, sarcoidosis, iron overload/haemochromatosis.	I	C
CMR with LGE should be considered in DCM to distinguish between ischaemic and non-ischaemic myocardial damage.	IIa	C
Invasive coronary angiography (in those who are considered eligible for potential coronary revascularization)		
Invasive coronary angiography is recommended in patients with angina despite pharmacological therapy or symptomatic ventricular arrhythmias.[5]	I	B
Invasive coronary angiography may be considered in patients with HFrEF with an intermediate to high pre-test probability of CAD and the presence of ischaemia in non-invasive stress tests.[89]	IIb	B
Non-invasive testing		
CTCA should be considered in patients with a low to intermediate pre-test probability of CAD or those with equivocal non-invasive stress tests in order to rule out coronary artery stenosis.	IIa	C
Non-invasive stress imaging (CMR, stress echocardiography, SPECT, PET) may be considered for the assessment of myocardial ischaemia and viability in patients with CAD who are considered suitable for coronary revascularization.[90–93]	IIb	B
Exercise testing may be considered to detect reversible myocardial ischaemia and investigate the cause of dyspnoea.[94–96]	IIb	C
Cardiopulmonary exercise testing		
Cardiopulmonary exercise testing is recommended as a part of the evaluation for heart transplantation and/or MCS.[94–96]	I	C
Cardiopulmonary exercise testing should be considered to optimize prescription of exercise training.[94–96]	IIa	C
Cardiopulmonary exercise testing should be considered to identify the cause of unexplained dyspnoea and/or exercise intolerance.[94–96]	IIa	C
Right heart catheterization		
Right heart catheterization is recommended in patients with severe HF being evaluated for heart transplantation or MCS.	I	C

Treatment


Management of patients with HFrEF
ACE-I/ARNI[a]
Beta-blocker
MRA
Dapagliflozin/Empagliflozin
Loop diuretic for fluid retention
(Class I)
LVEF ≤35% and QRS <130 ms and where appropriate
LVEF >35% or device therapy not indicated or inappropriate
SR and LVEF ≤35% and QRS ≥130 ms
ICD
Non-ischaemic (Class IIa)
Ischaemic (Class I)
CRT-D[b]/-P
QRS 130–149 ms (Class IIa)
QRS ≥150 ms (Class I)
If symptoms persist, consider therapies with Class II recommendations

Pharmacological treatments indicated in patients with (NYHA class II–IV) heart failure with reduced ejection fraction (LVEF ≤40%)

Recommendations	Class[a]	Level[b]
An ACE-I is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[110–113]	I	A
A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death.[114–120]	I	A
An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[121,122]	I	A
Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death.[108,109]	I	A
Sacubitril/valsartan is recommended as a replacement for an ACE-I in patients with HFrEF to reduce the risk of HF hospitalization and death.[105]	I	B

ACE-I = angiotensin-converting enzyme inhibitor; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association.

[a]Class of recommendation.

[b]Level of evidence.

Management of HFrEF

To reduce mortality - for all patients

- ACE-I/ARNI
- BB
- MRA
- SGLT2i

To reduce HF hospitalization/mortality - for selected patients

Volume overload

- Diuretics

SR with LBBB ≥ 150 ms

- CRT-P/D

SR with LBBB 130–149 ms or non LBBB≥ 150 ms

- CRT-P/D

Ischaemic aetiology

- ICD

Non-ischaemic aetiology

- ICD

Atrial fibrillation

- Anticoagulation

Atrial fibrillation

- Digoxin
- PVI

Coronary artery disease

- CABG

Iron deficiency

- Ferric carboxymaltose

Aortic stenosis

- SAVR/TAVI

Mitral regurgitation

- TEE MV Repair

Heart rate SR>70 bpm

- Ivabradine

Black Race

- Hydralazine/ISDN

ACE-I/ARNI intolerance

- ARB