Decoding the Rhythm of your Heart: A Personalised Cardiovascular Risk Assessment.

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Disclosure Information

I have no actual or potential conflict of interest in relation to this presentation.

Speaker's Bureau: MSD, Novartis, Servier, Pfizer, Astra Zeneca , Bayer and Boehringer Ingelheim.

What is Coronary artery disease

* Coronary artery disease is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive.

* The disease can have long, stable periods but can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion.

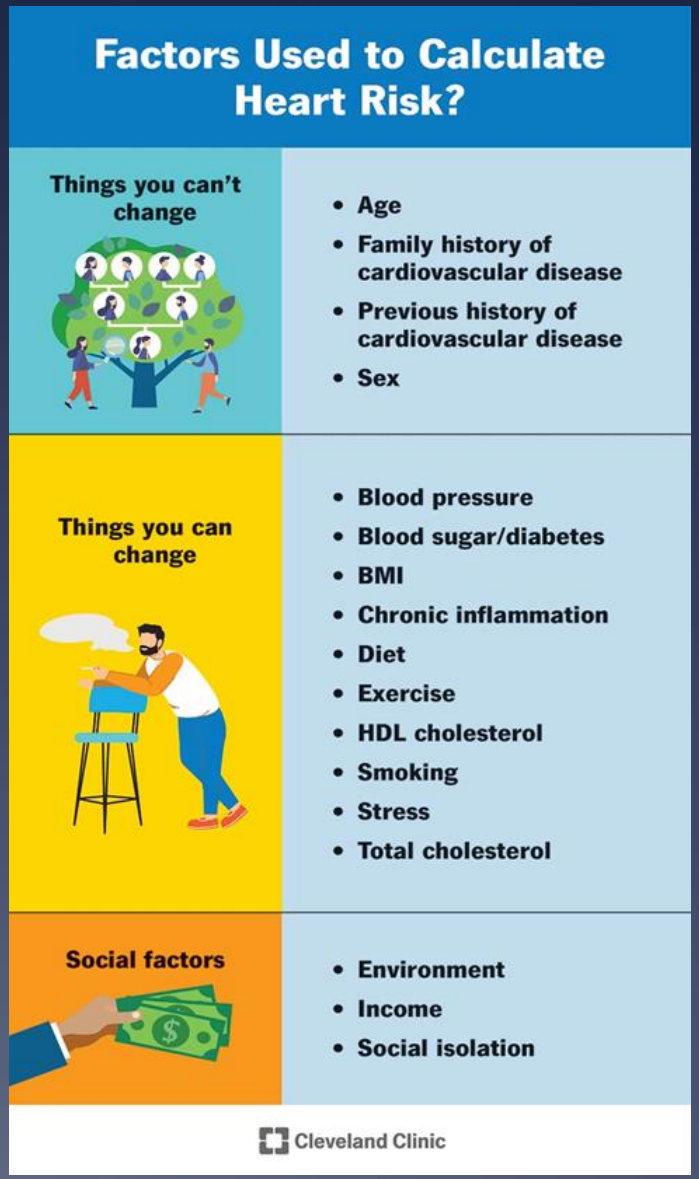
* However, the disease is chronic, most often progressive, and hence serious, even in clinically apparently silent periods.

* The dynamic nature of the CAD process results in various clinical presentations which can be categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS).

* This process can be modified by lifestyle adjustments, pharmacological therapies, and invasive interventions designed to achieve disease stabilization or regression.

Risk for Cardiovascular Events

* Aging, Obesity, diabetes, High Blood pressure, Smoking, High cholesterol levels and chronic kidney disease (CKD) are each associated with a high burden of cardiovascular disease (CVD) morbidity and mortality.
* They commonly co-occur and disproportionately affect disenfranchised populations (eg, under represented racial and ethnic groups).
* Absolute risk assessment for CVD remains the corner stone of clinical primary prevention efforts.



Importance of major risk factors for coronary heart disease

* In an analysis of 3 large prospective studies, nearly all individuals (92% of men and 87% of women) who experienced a nonfatal CHD event had at least *1 clinically elevated major risk factor (which was defined as elevated total cholesterol [≥6.22 mmol/L], systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, current cigarette smoking, or diabetes) before the event*. Similar estimates were observed for fatal CHD events.

* *VIRGO study* (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients), a prospective observational cohort of individuals 18 to 55 years of age who presented with premature onset myocardial infarction, the population-attributable fraction for traditional risk factors was 85%.

Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart .disease events. JAMA. 2003;290:891–897

Judith H. Lichtman et al: Role of Gender on Outcomes of Young AMI Patients (VIRGO) Study. Cardiovascular Quality and Outcomes. . Circulation. Volume 3, Issue 6, November 2010; Pages 684-693

Importance of major risk factors for coronary heart disease

* INTERHEART study…. A global case-control study including 27,098 participants from 52 countries, 6787 of whom were women.

* Nine modifiable risk factors were associated with MI in women and men. *Hypertension, diabetes, , physical activity, moderate alcohol use, association of abnormal lipids, current smoking, abdominal obesity, high risk diet, and psychosocial stress factors*.

* The population attributable risk (PAR) of all nine risk factors exceeded 94%, and was similar among women and men

Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusuf ali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J. 2008;29:932–940.

Presence of cumulative risk factors, NCVD-PCI Registry, 2019-2020 (N = 24,309)

3.7%	11.9%	23.3%	27.5%	33.6%
No risk factor	1 risk factor	2 risk factors	3 risk factors	>3 risk factors

W.A. Wan Azman (Ed). Annual Report of the NCVD-PCI Registry, Year 2019-2020. Kuala Lumpur, Malaysia: National Cardiovascular Disease Database, 2023.

How do You ‘ decode” your Patient

App should be used for primary prevention patients (those without ASCVD) only.

Current Age ℹ *

Age must be between 20-79

Sex *

Male | Female

Race *

White | African American | Other

Systolic Blood Pressure (mm Hg) *

Value must be between 90-200

Diastolic Blood Pressure (mm Hg) *

Value must be between 60-130

Total Cholesterol (mmol/L) *

Value must be between 3.367 - 8.288

HDL Cholesterol (mmol/L) *

Value must be between 0.518 - 2.59

LDL Cholesterol (mmol/L) ℹ ○

Value must be between 0.777-7.770

History of Diabetes? *

Yes | No

Smoker? ℹ *

Current ℹ | Former ℹ | Never ℹ

On Hypertension Treatment? *

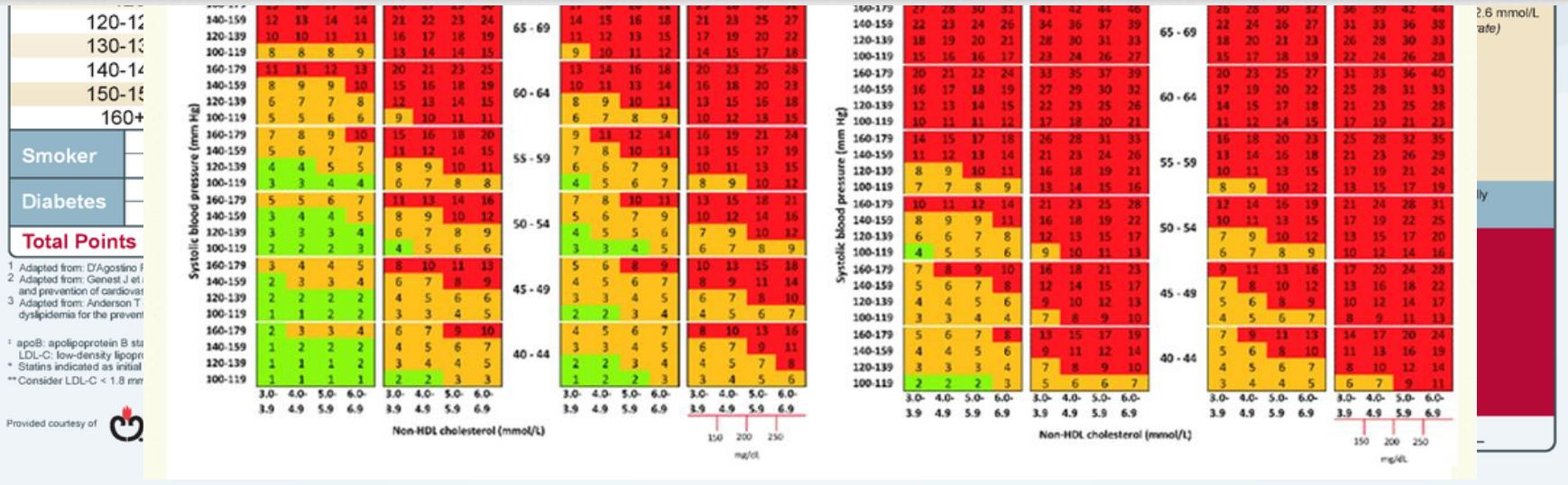
Yes | No

On a Statin? ℹ ○

Yes | No

On Aspirin Therapy? ℹ ○

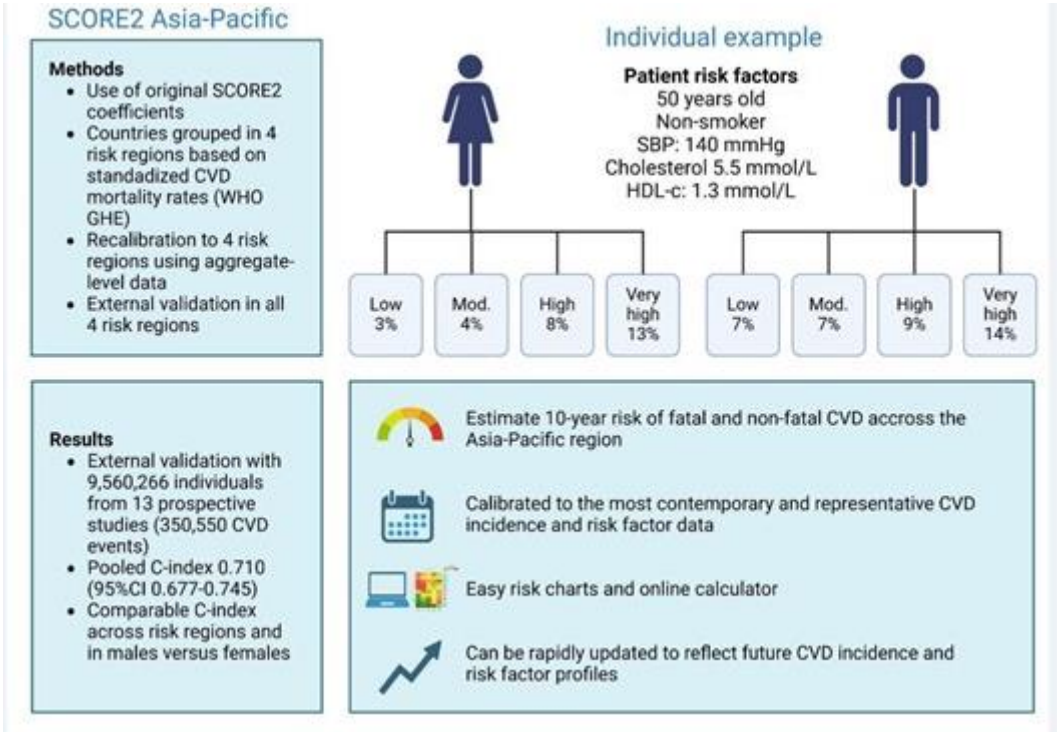
Yes | No



JOURNAL ARTICLE ACCEPTED MANUSCRIPT

Risk prediction of cardiovascular disease in the Asia-Pacific region: the SCORE2 Asia-Pacific model

SCORE2 Asia-Pacific writing group,
the SCORE2 Asia-Pacific collaborators, the European Society of Cardiology and European Association of Preventive Cardiology
,
Cardiovascular Risk Collaboration (ESC CRC), the ASEAN Federation of Cardiology (AFC),
the Asian-Pacific Society of Cardiology (APSC) Author Notes



Circulation

Circulation. 2023;148:1982–2004. December 12,

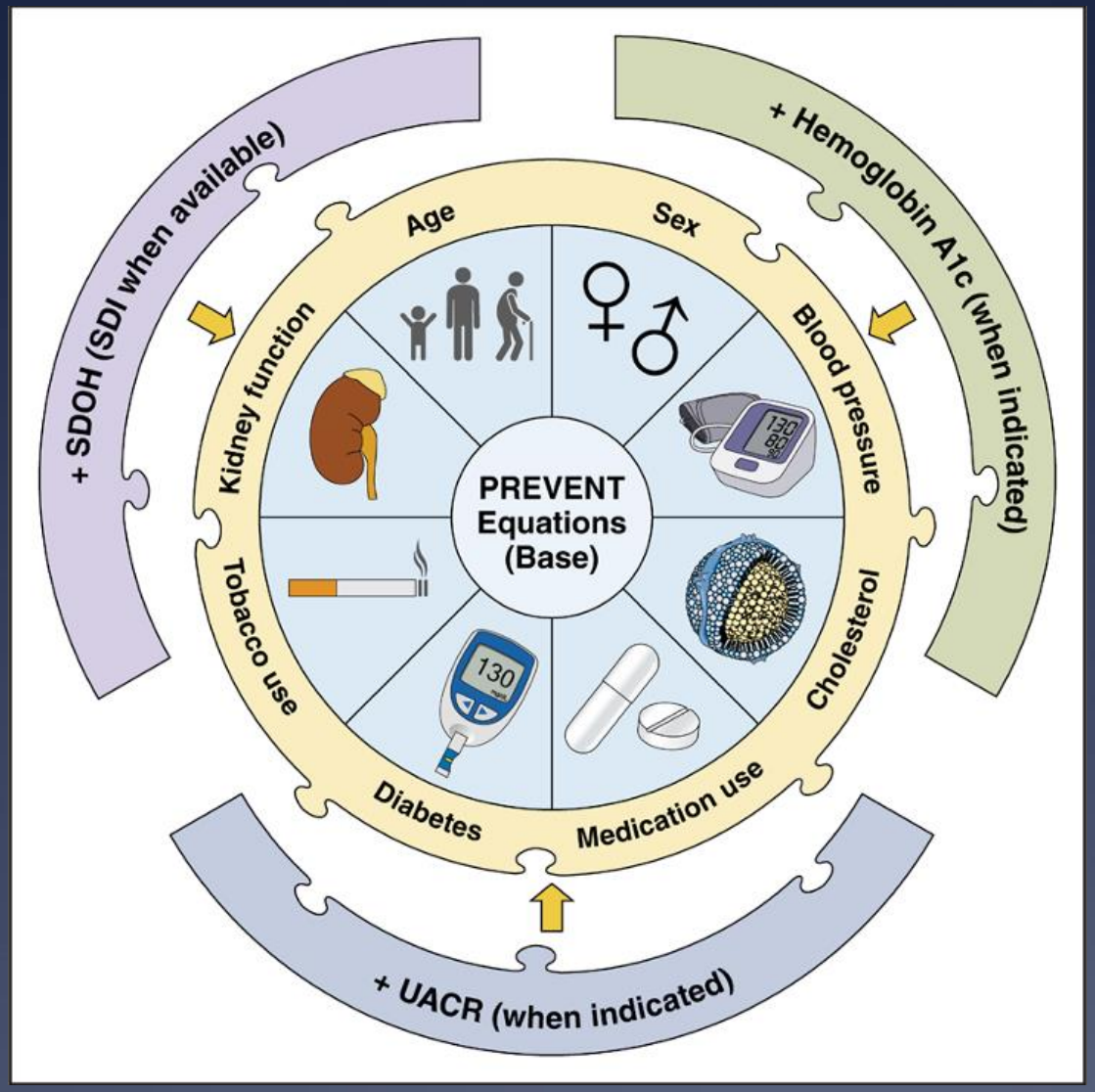
AHA SCIENTIFIC STATEMENT

Novel Prediction Equations for Absolute Risk Assessment of Total Cardiovascular Disease Incorporating Cardiovascular-Kidney-Metabolic Health: A Scientific Statement From the American Heart Association

Sadiya S. Khan, MD, MSc, FAHA, Chair; Josef Coresh, MD, PhD, FAHA, Vice Chair; Michael J. Pencina, PhD; Chiadi E. Ndumele, MD, PhD, FAHA; Janani Rangaswami, MD, FAHA; Sheryl L. Chow, PharmD, FAHA; Latha P. Palaniappan, MD, MS, FAHA; Laurence S. Sperling, MD, FAHA; Salim S. Virani, MD, PhD, FAHA; Jennifer E. Ho, MD, FAHA; Ian J. Neeland, MD, FAHA; Katherine R. Tuttle, MD, FAHA; Radhika Rajgopal Singh, PhD, FAHA; Mitchell S.V. Elkind, MD, MS, FAHA; Donald M. Lloyd-Jones, MD, ScM, FAHA; on behalf of the American Heart Association

ABSTRACT: Cardiovascular-kidney-metabolic (CKM) syndrome is a novel construct recently defined by the American Heart Association in response to the high prevalence of metabolic and kidney disease. Epidemiological data demonstrate higher absolute risk of both atherosclerotic cardiovascular disease (CVD) and heart failure as an individual progresses from CKM stage 0 to stage 3, but optimal strategies for risk assessment need to be refined. Absolute risk assessment with the goal to match type and intensity of interventions with predicted risk and expected treatment benefit remains the cornerstone of primary prevention. Given the growing number of therapies in our armamentarium that simultaneously address all 3 CKM axes, novel risk prediction equations are needed that incorporate predictors and outcomes relevant to the CKM context. This should also include social determinants of health, which are key upstream drivers of CVD, to more equitably estimate and address risk. This scientific statement summarizes the background, rationale, and clinical implications for the newly developed sex-specific, race-free risk equations: PREVENT (AHA Predicting Risk of CVD Events). The PREVENT equations enable 10- and 30-year risk estimates for total CVD (composite of atherosclerotic CVD and heart failure), include estimated glomerular filtration rate as a predictor, and adjust for competing risk of non-CVD death among adults 30 to 79 years of age. Additional models accommodate enhanced predictive utility with the addition of CKM factors when clinically indicated for measurement (urine albumin-to-creatinine ratio and hemoglobin A1c) or social determinants of health (social deprivation index) when available. Approaches to implement risk-based prevention using PREVENT across various settings are discussed.

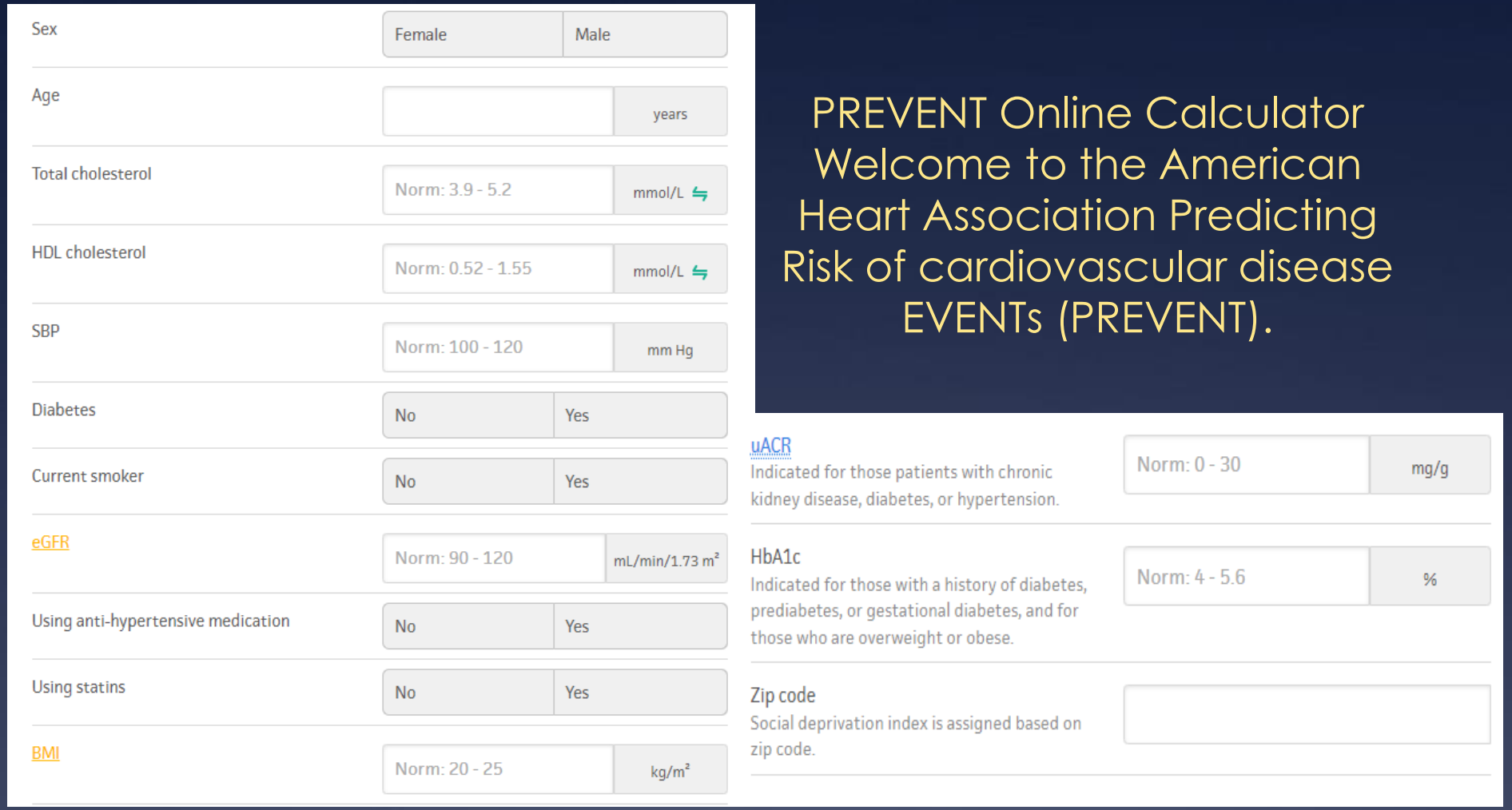
PREVENT base and additional equations.



CVD indicates cardiovascular disease; PREVENT, AHA Predicting Risk of CVD Events; SDI, social deprivation index; SDOH, social determinants of health; and UACR urine albumin-to-creatinine ratio.

Khan et al . Risk of Cardiovascular Disease Incorporating CKM Health. Circulation. December 12. 2023;148:1982–2004.

PREVENT Online Calculator Welcome to the American Heart Association Predicting Risk of cardiovascular disease EVENTs (PREVENT).

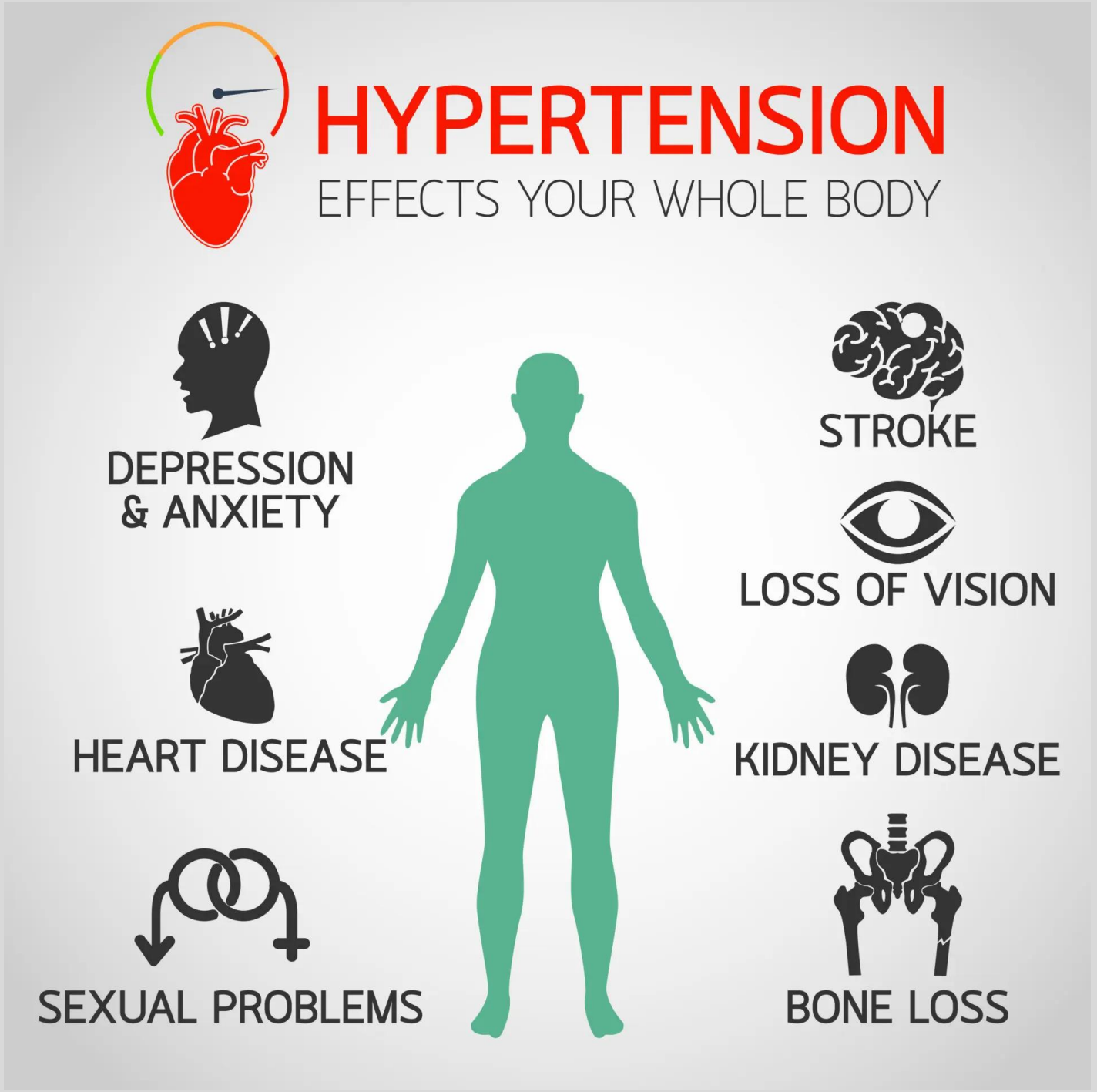


Interpretation of Risk Estimates: 10-year risk for CVD is categorized as:

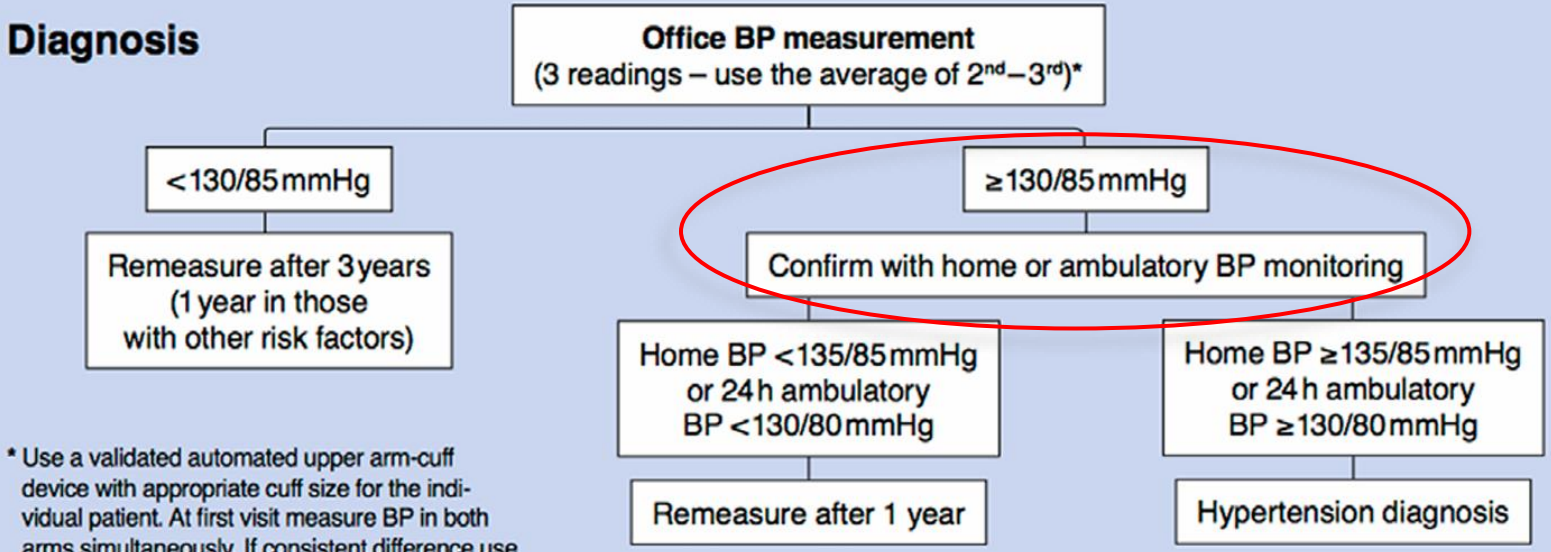
- Low risk (<5%)
- Borderline risk (5% to 7.4%)
- Intermediate risk (7.5% to 19.9%)
- High risk (≥20%)

Patients with risk factor values outside the validated ranges of this tool require individualized assessment and management

Risk Level†	Initiate Statin Treatment if:	Consider Add-on Therapy or Treatment Intensification
High FRS ≥ 20%	Consider treatment in all (Strong, High)	If LDL-C ≥ 2 mmol/L **or** Non-HDL-C > 2.6 mmol/L **or** ApoB ≥ 0.80 g/L on maximally tolerated statin dose
Intermediate FRS 10-19%	If LDL-C ≥ 3.5 mmol/L **or** (Strong, Moderate) If LDL-C < 3.5 mmol/L initiate if: • non-HDL-C ≥ 4.3 mmol/L **or** • ApoB ≥ 1.05 g/L **or** (Strong, Moderate) • Men ≥ 50 yrs and women ≥60 yrs with 1 additional risk factor: low HDL-C, impaired fasting glucose, high waist circumference, smoker, or hypertension, **or** with the presence of other risk modifiers: hsCRP ≥ 2 mg/L, CAC > 0 AU, family history of premature CAD, Lp(a) ≥ 100 mol/L (≥ 50 mg/dL)	If LDL-C ≥ 2 mmol/L **or** Non-HDL-C > 2.6 mmol/L **or** ApoB ≥ 0.80 g/L on maximally tolerated statin dose
Low FRS < 10%	Statins generally not indicated	N/A
Statin-indicated Conditions** (Consider treatment in all; Strong, High)		
LDL-C ≥ 5 mmol/L **or** non-HDL-C ≥ 5.8 mmol/L **or** ApoB ≥ 1.45 g/L (FH or genetic dyslipidemia)		If LDL-C ≥ 2.5 mmol/L **or** < 50% reduction, **or** non-HDL-C ≥ 3.2 mmol/L **or** ApoB ≥ 0.85 g/L
Most patients with diabetes: • Age ≥ 40 yrs old **or** Age ≥ 30 yrs & DM x ≥ 15 yrs duration **or** Microvascular disease		If LDL-C ≥ 2.0 mmol/L **or** non-HDL-C ≥ 2.6 mmol/L **or** ApoB ≥ 0.80 g/L on maximally tolerated statin dose
Chronic Kidney Disease: • Age ≥ 50 yrs & eGFR < 60 mL/min/1.73 m^2 **or** ACR > 3 mg/mmol.		
Atherosclerotic Cardiovascular Disease (ASCVD): • Myocardial infarction (MI), acute coronary syndrome (ACS), **or** • Stable angina, documented coronary artery disease (CAD) using angiography, **or** • Stroke, TIA, documented carotid disease, **or** • Peripheral arterial disease, claudication, and/or ankle-brachial index (ABI) < 0.9, **or** • Abdominal aortic aneurysm (AAA) – abdominal aorta > 3.0 cm or previous aneurysm surgery		If LDL-C ≥ 1.8 mmol/L **or** non-HDL-C ≥ 2.4 mmol/L **or** ApoB ≥ 0.70 g/L on maximally tolerated statin dose


HYPERTENSION
EFFECTS YOUR WHOLE BODY
DEPRESSION & ANXIETY
HEART DISEASE
SEXUAL PROBLEMS
STROKE
LOSS OF VISION
KIDNEY DISEASE
BONE LOSS

Diagnosis



* Use a validated automated upper arm-cuff device with appropriate cuff size for the individual patient. At first visit measure BP in both arms simultaneously. If consistent difference use the arm with the higher BP.

Treatment

Grade 1 Hypertension:
140–159/90–99 mmHg
1. Start lifestyle interventions
2. Start drug treatment:
- ***Immediately:*** In high-risk patients (CVD, CKD, diabetes or organ damage)
- ***After 3–6 months of lifestyle intervention:*** In low-moderate risk patients with persistent BP elevation

Grade 2 Hypertension:
≥160/100 mmHg
1. Start drug treatment immediately
2. Start lifestyle intervention

Lifestyle Interventions
- Stop smoking
- Regular exercise
- Lose weight
- Salt reduction
- Healthy diet and drinks
- Lower alcohol intake
- Lower stress
- Reduce exposure to air pollution

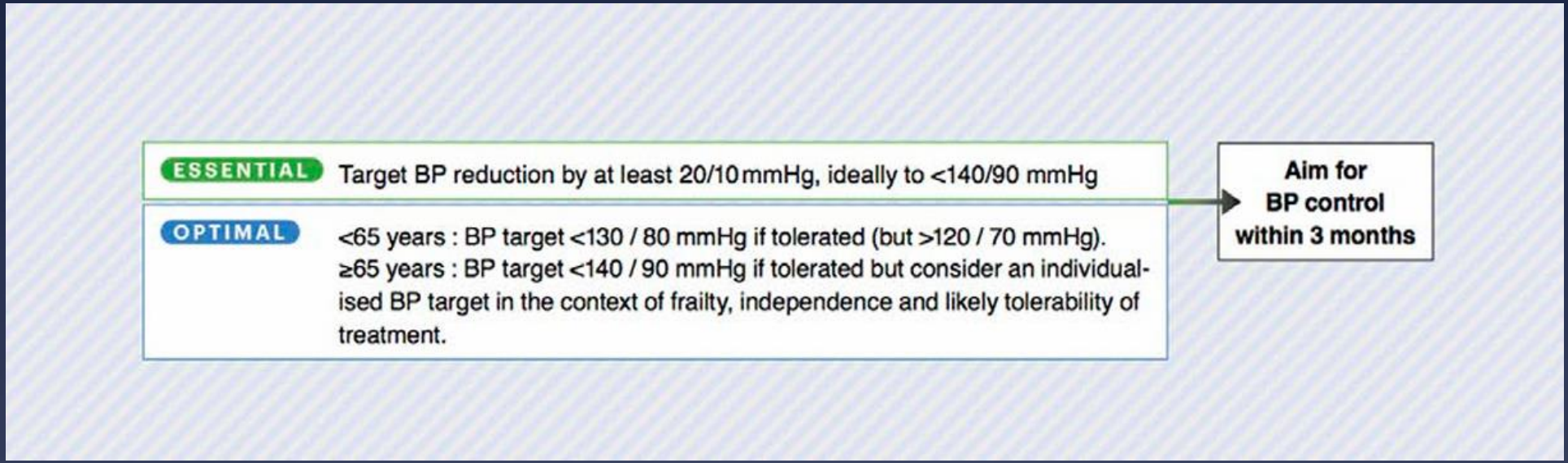
Drug Therapy Steps
Simplify regimen with once daily dosing and single pill combinations.
Consider monotherapy in low-risk grade 1 hypertension and in patients aged >80 years or frail

Non-Black Patients
1. Low dose ACEI/ARB* + DHP-CCB
2. Increase to full dose
3. Add thiazide-like diuretic
4. Add spironolactone or, if not tolerated or contraindicated, amiloride, doxazosin, eplerenone, clonidine or beta-blocker

Black Patients
1. Low dose ARB* + DHP-CCB or DHP-CCB + thiazide-like diuretic
2. Increase to full dose
3. Add diuretic or ACEI/ARB
4. Add spironolactone or, if not tolerated or contraindicated, amiloride, doxazosin, eplerenone, clonidine or beta-blocker

* No ACEI/ARB in women with or planning pregnancy

Office blood pressure targets for treated hypertension



1. Treatments should be evidence-based in relation to morbidity/mortality prevention.
2. Use a once-daily regimen which provides 24-hour blood pressure control.
3. Treatment should be affordable and/or cost-effective relative to other agents.
4. Treatments should be well-tolerated.
5. Evidence of benefits of use of the medication in populations to which it is to be applied

Unger et al. Hypertension. 2020;75:1334-1357. ISH Global Hypertension Practice Guidelines

Targets Blood Pressure <130/80mmHg to achieve

* Previous stroke subjects : BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80mmHg.
* Heart failure subjects: Treating hypertension has a major impact on reducing the risk of incident HF and HF hospitalization. BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80mmHg but >120/70 mm Hg.
* CAD subjects : BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80mmHg.
* Diabetes subjects : BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80mmHg
* Renal impairment subjects : BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80mmHg

Target Blood Pressure in the elderly

* Geriatric medicine proposes taking into account the function/frailty/autonomy status of older people.
* The 2017 American College of Cardiology/American Heart Association guidelines indicate that a BP <130/80 mm Hg should be targeted after the age of 65 years.
* The 2017 American College of Physicians/ American Association of Family Physicians guidelines propose to target a BP <150/90 mm Hg.
* The 2018 ESC /ESH guidelines propose a BP goal of <140/90 mm Hg for individuals older than 65 years.

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:1269–1324.

Williams B, Mancia G, Spiering W, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–3104.

Qaseem A, Wilt TJ, Rich R, Humphrey LL, Frost J, Forciea MA; Clinical Guidelines Committee of the American College of Physicians and the Commission on Health of the Public and Science of the American Academy of Family Physicians. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2017;166:430–437

CLINICAL PRACTICE GUIDELINES

Management of Hypertension

Older Adult Population	Target SBP (mmHg)
>80 years old	<150
65-80 years old	<140
Multiple comorbidities Functional and cognitive impairment Frail Institutionalized Experiencing ADRs	Consider less strict targets Limit number of antihypertensive agents

For fit* 65-80 years old patients consider target SBP <130 mmHg.

* free from health conditions that limit mobility and/or functional ability with good nutrition and cognitive status.

Malaysian Society of Hypertension

Ministry of Health Malaysia

Academy of Medicine of Malaysia

Hypertension and Dyslipidaemia

* The lower the absolute LDL-C achieved and the greater the percentage LDL-C reduction, the greater the magnitude of the CV benefits.

* Meta regression analysis showed that statin therapy effectively decreased CV morbidity and mortality to the same extent in both hypertensive and non-hypertensive patients.

* Meta-analysis of the role of statins in hypertensive patients not just to reduce Cardiovascular events but also to reduce the systolic and diastolic pressure in Hypertensive patients.

* For patients with Hypertension, initiate statins for Primary Prevention if they also have elevated cholesterols (LDL-C > 3.4mmol/L)….Aim for minimal < 3.0 mmol/L OR lower depending on the other risk factors.

Baigent C, Blackwell L, Emberson J, Holland LE, Reith C, Bhalla N et al for the Cholesterol Treatment Trialists' (CTT) Collaboration,. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. Lancet 2010 ;376:1670-81.

Collins R, Reith C, Emberson J, Armitage J, Baigent C et al. Interpretation of the evidence for the efficacy and safety of statin therapy. Lancet 2016; 388: 2532-61

Silverman MG, Ference BA, Im K, Wiviott SD, Giugliano RP, Grundy SM, et al. Association Between Lowering LDL-C and Cardiovascular Risk Reduction Among Different Therapeutic Interventions: A Systematic Review and Meta-analysis. JAMA. 2016; 316:1289-97.

Messerli FH, Pinto L, Tang SSK, Thakker KM, Cappelleri JC, Sichrovsky T, Dubois RW. Impact of systemic hypertension on the cardiovascular benefits of statin therapy-a meta-analysis. Am J Cardiol. 2008;101:319-325.

Khan Z, Gul A, Mlawa G, et al. (April 08, 2024) Statins As Anti-Hypertensive Therapy: A Systematic Review and Meta-Analysis. Cureus 16(4): e57825


DIABETES

Criteria for the diagnosis of diabetes in non pregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

Individualised HbA_{1c} targets based on patient profile

≤6.5 % (Tight)	6.6%-7.0%	7.1%-8.0% (Less tight)
• Newly and recently diagnosed • Younger age • Healthier (no complications) • Low risk of hypoglycaemia	• All others	• Elderly patients • Presence of co-morbidities • High risk of severe hypoglycaemia; hypo unawareness • Short life expectancy

In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024 Diabetes Care 2024;47(Suppl. 1):S20–S42 |

Criteria defining prediabetes in non pregnant individuals

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

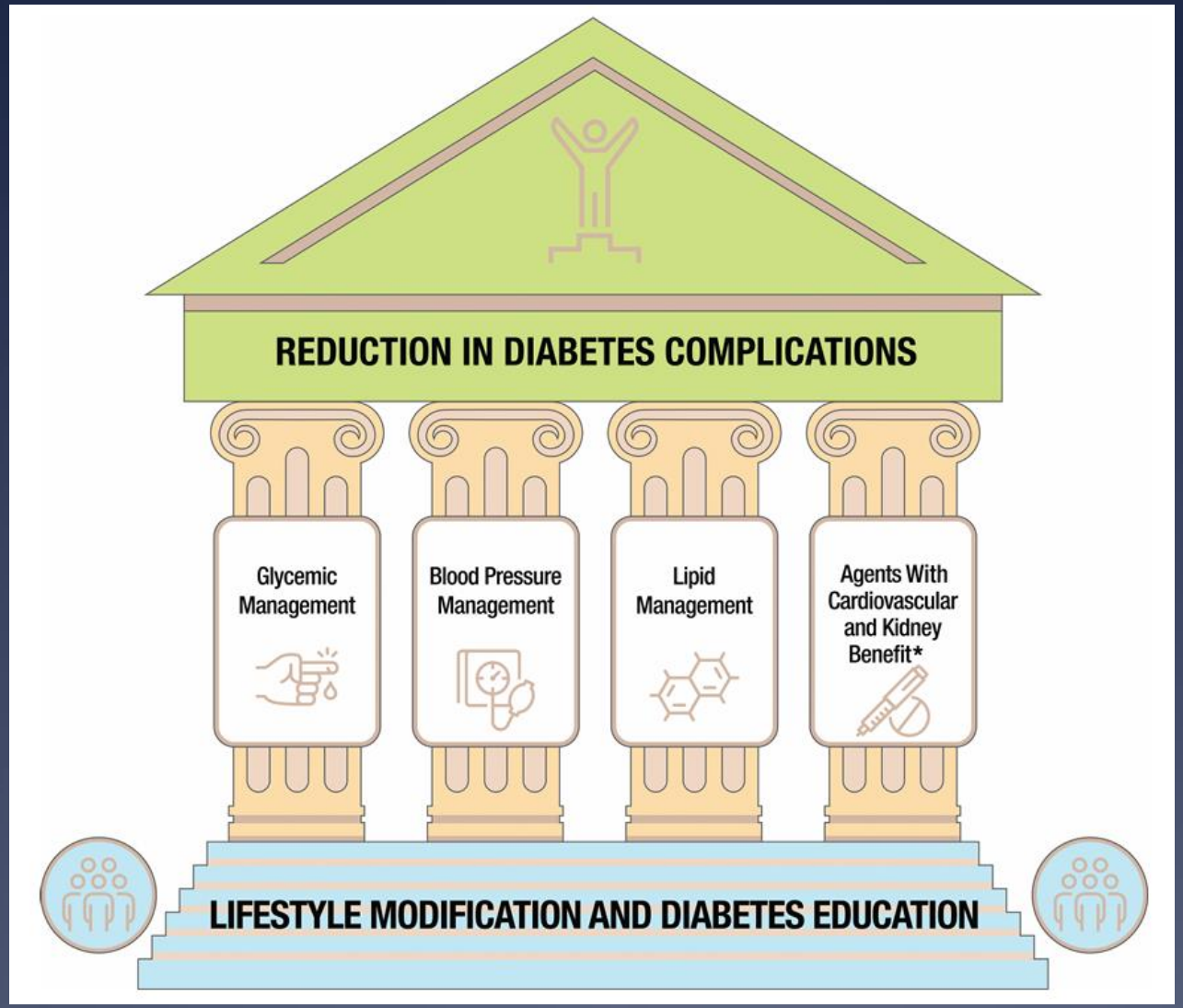
The most important management in prediabetes is a lifestyle change and promotion of intense weight loss. Reducing weight by 7% through a low-fat diet, in addition to an exercise regimen of about 30 minutes per day, is the overall goal of management.

Approximately 70% of people with prediabetes will go on to be diagnosed with diabetes mellitus. However, this is not inevitable. Prediabetes managed appropriately can prevent diabetes mellitus and lower the risk of cardiovascular disease.

Some patients will need to take some medications. These patients include those that have failed to maintain adequate lifestyle therapy or are at high-risk for developing type 2 diabetes. The most common medications used for prediabetes are metformin and acarbose, which will help prevent the development of diabetes mellitus. These two drugs have minimal side effects and work well in prediabetic patients.

Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024 Diabetes Care 2024;47(Suppl. 1):S20–S42

Multifactorial approach to reduction in risk of diabetes complications



Diabetes Care Volume 47, Supplement 1, January 2024.Diabetes Care Volume 47, Supplement 1, January 2024

Definition of Hypertension and the Target to achieved in Diabetic

1. Hypertension is defined as a systolic blood pressure >130mmHg or a diastolic blood pressure >80 mmHg .

2. The recommendation to support a blood pressure goal of <130/80 mmHg in people with diabetes is consistent with guidelines from the American College of Cardiology and American Heart Association, the International Society of Hypertension , and the European Society of Cardiology .

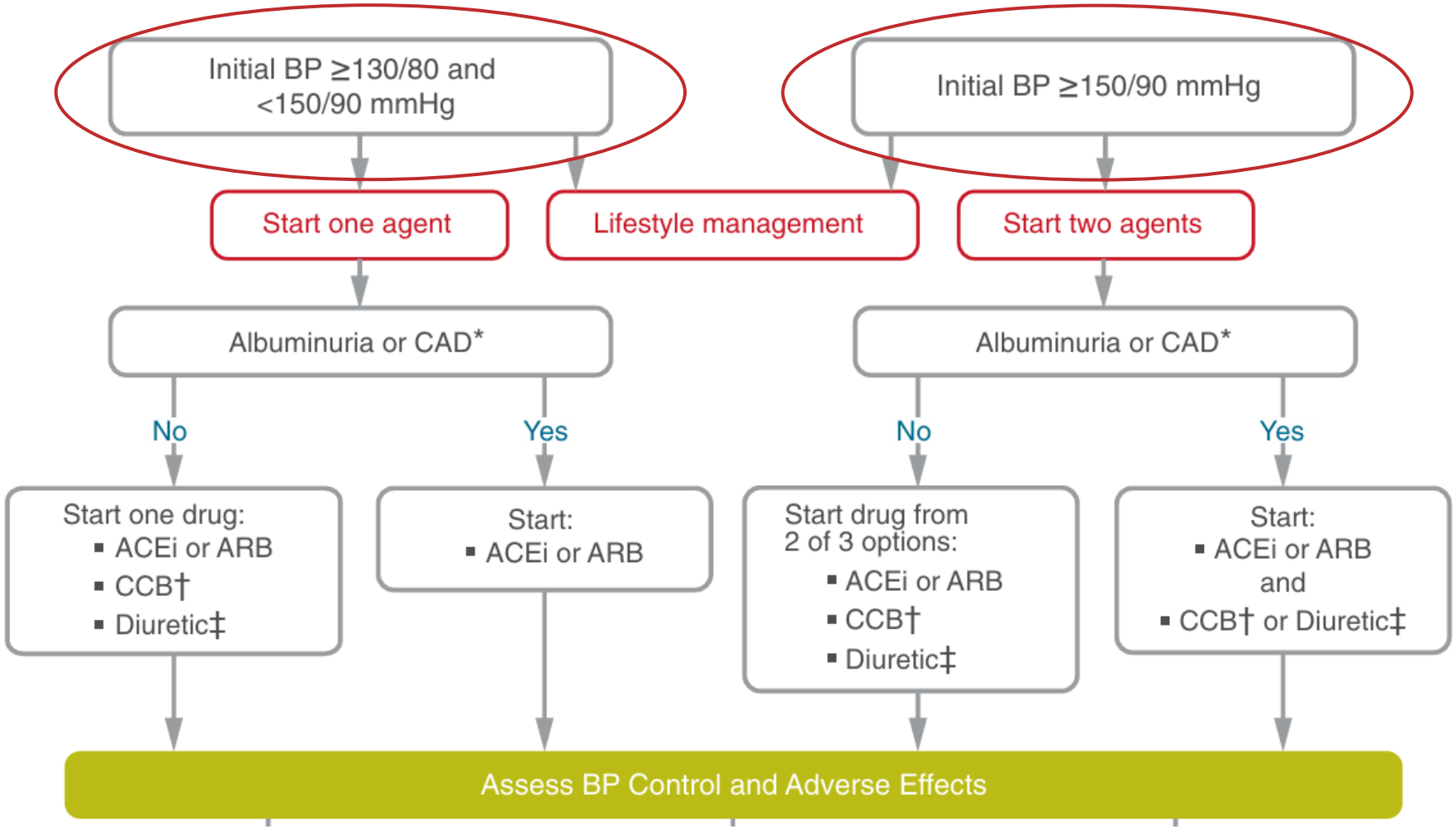
De Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284

Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. Hypertension 2020;75:1334–1357

Williams B, Mancia G, Spiering W, et al.; ESC Scientific Document Group. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–3104

Diabetes Care Volume 47, Supplement 1, January 2024.Diabetes Care Volume 47, Supplement 1, January 2024

Recommendations for the Treatment of Confirmed Hypertension in Nonpregnant People With Diabetes



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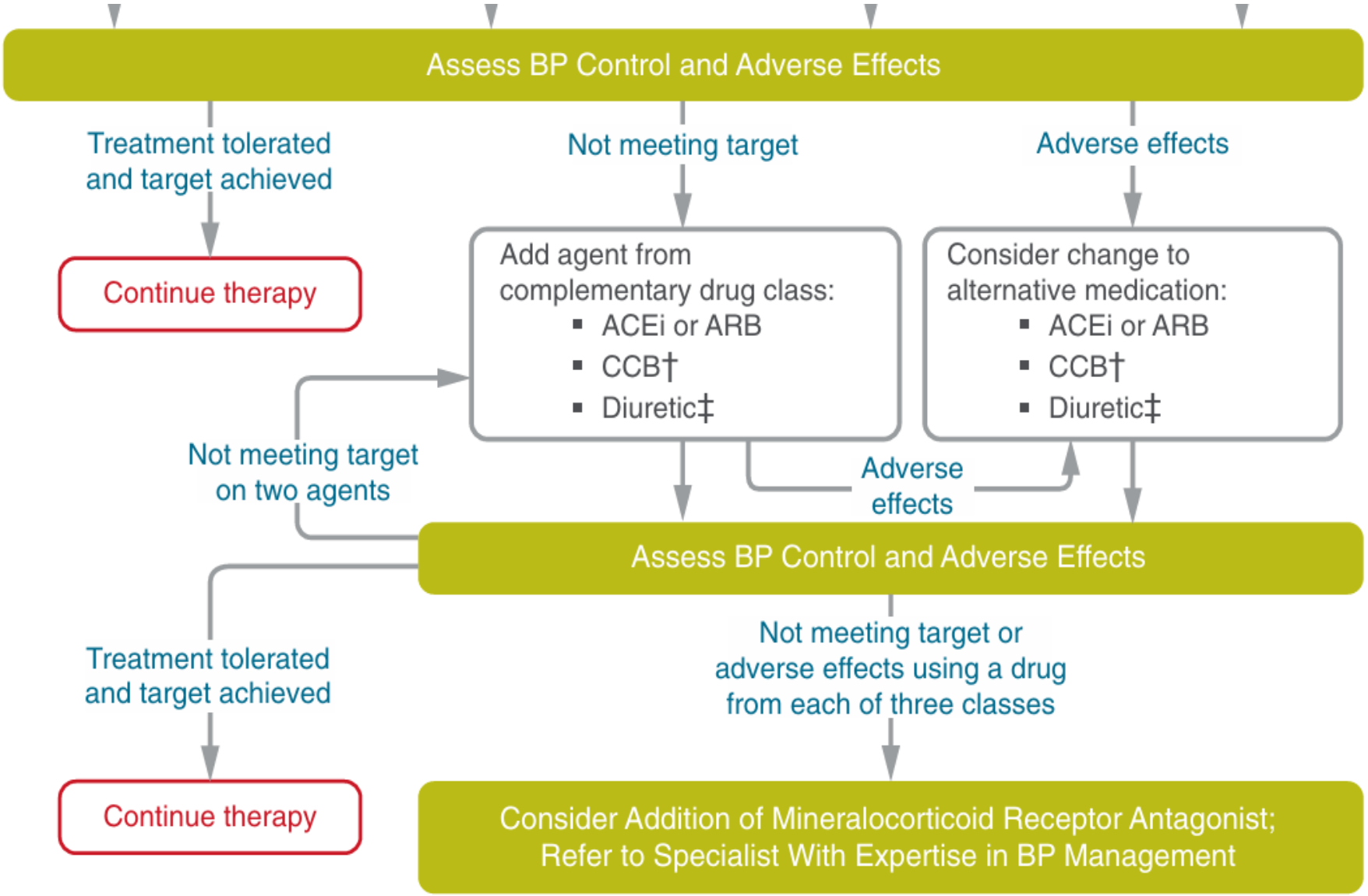

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Hyperlipidemia and Diabetes

* For people with diabetes aged *40–75 years without ASCVD, use moderate-intensity statin therapy in addition to lifestyle therapy.*
* For people with diabetes aged 20–39 years with additional ASCVD risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy.
* For people with diabetes aged 40–75 years at higher cardiovascular risk, including those with one or more ASCVD risk factors, it is recommended to use high-intensity statin therapy to *reduce LDL cholesterol by >50% of baseline and to target an LDL cholesterol goal of <1.8mmol/L.*
* For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. It is recommended to *target an LDL cholesterol reduction of >50% from baseline and an LDL cholesterol goal of <1.4mmol/L*

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Screening Asymptomatic Diabetic Individuals for Atherosclerotic Cardiovascular Disease

* The screening of asymptomatic individuals with high ASCVD risk is not recommended, in part because these high-risk people should already be receiving intensive medical therapy…… an approach that provides benefits similar to those of invasive revascularization.

* The ultimate balance of benefit, cost, and risk of such an approach in asymptomatic individuals remains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO; ADA. Screening for coronary artery disease in patients with diabetes. Diabetes Care 2007;30:2729–2736 192.

Boden WE, O'Rourke RA, Teo KK, et al.; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med2007;356:1503–1516 193.

Frye RL, August P, Brooks MM, et al.; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. NEngl J Med2009;360:2503–2515

Role of Statin Therapy in Patients With HyperTriglyceridemia

* Statins also provide a 10% to 30% dose-dependent reduction in triglycerides in patients with elevated triglyceride levels .

* Analysis of the *4S (Scandinavian Simvastatin Survival Study)* trial stratified 1,003 patients by quartile of triglyceride and HDL-C levels . The ASCVD event rate was highest in the patients with high triglycerides and low HDL-C, and this group had a greater treatment effect with simvastatin than the group with isolated elevated LDL-C levels.

* *PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22)* trial, LDL-C <1.8mmol/L was associated with greater coronary heart disease event reduction compared with LDL-C < 2.6 mmol/L after acute coronary syndrome . An on-treatment triglyceride level <1.7 mmol/L was independently associated with a lower risk of recurrent coronary heart disease events compared with a triglyceride level > 1.7mmol/L in univariate analysis

Christie M. Ballantyne et al. Influence of Low High-Density Lipoprotein Cholesterol and Elevated Triglyceride on Coronary Heart Disease Events and Response to Simvastatin Therapy in 4S. CirculationVolume 104, Issue 25, 18 December 2001; 3046-3051

Michael Miller et al. Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association . Circulation. Volume 123, Number 20 : 2292-2333

Michael Miller et al. Impact of Triglyceride Levels Beyond Low-Density Lipoprotein Cholesterol After Acute Coronary Syndrome in the PROVE IT-TIMI 22 Trial. JACC. Volume 51, Issue 7
, 19 February 2008 : 724-73

Practical Pearls: Statins and Fibrates: A Re-Interpretation of the Data

As a way to further reduce CV events in patients with metabolic syndrome or diabetes, consider adding a fibrate to those on statin therapy ….

1. Evidence of insulin resistance: elevated insulin level, metabolic syndrome, or diabetes.

2. Elevated triglyceride: ≥ 2.3mmol/L.

3. Low HDL-C: < 1.0 mmol/L mg/dL for male, and < 1.3 mmol/L for female.

- ✓ ACCORD study : The addition of fenofibrate to 40 mg simvastatin yielded no significant benefit in the primary outcome of nonfatal MI, nonfatal stroke, or death from cardiovascular causes.
- ✓ FIELD study : Not taking statin therapy and only fenofibrate daily or matching. There was a significant 24% reduction in nonfatal MI and a nonsignificant increase in coronary heart disease mortality .
- ✓ PROMINENT study : Pemafibrate was not associated with a reduction in adverse cardiovascular events. Pemafibrate was associated with an increased incidence of adverse renal events and venous thromboembolism.

Fish oil in Primary and Secondary cardiac events

ASCEND trial: 15,480 primary prevention patients with diabetes mellitus were randomized to 1-g capsules containing either 840 mg of marine n-3 fatty acids (460 mg of EPA and 380mg of DHA) or matching placebo (olive oil) daily. *During a mean follow-up of 7.4 years, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n-3 fatty acid supplementation compared with placebo…. NEJM 2018. 379:1540-1550*

VITAL study : 25,871 primary prevention participants were randomly assigned to either active fish oil (1,000-mg capsule containing 840 mg EPA and DHA) or matching placebo (olive oil) . *During a median follow-up of 5.3 years, there was no significant difference in the 2 primary endpoints of major cardiovascular events (a composite of MI, stroke, or death from cardiovascular causes)* or invasive cancer of any type….*NEJM 2019 380: 23-32*

OMEMI study : 1.8 g omega-3 fatty acids (930 mg EPA and 660 mg DHA) versus corn oil placebo to standard of care in 1,027 individuals aged 70 to 82 years with recent (2 to 8 weeks) acute MI. *The primary endpoint, which was a composite of nonfatal acute MI, unscheduled revascularization, stroke, all-cause death, and heart failure hospitalization, occurred in 108 (21.4%) patients on n-3 polyunsaturated fatty acids (PUFAs) versus 102 (20.0%) on placebo (hazard ratio [HR]: 1.08; 95% confidence interval [CI]: 0.82-1.41; P = 0.60*)…. *Circulation 2021.143: 528-539*

STRENGHT Study : Comparing 1 gm per day of omega-3 dietary supplements n containing EPA or DHA with corn oil in statin-treated participants with high cardiovascular risk, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C). A total of 13 078 patients were randomized. Among statin-treated patients at high cardiovascular risk, the addition of omega-3 CA, compared with corn oil, to usual background *therapies resulted in no significant difference in a composite outcome of major adverse cardiovascular events*. *JAMA.2020;324(22):2268-2280*.

These findings do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in high-risk patients

High-purity Eicosapentaenoic acid (Icosapent ethyl)

JELIS study : (Japan EPA Lipid Intervention Study) was an open-label, blinded end point trial in 18,645 Japanese participants with hypercholesterolemia (baseline total cholesterol approximately 250 mg/dL) that compared EPA (as an ethyl ester preparation) at 1.8 g daily plus a low-intensity statin versus a low-intensity statin alone, with a mean follow-up of 4.6 years.

The primary endpoint of major coronary events was reduced by 19% in the EPA group compared with those in the control group, with a modest 9% reduction in triglycerides with EPA compared with placebo. The greatest benefit appeared to be in the subgroup of patients with triglycerides > 2.0 mmol/L and low levels of HDL-C…. *Lancet. Volume 369, Issue 9567, 31 March–6 April 2007, Pages 1090-1098 and Atherosclerosis. Volume 200, Issue 1. September 2008, Pages 135-140*

REDUCE-IT : A multinational study with a randomized, placebo controlled design that enrolled 8,179 patients *(70.7% secondary prevention patients aged >45 years and 29.3% high-risk primary prevention patients aged >50 years with diabetes mellitus and >1 other risk factor), with LDL-C 1.0 to 2.6 mmol/L and triglycerides 1.5 to 5.7 mmol/L. Participants were on baseline statin therapy, with most patients (93%) having received moderate- or high intensity statins . Patients were randomized to 4 g of EPA (in the form of IPE) daily versus mineral oil placebo*.

The primary composite endpoint of cardiovascular death, nonfatal MI (including silent MI), nonfatal stroke, coronary revascularization, or unstable angina was reduced by 25% (HR: 0.75; 95% CI: 0.68-0.93) over a median follow-up of 4.9 years. The key secondary efficacy (a composite of cardiovascular death, nonfatal MI, or nonfatal stroke) was also met (HR: 0.74; 95% CI: 0.65 .0.83), as were all of the individual endpoints including a reduction in cardiovascular mortality… JACC. Volume 74, Issue 8. , 27 August 2019, Pages 1159-1161

LifestyleModifications and Estimated Triglyceride-Lowering Response in Patients With Hypertriglyceridemia

Lifestyle Intervention	Reduction in Triglycerides (%)	Qualifier
Weight loss	Up to 70%	Although most patients will likely experience reductions in triglyceride levels of 10%-20% with weight loss, evidence suggests that in some patients, a reduction in triglyceride levels of up to 70% may be achieved
Dietary modifications (including alcohol—restrict or abstain completely	>70%	Response may vary depending on the baseline triglyceride level and how strictly dietary recommendations are followed
Physical activity and exercise	Up to 30%	Response may vary depending on the type, duration, and intensity of activity

Alexandra Byrne et al Optimizing Non-Pharmacologic Management of Hypertriglyceridemia. Archive of Medical Research. Volume 48, Issue 6, August 2017, Pages 483-487.

Hypertriglyceridemia: the importance of identifying patients at risk Pamela A. Kushner &Michael E. Cobble Clinical Focus: Poat Grad Medicine. Cardiometabolic Conditions - *Review.* Pages 848-858 | Received 07 Jun 2016, Accepted 27 Sep 2016,

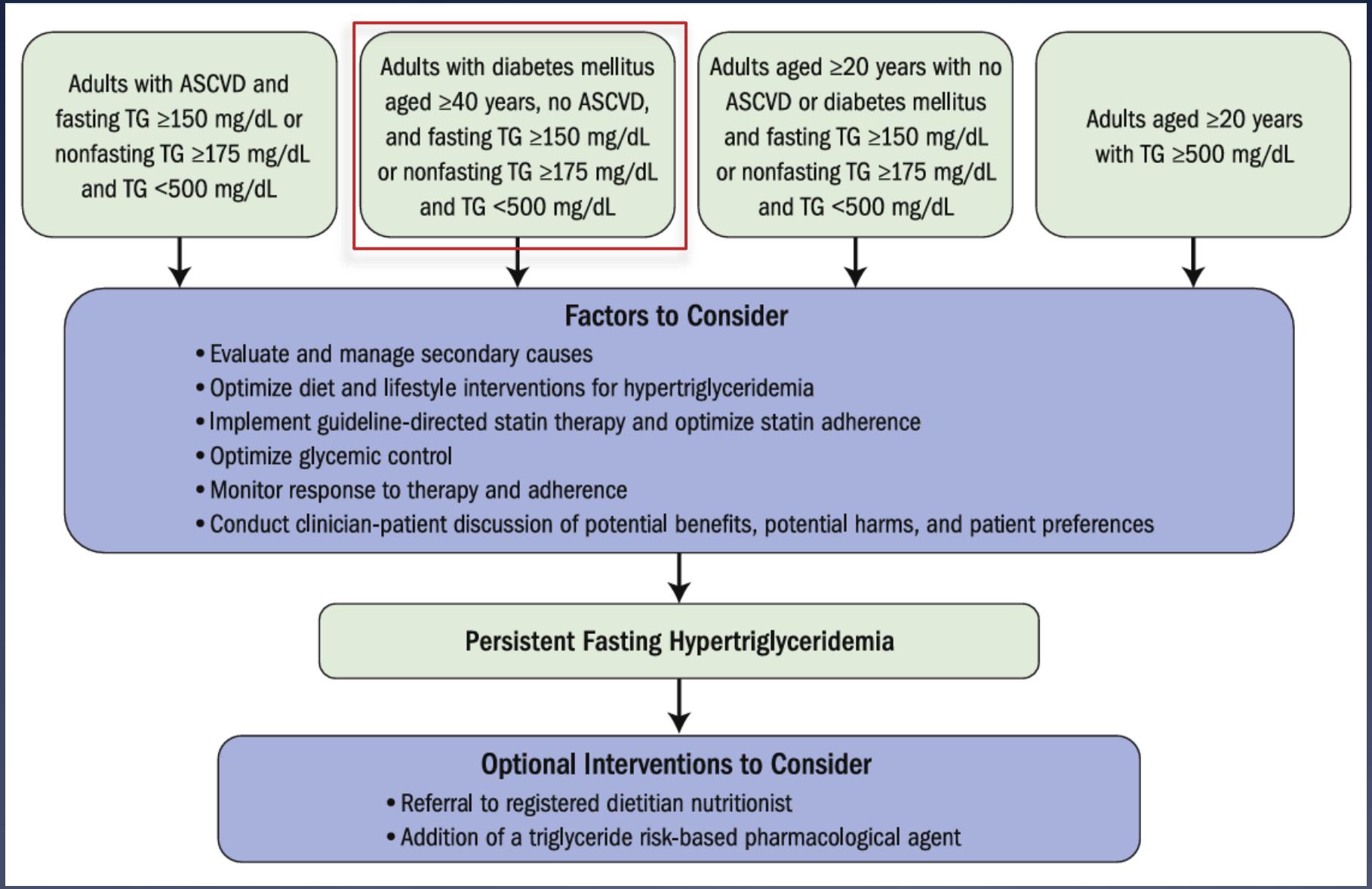
Parhhofer KG, Laufs U. The diagnosis and treatment of hypertriglyceridemia. Dtsch Arztebl Int. 2019;116: 825–832.

Gordon B, Chen S, Durstine JL. The effects of exercise training on the traditional lipid profile and beyond. Curr Sports Med Rep. 2014;13:253–259.

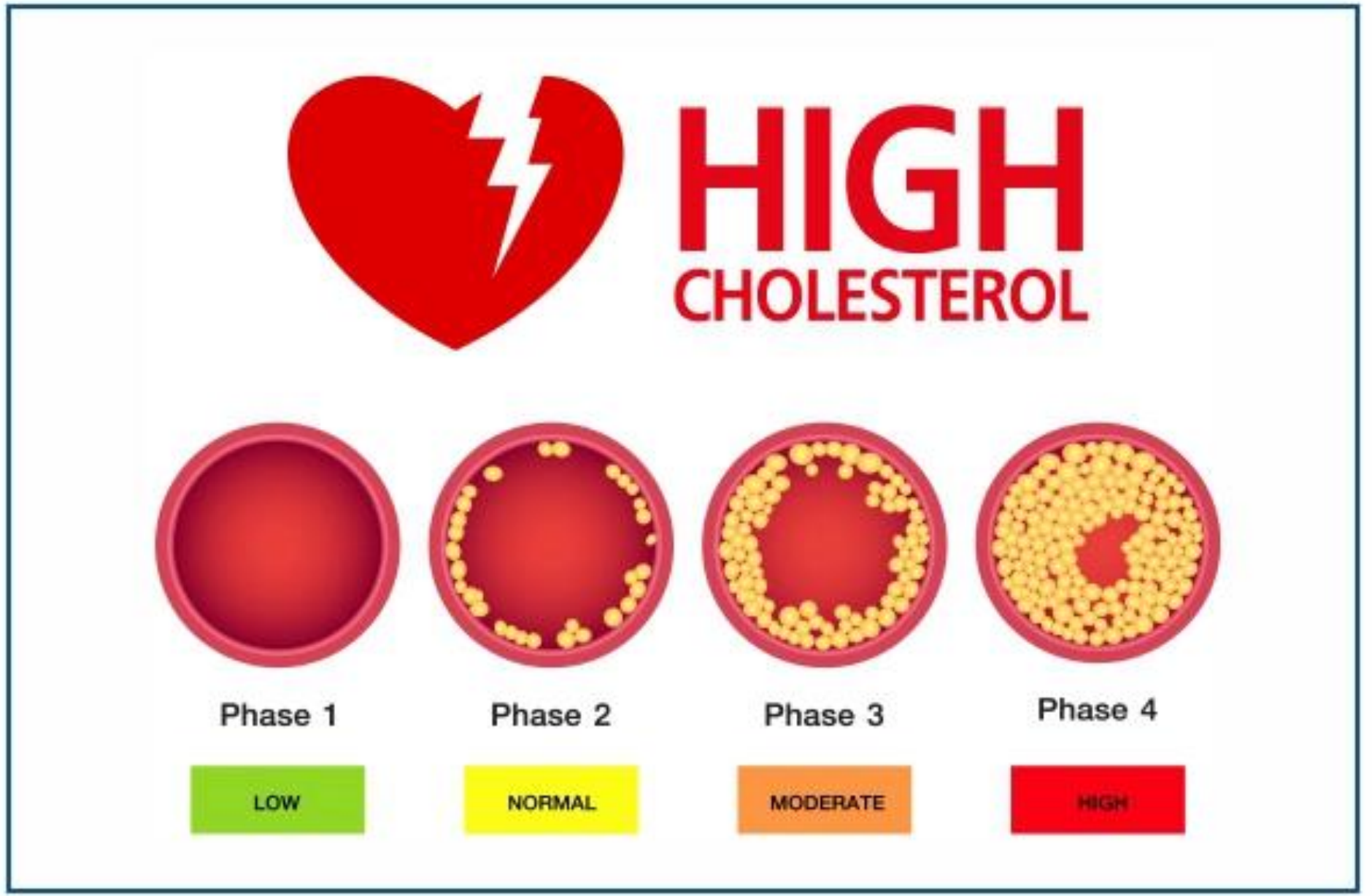
Gordon B, Chen S, Durstine JL. The effects of ex ercise training on the traditional lipid profile and beyond. Curr Sports Med Rep. 2014;13:253–259.

Kraus WE, Houmard JA, Duscha BD,et al. Effects of the amount and intensity of exercise on plasma lipo proteins. N Engl J Med. 2002;347:1483–1492.

Triglycerides Management



Virani et al. JACC VOL. 78, NO. 9, 2021 961 AUGUST 31, 2021:960–99 Hypertriglyceridemia Management Expert Consensus Decision Pathway


HIGH
CHOLESTEROL
Phase 1
Phase 2
Phase 3
Phase 4
LOW
NORMAL
MODERATE
HIGH

Target LDL-C levels

Global Risk	LDL-C Initiate Drug Therapy (mmol/L)	Target LDL-C levels (mmol/L)	Target Non-HDL-C (mmol/l)
Low CV Risk* <10%10-year CVD risk	clinical judgement**	<3.0	<3.8
Intermediate (Moderate) CV Risk* ➢ 10-20% 10-year CVD risk ➢ Diabetics < 50 years old and< 10-year duration and no CV risk factors	>2.6 **	<2.6	<3.4
High CV Risk ➢ > 20% 10-year CVD risk ➢ diabetes >10-year duration without target organ damage + 1 other CV risk factor ➢ CKD with eGFR 30-<60ml/min-1/1.73 m^2	> 1.8	≤ 1.8 ***and*** a reduction of >50% from baseline	≤ 2.6 ***and*** a reduction of >50% from baseline
Very high CV Risk* ➢ established CVD ➢ diabetes with CVD or other target organ damage or > 3 CV risk factors ➢ CKD with eGFR <30ml/min-1/1.73 m^2 ****	>1.4	≤ 1.4 ***and*** a reduction of > 50% from baseline	≤ 2.2 ***and*** a reduction of >50% from baseline
***Those with recurrent CV events within 2 years despite achieving a LDL-C target of <1.4mmol/l		<1.0	

1) LDL-C is the primary target of therapy.

2) The target LDL-C level will depend on the individual's CV global risk.

3) Non-HDL-C may be considered as a secondary target when treating patients with:

- combined hyperlipidemias
- diabetes
- cardio metabolic risk
- chronic kidney disease

4) Non-HDL-C however, becomes the primary target of therapy in situations where the TG >4.5 mmol/l

Statins for Elderly

* The elderly derive a greater absolute benefit from lipid lowering therapy as a secondary prevention and hence they should not be deprived from lipid lowering therapy solely based on their age although there is limited clinical trial data in patients over the age of 80 years.

* In patients age 75 and younger, the efficacy of statins for primary prevention is well-established on the basis of multiple randomized trials, which have found that they reduce the relative risk of major vascular events by 20-30%.

Mihaylova B, Emberson J, Blackwell L, et al. The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet 2012;380:581-90.

Ridker PM, Danielson E, Fonseca FAH, et al. Rosuvastatin to prevent vascular events in men and women with elevated c-reactive protein. N Engl J Med 2008;359:2195-2207.

Marcellaud E, Jost J, Tchalla A, Magne J, Aboyans V. Statins in Primary Prevention in People Over 80 Years. Am J Cardiol. 2023 Jan 15;187:62-73.

Statins in Primary Prevention in People Over 80 Years

* Statins in elderly ….issues requiring attention are (16 studies, 121,250 participants)

(1) the impact of hypercholesterolemia on mortality and major adverse cardiovascular events in subjects >80 years

(2) the efficacy of statins to prevent cardiovascular events at this age

(3) the safety and tolerance of statins in this population

* Regarding the first objective, *7 studies (10,241 participants) did not find total cholesterol and low-density lipoprotein levels associated with an increased rate of major cardiovascular events in octogenarians. 6 studies (14,493 participants) found increased levels associated with events, whereas 3 studies (96,516 participants) found the opposite, with increased risk of major adverse cardiovascular events with lower levels of cholesterol*

* Regarding the second objective, 8 studies (436,005 participants) addressing the efficacy of statins*, most did not indicate a significant decrease in the rate of major cardiovascular events in these subjects*.

* Regarding the third objective, 9 studies, (217,088 participants), *the most important side effects in this population were muscular, hepatic, and gastrointestinal disorders*. These events were more frequent than in the younger population.

Marcellaud E, Jost J, Tchalla A, Magne J, Aboyans V. Statins in Primary Prevention in People Over 80 Years. Am J Cardiol. 2023 Jan 15;187:62-73.

Statins in Primary Prevention in Elderly

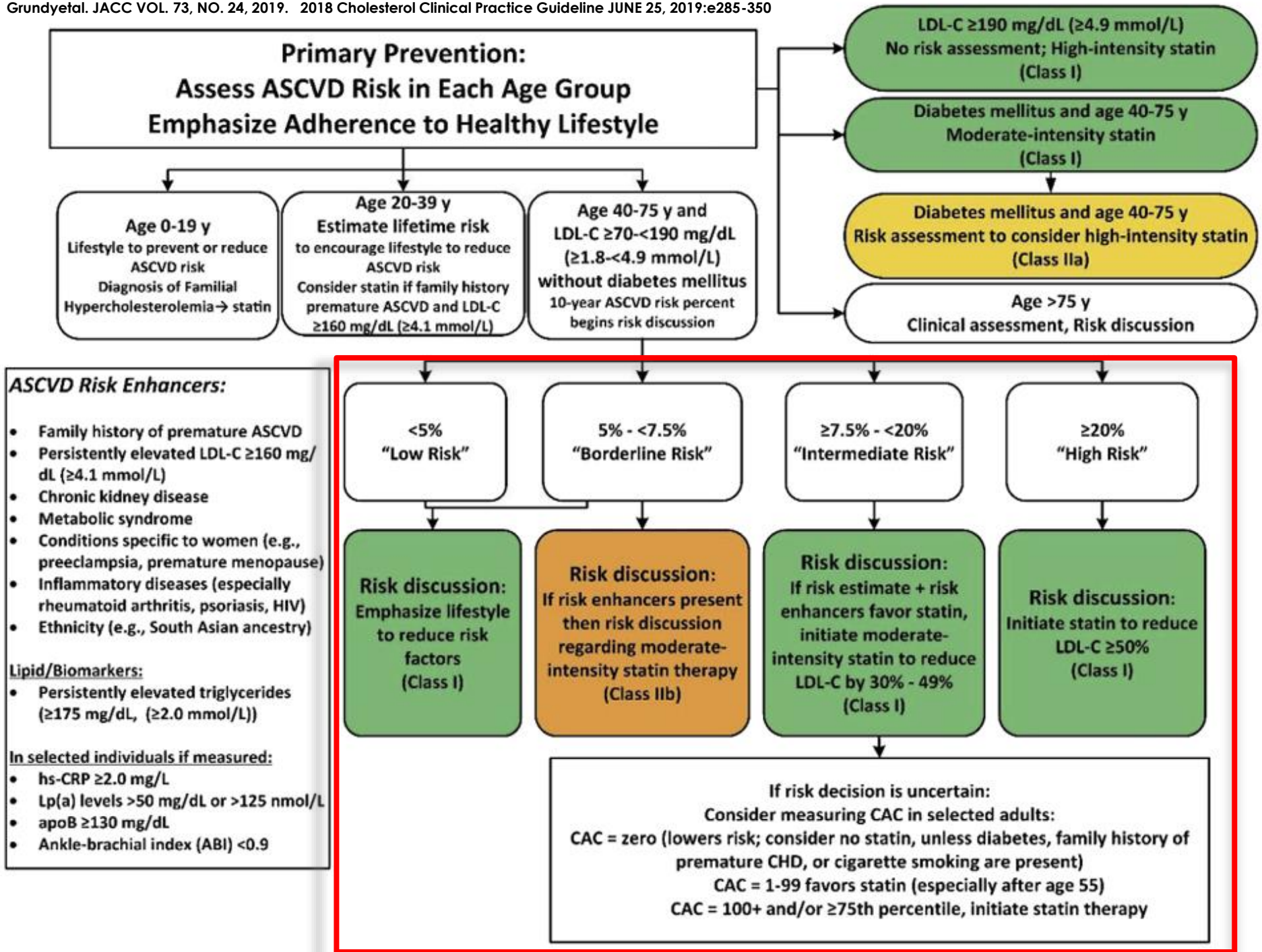
* The PREVENTABLE trial is aiming to enroll 20,000 community-dwelling primary prevention patients age ≥75 and randomize individuals to atorvastatin 40 mg daily, or placebo. The primary outcomes include dementia and physical disability over 4 years.

* STAREE trial will assess the efficacy of atorvastatin 40 mg daily versus placebo in the improvement of overall survival or disability-free survival in 18,000 community-dwelling patients age ≥70 years.

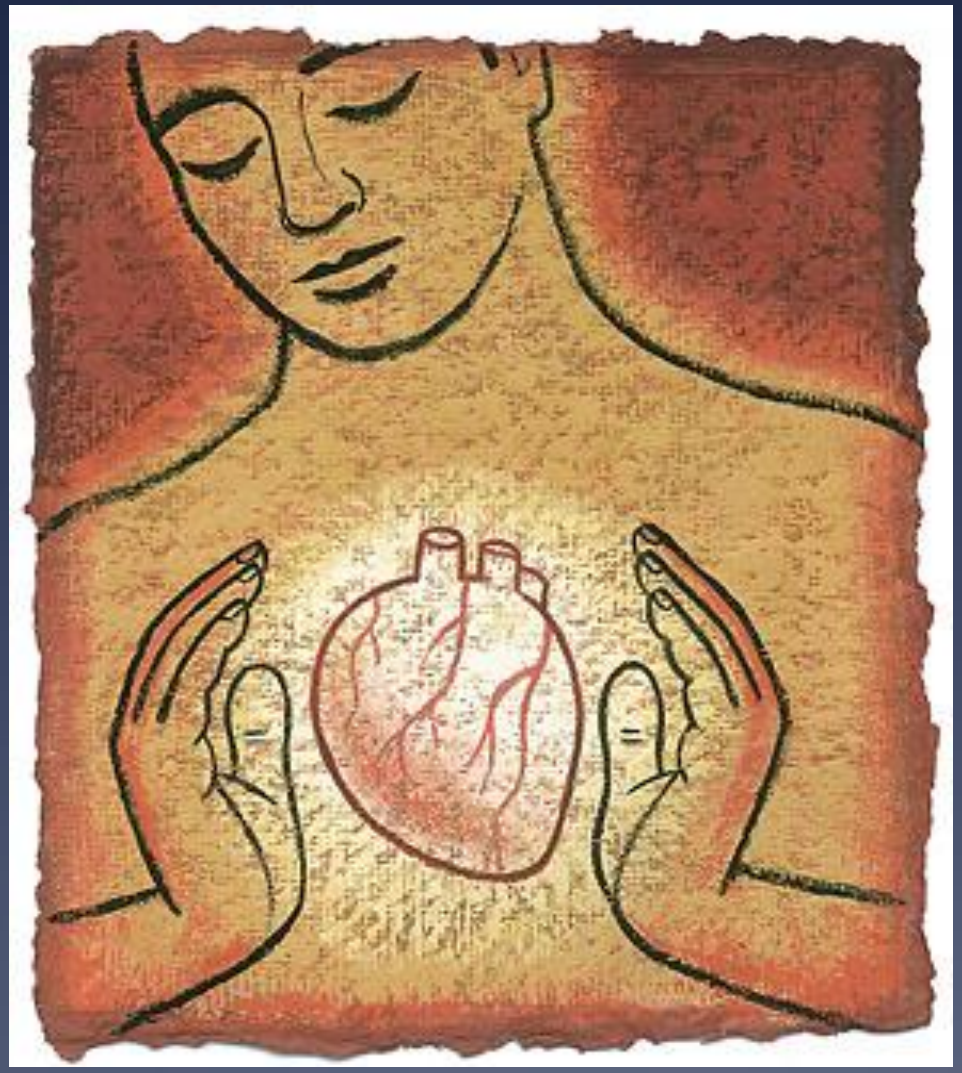
Concluding……My personalized CVS Risk Assessment

- For all risk groups, a heart healthy lifestyle is recommended. In those considered at low risk, the emphasis is on therapeutic lifestyle changes.
- Achieving target values are important.
- For high-risk category, initiation of high-intensity statin therapy is recommended in addition to a heart healthy lifestyle (Class I recommendation).
- Among those at borderline or intermediate risk, evaluation of risk enhancing factors should be pursued to guide decisions regarding statin therapy (Class IIb and I recommendation), respectively.
- One can redefine these patients with coronary calcium scoring on subclinical atherosclerosis

Grundyetal. JACC VOL. 73, NO. 24, 2019. 2018 Cholesterol Clinical Practice Guideline JUNE 25, 2019:e285-350



Thank You



Criteria defining prediabetes in non pregnant individuals

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

The most important management in prediabetes is a lifestyle change and promotion of intense weight loss. Reducing weight by 7% through a low-fat diet, in addition to an exercise regimen of about 30 minutes per day, is the overall goal of management.

Approximately 70% of people with prediabetes will go on to be diagnosed with diabetes mellitus. However, this is not inevitable. Prediabetes managed appropriately can prevent diabetes mellitus and lower the risk of cardiovascular disease.

Some patients will need to take some medications. These patients include those that have failed to maintain adequate lifestyle therapy or are at high-risk for developing type 2 diabetes. The most common medications used for prediabetes are metformin and acarbose, which will help prevent the development of diabetes mellitus. These two drugs have minimal side effects and work well in prediabetic patients.

Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024 Diabetes Care 2024;47(Suppl. 1):S20–S42

Criteria for the diagnosis of diabetes in non pregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

Individualised HbA_{1c} targets based on patient profile

≤6.5 % (Tight)	6.6%-7.0%	7.1%-8.0% (Less tight)
• Newly and recently diagnosed • Younger age • Healthier (no complications) • Low risk of hypoglycaemia	• All others	• Elderly patients • Presence of co-morbidities • High risk of severe hypoglycaemia; hypo unawareness • Short life expectancy

In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024 Diabetes Care 2024;47(Suppl. 1):S20–S42 |

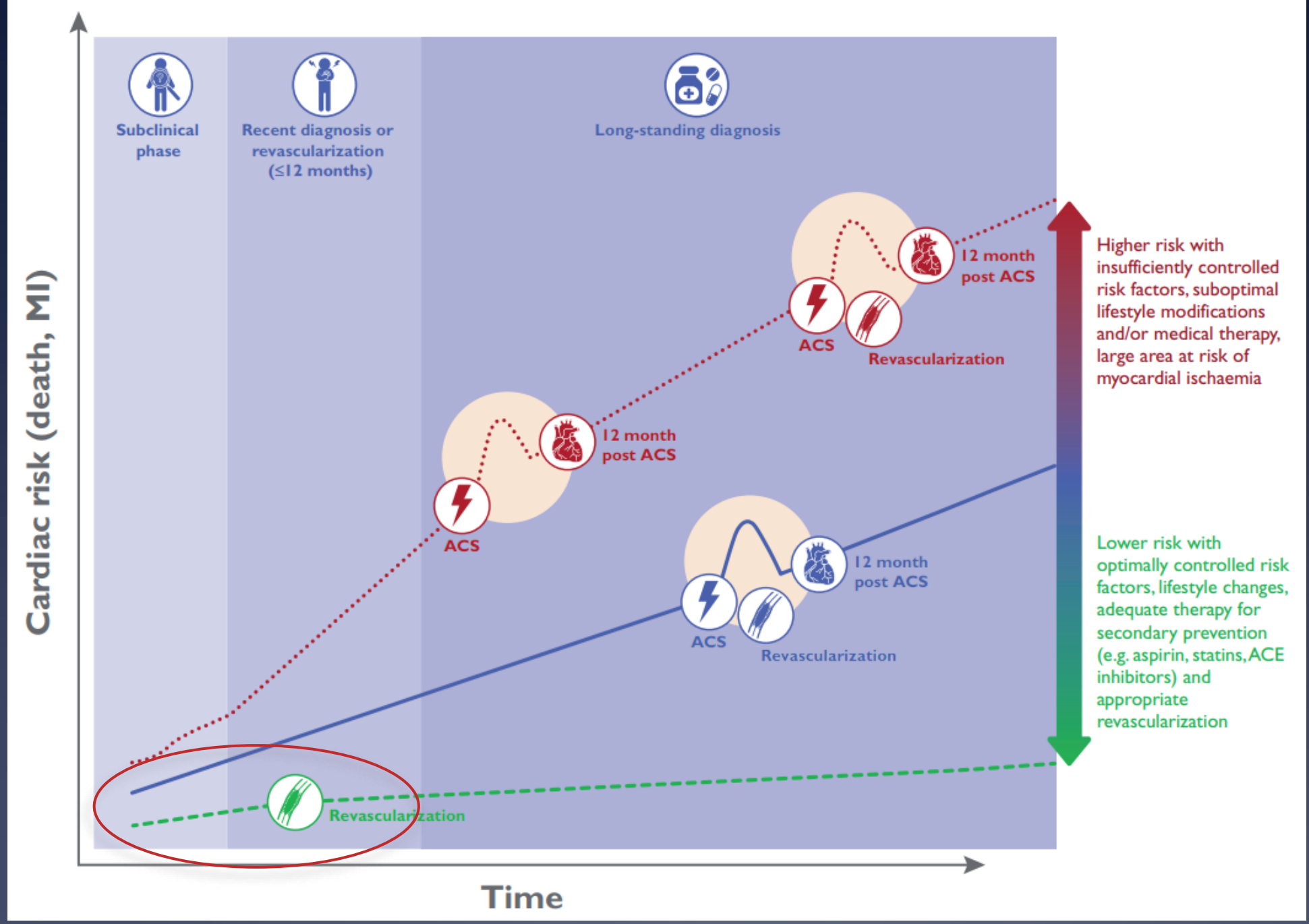
Risk	ApoB	LDL-C
High risk: CHD or CHD risk equivalent	< 90 mg/dL	< 100 mg/dL
Moderate risk: ≥2 risk factors	< 110 mg/dL	< 130 mg/dL
Low risk: 0-1 risk factors	< 130 mg/dL	< 160 mg/dL

CHD, coronary heart disease

Table 2. ADA/ACC Consensus Report Treatment Goals in Patients with Cardiometabolic Risk and Lipoprotein Abnormalities [3] (Open Table in a new window)

Risk	ApoB	LDL-C	Non-HDL-C
Highest-risk patients: Known CVD or DM plus ≥1 additional major CVD risk factor	< 80 mg/dL	< 70 mg/dL	< 100 mg/dL
High-risk patients: ≥2 CVD risk factors but no DM or known CVD or DM but no other major risk factors	< 90 mg/dL	< 100 mg/dL	< 130 mg/dL

CVD, cardiovascular disease; DM, diabetes mellitus; non-HDL-C, non-high



2019 ESC Guidelines for the diagnosis and management of chronic coronary syndrome. European Heart Journal (2020) 41, 407-477

The Role of Non-Invasive Multimodality Imaging in Chronic Coronary Syndrome: Anatomical and Functional Pathways

Functional and Anatomy Assessment…..What does it means

* Functional assessment measures an individual's level of function and ability to perform specific tasks on a safe and dependable basis over a defined period.

* Anatomy assessment measures the structure of an individual lesion without any level of functional understanding or specific safety task over a period of time.

Principle ……treat a coronary stenosis on the basis of whether it is hemodynamically significant rather than the degree of luminal stenosis

Non-invasive testing of CAD

* The primary purpose of non-invasive diagnostic testing of patients suspected to have CAD is to *rule out the presence of significant underlying CAD and/or myocardial ischemia* and thus avoid unnecessary testing for those who gain no benefit from invasive catheterization.

* The non-invasive testing seeks to provide *risk-stratification* to determine the need of medical therapy as well as determine conditions, when revascularization results in fewer future events, specifically in left main and three vessel disease.

* Hence, an ideal first-line non-invasive diagnostic strategy is desired to have *high diagnostic accuracy* to identify significant CAD. In addition a testing strategy should be proven to fit the standard *cost effectiveness* criteria.

* However, unless specific recommendations are available, test selection ultimately depends on availability, local expertise, cost, radiation considerations and patient characteristics leading to a degree of geographic variability.

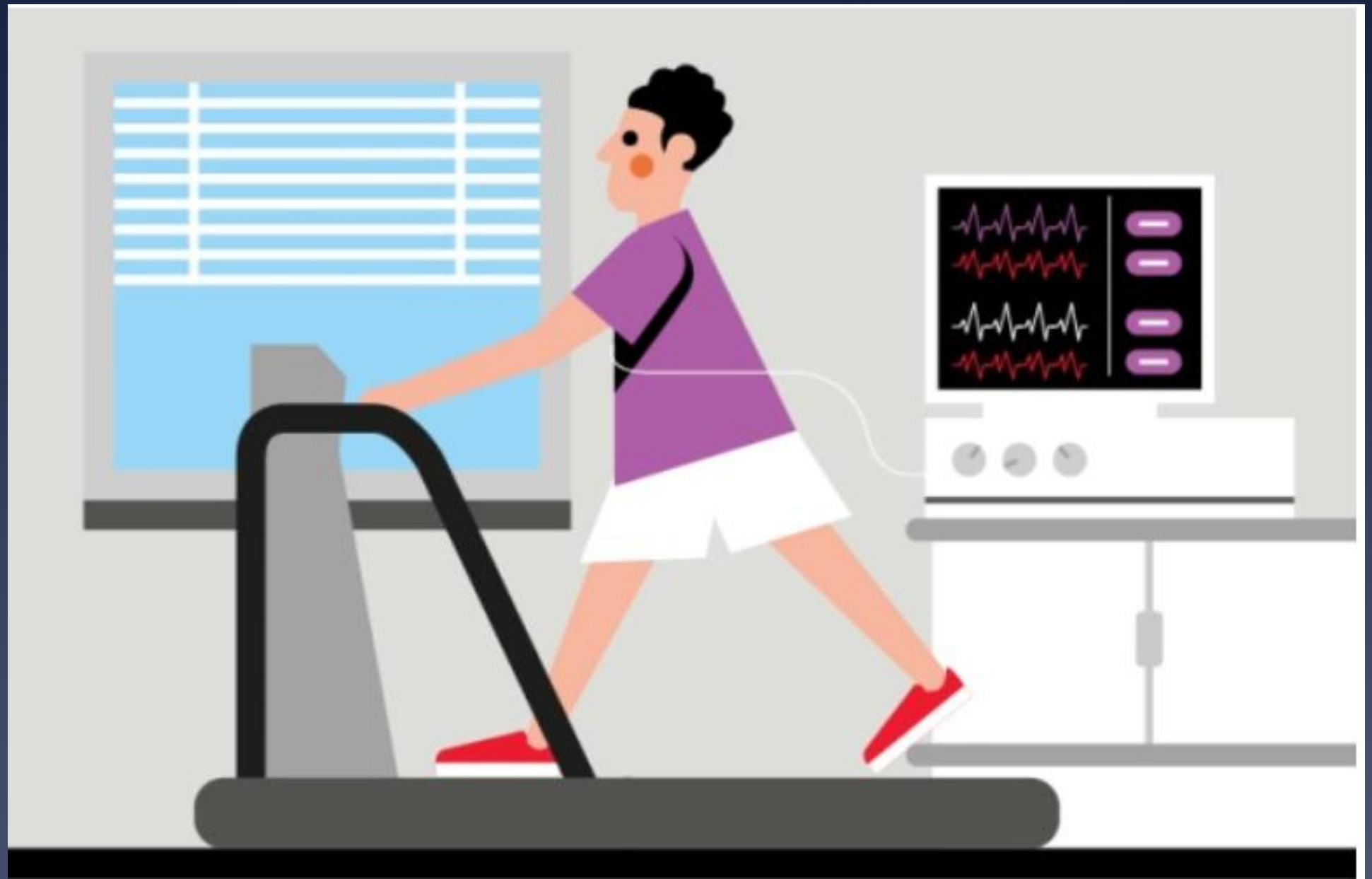
Which Modality to choose?

* It is essential to understand the limitations and strengths of each imaging method and, specifically, when to choose a functional approach focused on the ischemia versus a coronary anatomy-based one.
* Ultimately the goal of using non-invasive testing is to guide further non-invasive medical or invasive therapy.
* Overview of non-invasive imaging modalities for the comprehensive management of CCS patients

Sensitivity (true positive rate) is the probability of a positive test result, conditioned on the individual truly being positive.

Specificity (true negative rate) is the probability of a negative test result, conditioned on the individual truly being negative.

Stress Testing



Exercise Stress Testing

- ✓ Stress testing is generally safe. There is a small risk of acute myocardial infarction (~1:5000 tests) and death (~1:10 000 tests)
- ✓ The is sensitivity 68% and the specificity is 70-77%
- ✓ Advantage : Assessment of exercise capacity, Cost effective, First line test in absence of contraindications.
- ✓ Disadvantage : Lowest sensitivity of all stress tests: risk of false negative test and Lower diagnostic accuracy in women.

Stress ECG is functional tests and it cannot state a percentage of coronary stenosis (as commonly reported in CT coronary angiography). Stress ECG does not specify which coronary artery is the culprit vessel.

When should cardiac stress testing be ordered?

* Risk stratification of known or possible CAD. The annual risk of cardiovascular mortality can be quantified from stress test results by measures such as the Duke treadmill score (low risk equating to <1% per year cardiovascular mortality, high risk >5% per year cardiovascular mortality).
* Work-up for potential cardiac causes of dyspnoea (noting dyspnoea can be a cardiac equivalent symptom of CAD)
* Evaluation of the effects of exercise on valvular dysfunction, pulmonary pressures or arrhythmia (eg. chronotropic incompetence),
* Risk assessment in the postinfarct, preoperative or high risk patient populations.

Who should not have an Exercise Stress testing

* Stress ECG should not be ordered when the baseline ECG shows a complete LBBB.

* Paced ventricular rhythm.

* Pre-excitation syndrome (Wolf-Parkinson-White syndrome) or AF

* More than 1 mm ST segment depression (eg. associated with left ventricular hypertrophy or digitalis effect).

In these cases, ischaemic ECG changes cannot be identified and an imaging stress test should be considered.

Acute myocardial infarction , high risk unstable angina, symptomatic severe aortic stenosis, uncontrolled arrhythmia causing symptoms or haemodynamic instability, unstable heart failure, acute pulmonary embolus and acute aortic dissection…. Big NO NO …!

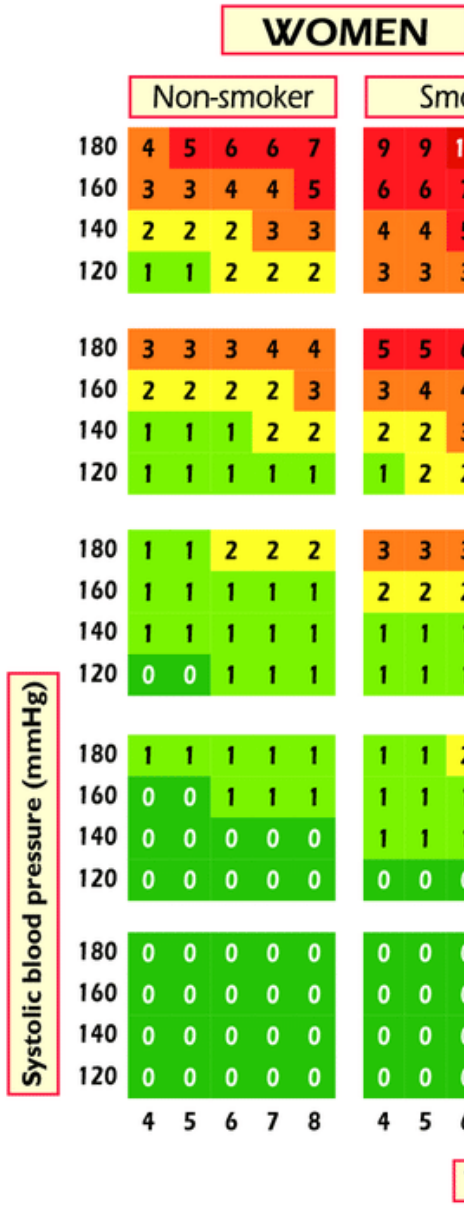
Stress test results… What does it means

Test result	What it could mean	What could still happen	What is the next step?
Normal	You do not have significant coronary artery disease (70% or greater artery blockage).	You could still have a heart attack if a smaller blockage (less than 70%) ruptures and forms a clot.	Your doctor may want to do further testing if you have other risk factors for heart disease that raise concern.
Abnormal	You may have significant coronary artery disease (70% or greater blockage).	The abnormal result may be a false alarm, and could require further testing to confirm.	The doctor may order additional tests to confirm that you have coronary artery disease.

Where do Exercise stress testing Stand now

2019	Class[a]
Exercise ECG is recommended for the assessment of exercise tolerance, symptoms, arrhythmias, BP response, and event risk in selected patients.	I
Exercise ECG may be considered as an alternative test to rule-in or rule-out CAD when other non-invasive or invasive imaging methods are not available.	IIb
Exercise ECG may be considered in patients on treatment to evaluate control of symptoms and ischaemia.	IIb

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. European Heart Journal (2020) 41, 407- 477



Low CVD countries are Andorra, Austria, Belgium, Luxembourg, Malta, Monaco, The Netherlands, No

Step 1: Age

Years	Points	Years	Points
30 to 34	–1	55 to 59	4
35 to 39	0	60 to 64	5
40 to 44	1	65 to 69	6
45 to 49	2	70 to 74	7
50 to 54	3		

Step 2: LDL or TC Level

LDL

mg per dL	mmol per L	Points
< 100	< 2.59	–3
100 to 129	2.59 to 3.35	0
130 to 159	3.36 to 4.13	0
160 to 190	4.14 to 4.92	1
> 190	> 4.92	2

TC

mg per dL	mmol per L	Points
< 160	< 4.14	–3
160 to 199	4.14 to 5.16	0
200 to 239	5.17 to 6.20	1
240 to 279	6.21 to 7.23	2
≥ 280	≥ 7.24	3

Step 3: HDL Level

mg per dL	mmol per L	Points (if LDL used in step 2)	Points (if TC used in step 2)
< 35	< 0.91	2	2
35 to 44	0.91 to 1.15	1	1
45 to 49	1.16 to 1.28	0	0
50 to 59	1.29 to 1.54	0	0
≥ 60	≥ 1.55	–1	–2

Step 4: Blood Pressure

Systolic (mm Hg)	Diastolic (mm Hg) < 80	80 to 84	85 to 89	90 to 99	≥ 100
< 120	0 points				
120 to 129		0 points			
130 to 139			1 point		
140 to 159				2 points	
≥ 160					3 points

NOTE: When systolic and diastolic pressures provide different point scores, use the higher score.

Step 5: Diabetes Mellitus

Present?	Points
No	0
Yes	2

Step 6: Smoking

Smoker?	Points
No	0
Yes	2

Step 7: Total Points

Step 1: Age _____
Step 2: LDL or TC level _____
Step 3: HDL level _____
Step 4: Blood pressure _____
Step 5: Diabetes mellitus _____
Step 6: Smoking _____
Total points _____

Step 8: CHD Risk

Total points	10-year risk if LDL used in step 2 (%)	10-year risk if TC used in step 2 (%)
≤ –3	1	—
–2	2	—
–1	2	2
0	3	3
1	4	3
2	4	4
3	6	5
4	7	7
5	9	8
6	11	10
7	14	13
8	18	16
9	22	20
10	27	25
11	33	31
12	40	37
13	47	45
≥ 14	≥ 56	≥ 53

Step 9: Comparative Risk

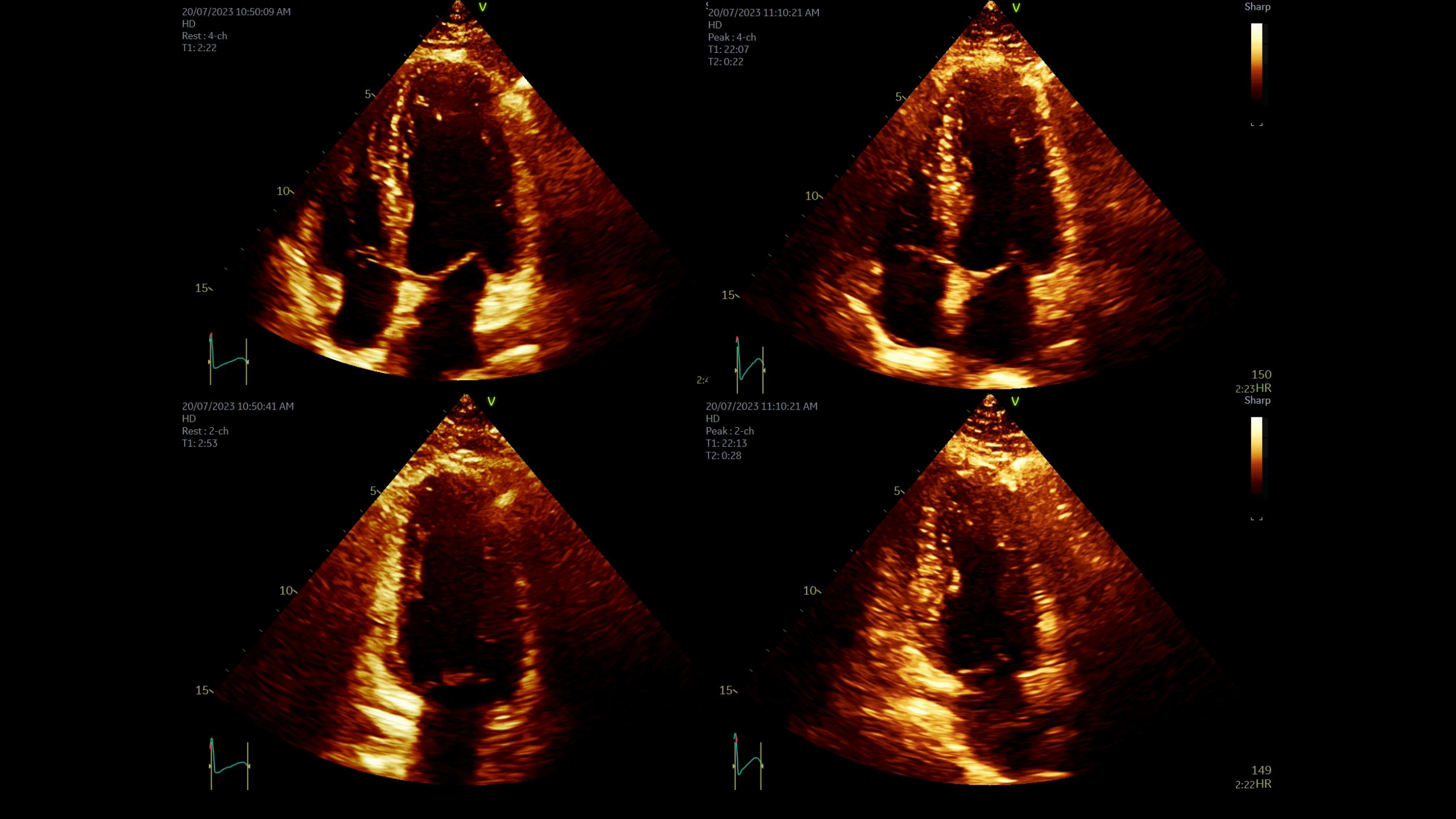
Age (years)	Average 10-year CHD risk (%)	Average 10-year risk of hard event* (%)	Low 10-year CHD risk† (%)
30 to 34	3	1	2
35 to 39	5	4	3
40 to 44	7	4	4
45 to 49	11	8	4
50 to 54	14	10	6
55 to 59	16	13	7
60 to 64	21	20	9
65 to 69	25	22	11
70 to 74	30	25	14

*—Hard events exclude angina pectoris.
†—Low risk as calculated for a man of the same age who does not smoke or have diabetes, and has optimal blood pressure, an LDL level of 100 to 129 mg per dL or TC level of 160 to 199 mg per dL, and an HDL level of 45 mg per dL.

Key

Color	Relative risk	Color	Relative risk
Green	Very low	Orange	High
White	Low	Red	Very high
Yellow	Moderate		

Point Total	10-Year Risk	
	Men	Women
≤ -3	< 1%	< 1%
-2	1.1%	< 1%
-1	1.4%	1.0%
0	1.6%	1.2%
1	1.9%	1.5%
2	2.3%	1.7%
3	2.8%	2.0%
4	3.3%	2.4%
5	3.9%	2.8%
6	4.7%	3.3%
7	5.6%	3.9%
8	6.7%	4.5%
9	7.9%	5.3%
10	9.4%	6.3%
11	11.2%	7.3%
12	13.2%	8.6%
13	15.6%	10.0%
14	18.4%	11.7%
15	21.6%	13.7%
16	25.3%	15.9%
17	29.4%	18.5%
18	>30%	21.5%
19	>30%	24.8%
20	>30%	28.5%
21+	>30%	>30%


20/07/2023 10:50:09 AM
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Rest : 4-ch
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T2: 0:22
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Rest : 2-ch
T1: 2:53
20/07/2023 11:10:21 AM
HD
Peak : 2-ch
T1: 22:13
T2: 0:28
150
2:23HR
Sharp
149
2:22HR

Exercise Stress Echocardiography

* Sensitivity is about 80-85% and the specificity is 84-86%
* Advantage : Assessment of exercise capacity, cardiac structure/function, No radiation, Highly specificity.
* Disadvantage : False negatives in single vessel/circumflex territory ischaemia (increased sensitivity with cycle ergometry).

Stress echocardiography is a functional tests, and although it cannot state a percentage of coronary stenosis (as commonly reported in CT coronary angiography) BUT it can imply which artery may be stenosed by looking at the regional LV wall of the Left Ventricle supplied by the culprit vessel.

World Journal of Cardiology

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ISSN 1949-8462 (online)

REVIEW

Exercise stress echocardiography: Where are we now?

Carlos Alberto Cotrim, Hugo Café, Isabel João, Nuno Cotrim, Jorge Guardado, Pedro Cordeiro, Hortense Cotrim, Luis Baquero

Specialty type: Cardiac and cardiovascular systems

Provenance and peer review: Invited article; Externally peer reviewed.

Peer-review model: Single blind

Peer-review report's scientific quality classification

Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): C
Grade D (Fair): 0
Grade E (Poor): 0

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Exercise stress echocardiography: Where are we now?

* Exercise is the most physiologic stressor of all and should thus be preferable in patients who are able to exercise. In coronary artery disease diagnosis, exercise echocardiography is the appropriate first-line test for patients who are asymptomatic or with chest pain or dyspnea as the chief complaint.

* A major advantage of exercise echocardiography over the other forms of stress is that it may offer helpful and versatile evaluation of valve function and pulmonary hemodynamics and of special subsets of patients, such as patients with heart failure, pulmonary hypertension, valve disease, congenital heart disease, or athletes with symptoms of unknown etiology in search of intraventricular gradients.

* More importantly, the option of ESE is advantageous over techniques with higher cost and radiation burden for effective primary prevention of cancer, which should begin in the cardiac imaging laboratory.

Cotrim CA et al. Exercise stress echocardiography. World J Cardiol 2022 February 26; 14(2): 64-82

Strengths and weaknesses of stress echocardiography: key points

Strengths

– "patient friendly", versatility

– accuracy

– prognostic value

– detection of viable myocardium after infarction

– assessment of left ventricular reserve (for example, valvar heart disease)

Weaknesses

– dependence on image quality

– subjectivity, need for an expert reader

– dependence on ischaemia (hence problems with mild disease, submaximal stress, and testing on treatment)

– recognition of ischaemia with resting wall motion abnormalities

– recognition of multivessel disease

Open Access Full Text Article

REVIEW

Dobutamine stress echocardiography: a review and update

This article was published in the following Dove Press journal:
Research Reports in Clinical Cardiology
5 April 2014
Number of times this article has been viewed

Lauren Gray Gilstrap[1]
R Sacha Bhatia[2]
Rory B Weiner[3]
David M Dudzinski[3]

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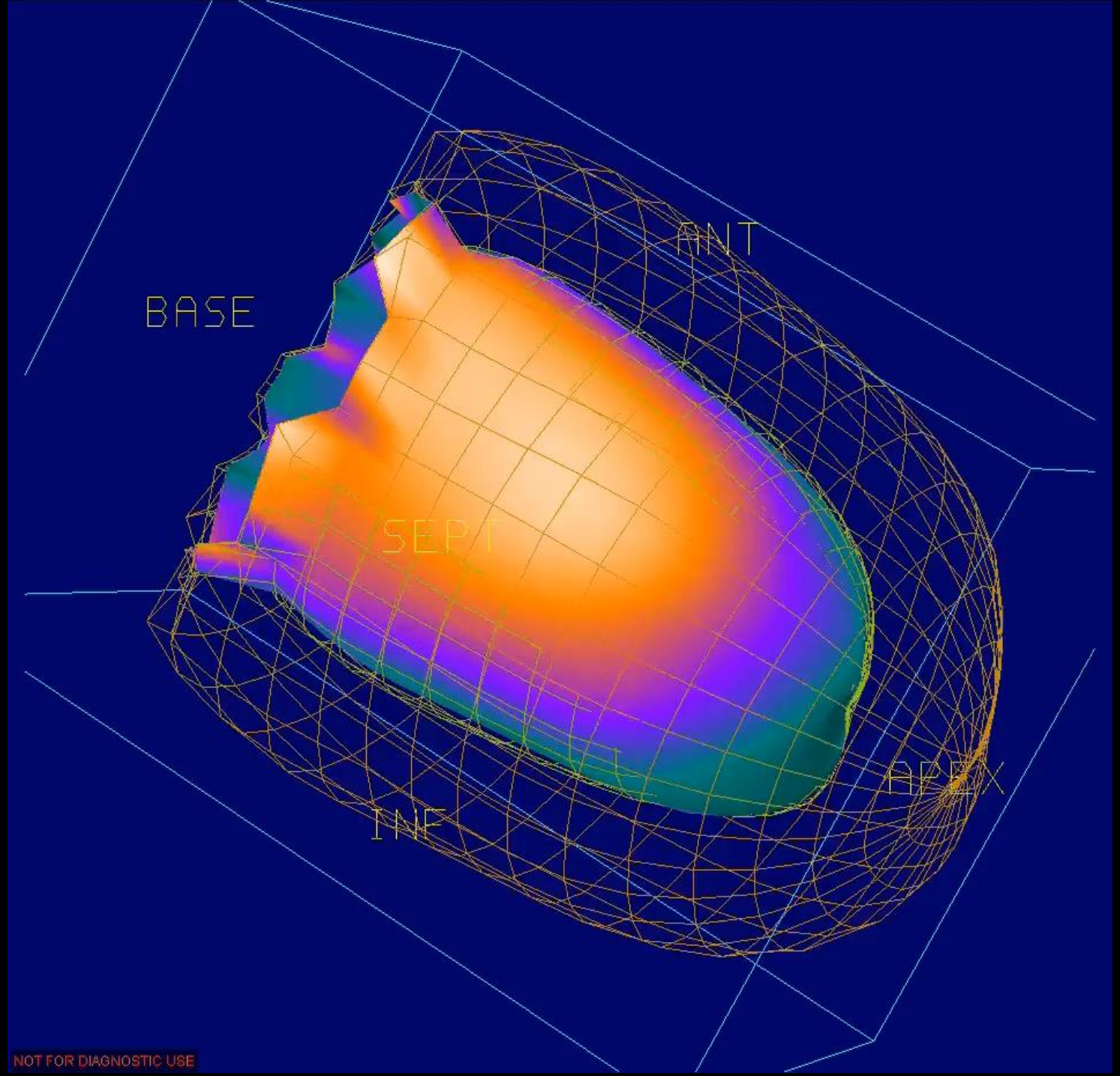
Abstract: Stress echocardiography is a noninvasive cardiovascular diagnostic test that provides functional and hemodynamic information in the assessment of a number of cardiac diseases. Performing stress echocardiography with a pharmacologic agent such as dobutamine allows for simulation of increased heart rate and increased myocardial physiologic demands in patients who may be unable to exercise due to musculoskeletal or pulmonary comorbidities. Dobutamine stress echocardiography (DSE), like exercise echocardiography, has found its primary application in ischemic heart disease, with roles in identification of obstructive epicardial coronary artery disease, detection of viable myocardium, and assessment of the efficacy of anti-ischemic medical therapy in patients with known coronary artery disease. DSE features prominently in the evaluation and management of valvular heart disease by helping to assess the effects of mitral and aortic stenoses, as well as a specific use in differentiating true severe valvular aortic stenosis from pseudostenosis that may occur in the setting of left ventricular systolic dysfunction. DSE is generally well tolerated, and its side effects and contraindications generally relate to consequences of excess inotropic and/or chronotropic stimulation of the heart. The aim of this paper is to review the indications, contraindications, advantages, disadvantages, and risks of DSE.

Keywords: stress echocardiography, dobutamine, coronary artery disease, myocardial ischemia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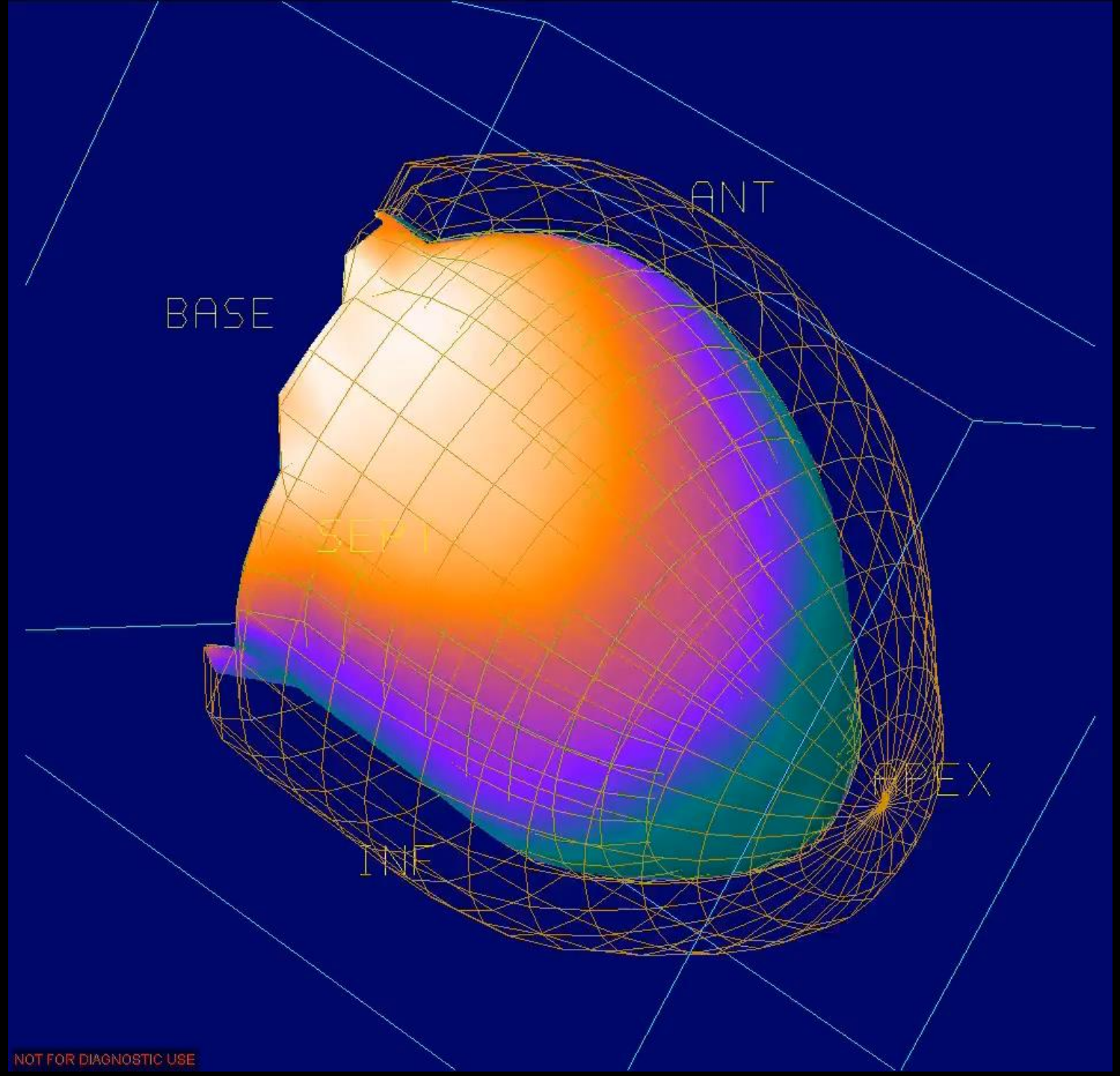
Nuclear perfusion study

* Sensitivity is about 85-90% and the specificity is 70-75%
* Advantage : Exercise capacity can be assessed and High sensitivity.
* Disadvantage : Radiation (9-10 mSv) and False positives due to higher sensitivity/ diaphragmatic attenuation as in SPECT scan …… BUT have improved with PET scan.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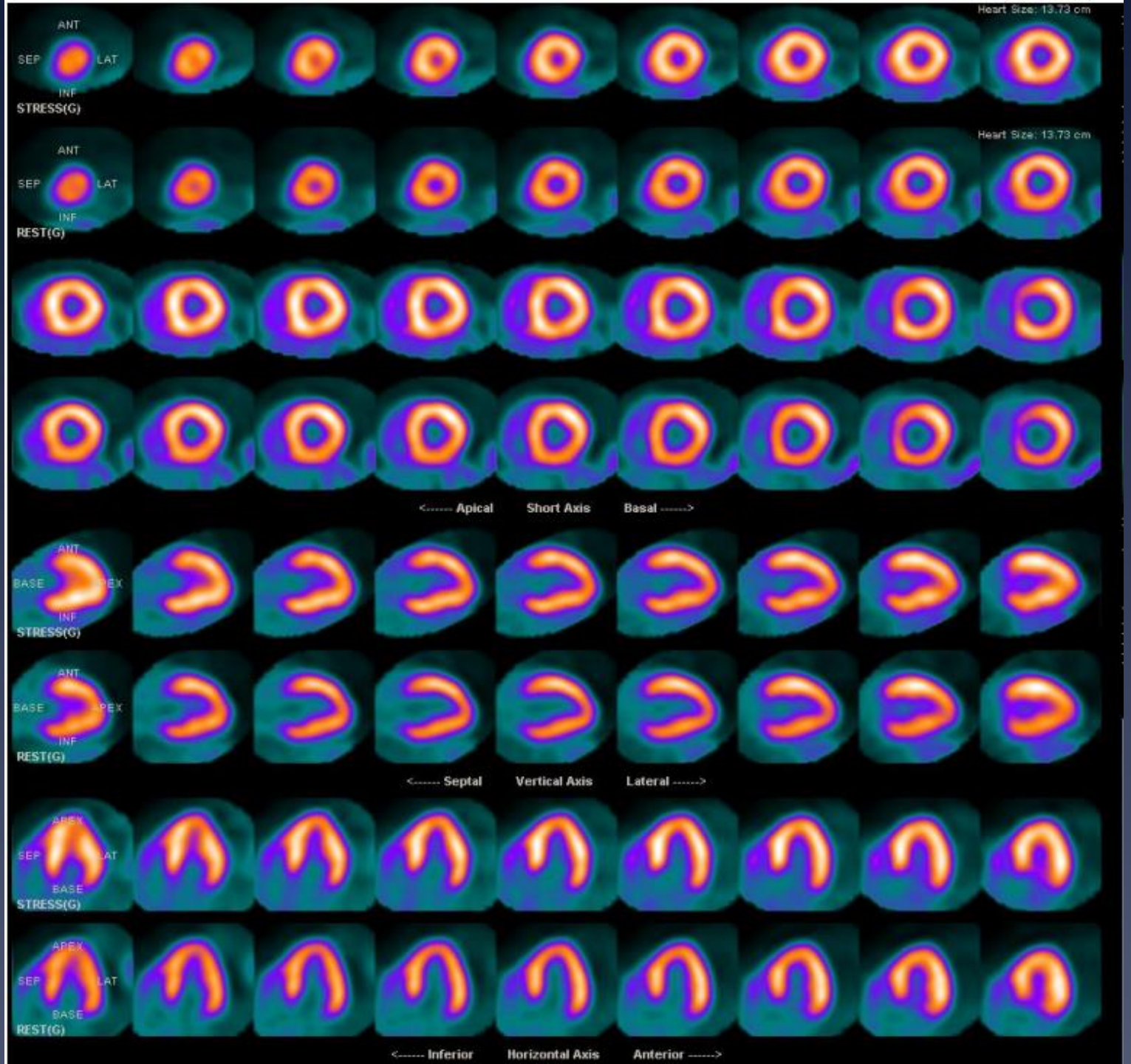
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Heart Size: 13.73 cm
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Anterior ------>

Cardiac Single photon emission computed tomography (SPECT)

- ✓ is lower cost
- ✓ uses gamma emitting radioisotope (tracer):

  technetium-99m

  iodine-123

  iodine-131
- ✓ gives poorer contrast and spatial resolution (cf. PET)
- ✓ usually one large crystal based detector

Cardiac Positron emission tomography

- ✓ is very expensive
- ✓ uses positron emitting radioisotope (tracer)
  rubidium-82 as the radiotracer
- ✓ gives better contrast and spatial resolution (cf. SPECT)
- ✓ has a ring of multiple detectors
- ✓ Cardiac MPI with PET imaging have reported radiation exposure ranging from 2.5 to 5 mSv for rest/stress studies.

Clinical PET Myocardial Perfusion Imaging and Flow Quantification

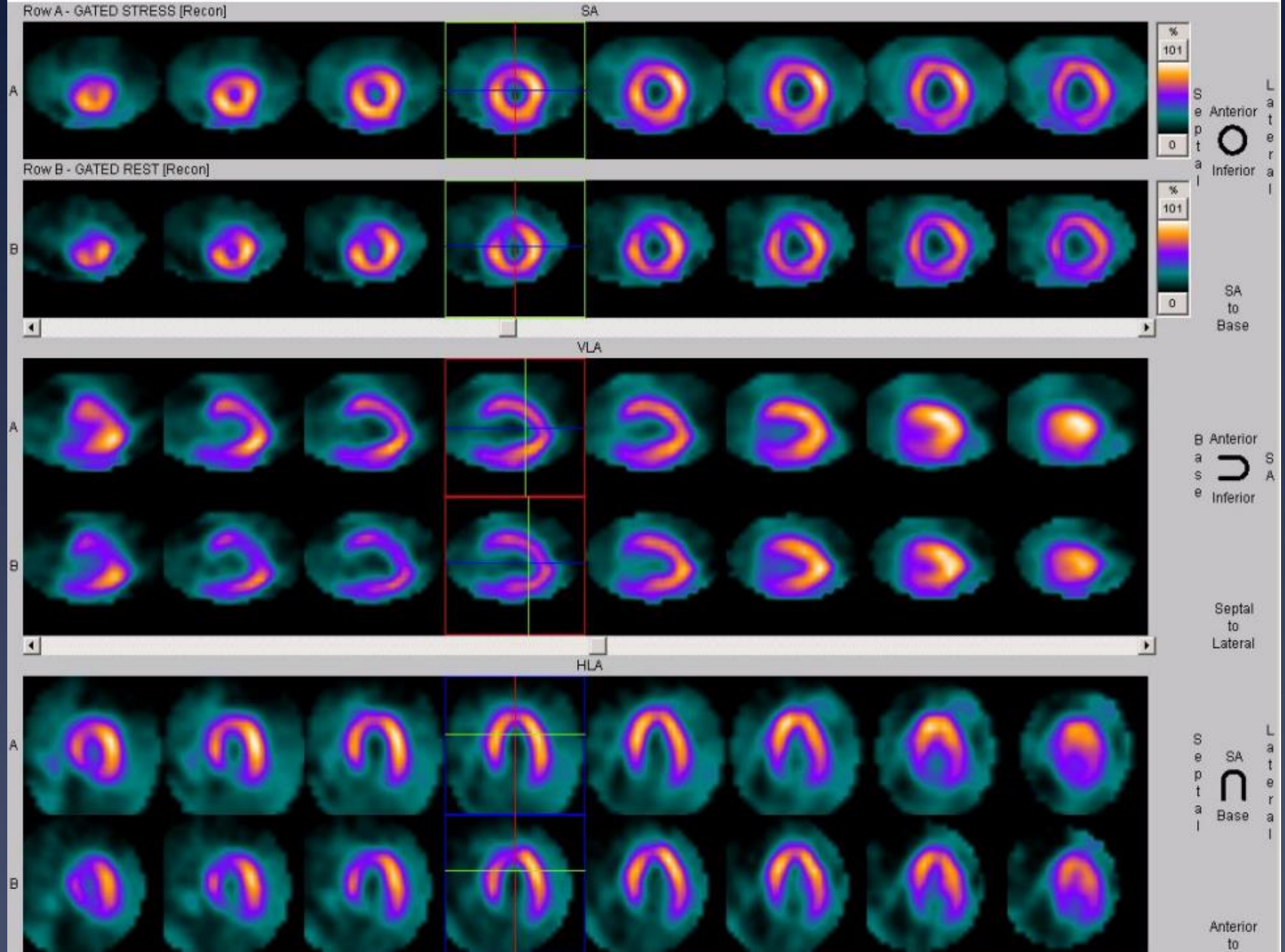
Daniel Juneau, MD, FRCPC[a,1], Fernanda Erthal, MD[a,1],
Hiroshi Ohira, MD, PhD[a,b], Brian Mc Ardle, MD[a],
Renée Hessian, MD, FRCPC[a],
Robert A. deKemp, PhD, PEng, PPhys[a],
Rob S.B. Beanlands, MD, FRCPC[a,*]

* Cardiac PET has inherent advantages over single photon emission computed tomography (SPECT) myocardial perfusion imaging (MPI), including better imaging characteristics and the ability to quantify blood flow routinely.

* PET MPI has better sensitivity, specificity and accuracy than SPECT MPI in the detection of obstructive coronary artery disease.

* Myocardial flow reserve assessment can overcome the pitfall of balanced ischemia otherwise observed using conventional MPI in some patients with multivessel disease.

* PET MPI and flow quantification provide independent and incremental prognostic information for risk stratification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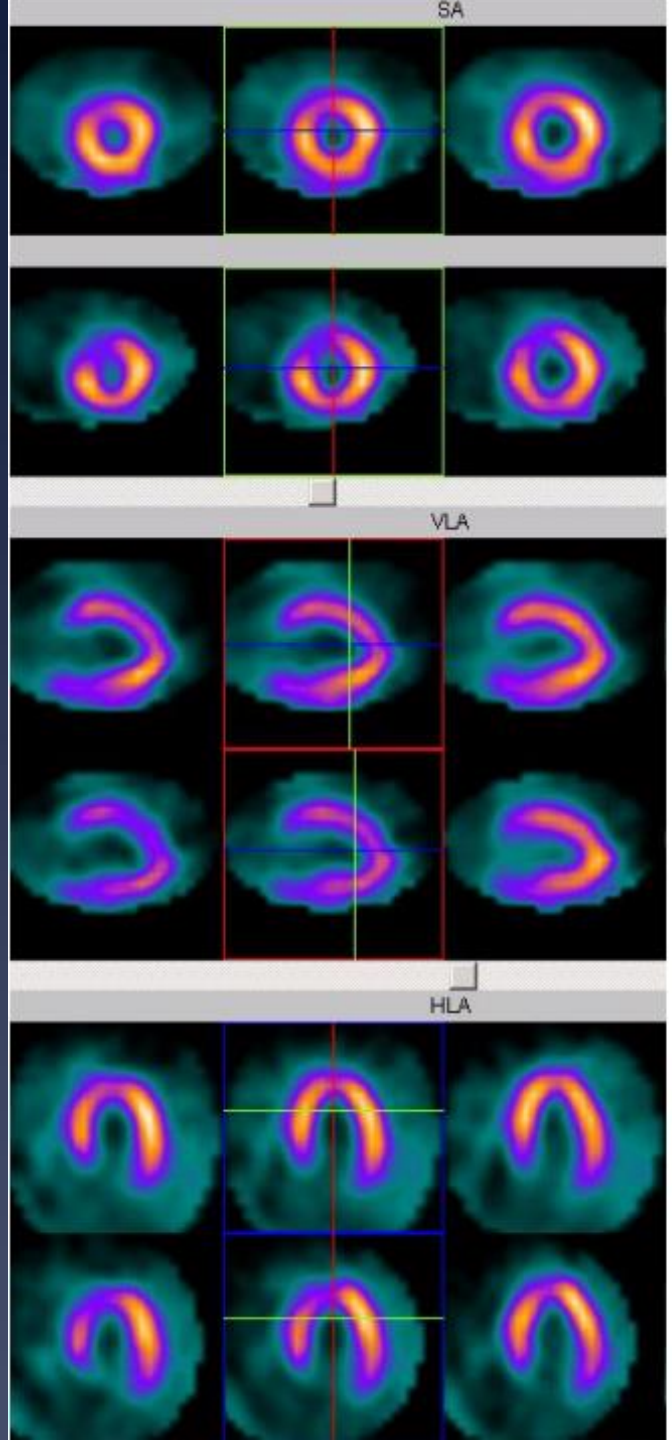
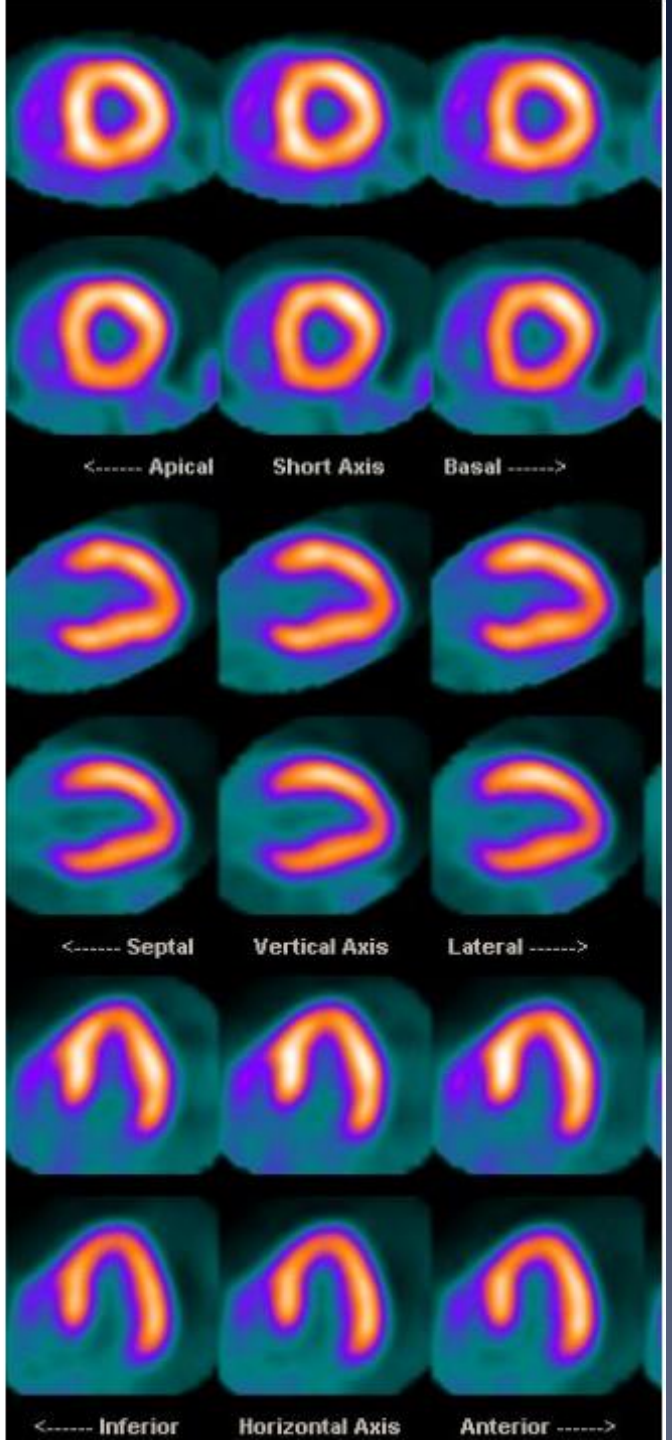




SPECT MPI Report

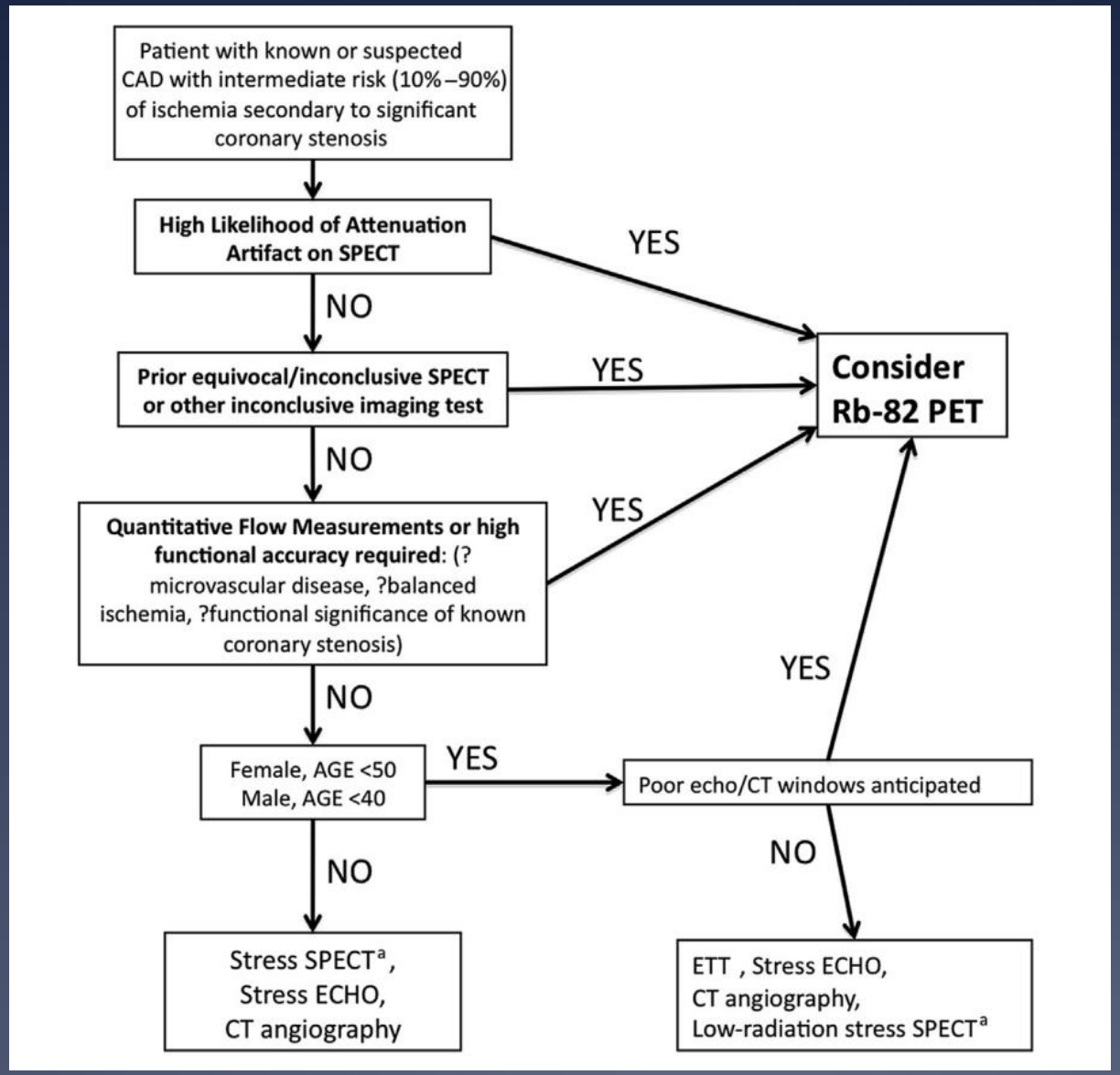
There was a small defect of moderate intensity in the mid to apical anterior wall that remained fixed on the rest images and most likely is due to breast attenuation artifact; however a non-transmural myocardial scar cannot be excluded.

PET MPI Report

There were no regional perfusion defects seen on the stress or rest images. The patient's PET/CT test results are normal and suggest no evidence of flow-limiting CAD. The results suggest that the previously described fixed anterior wall defect (her prior SPECT study) is likely to represent an attenuation artifact.

Cardiac catheterization was not performed because the PET MPI study was normal.

Proposed clinical algorithm for use of rubidium-82-chloride (Rb-82) PET myocardial perfusion imaging

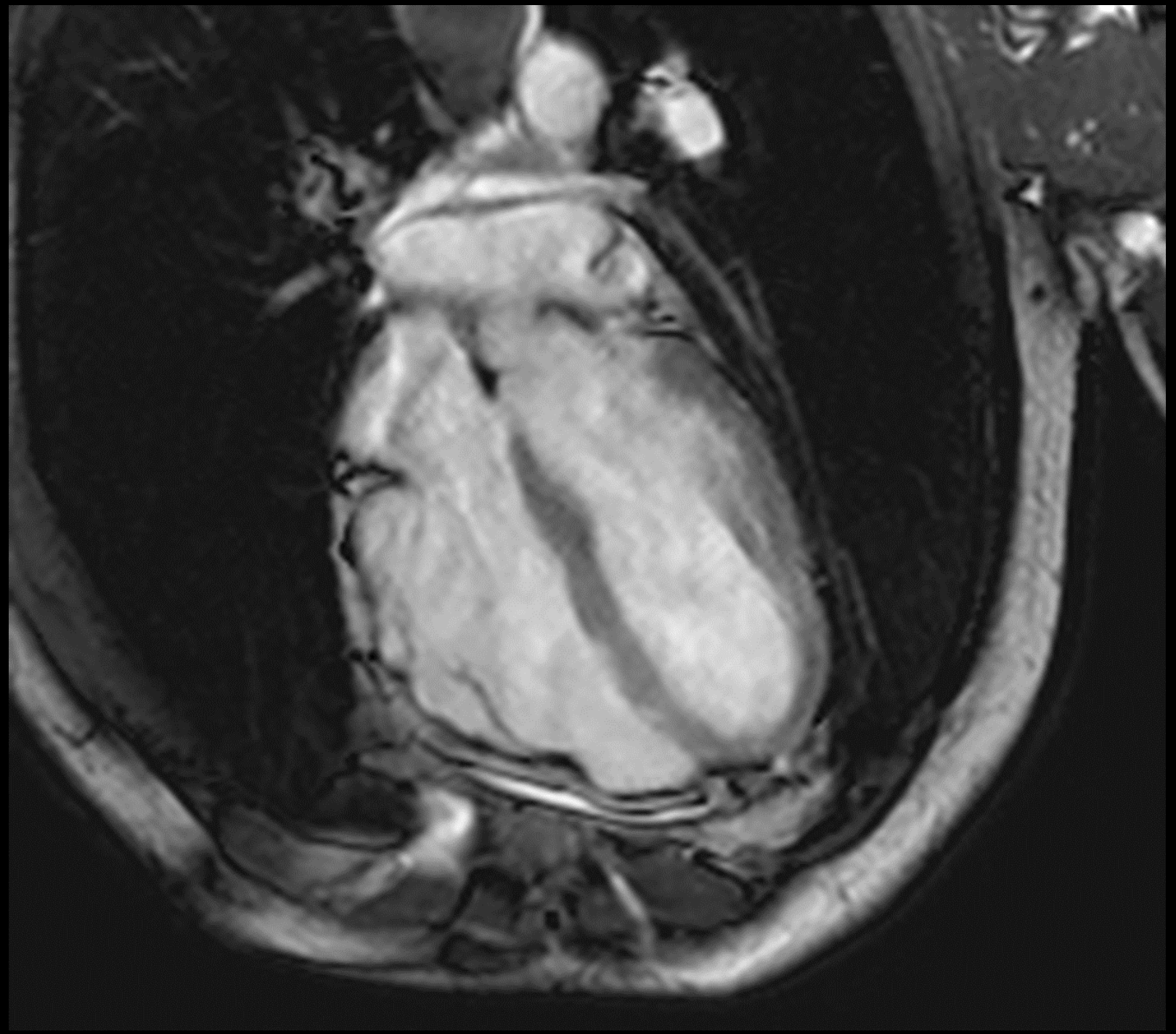


The Prognostic Value of Normal Exercise Myocardial Perfusion Imaging and Exercise Echocardiography A Meta-Analysis

Summary…..The negative predictive value (NPV) for MI and cardiac death was 98.8% (95% confidence interval [CI] 98.5 to 99.0) over 36 months of follow-up for MPI, and 98.4% (95% CI 97.9 to 98.9) over 33 months for echocardiography.

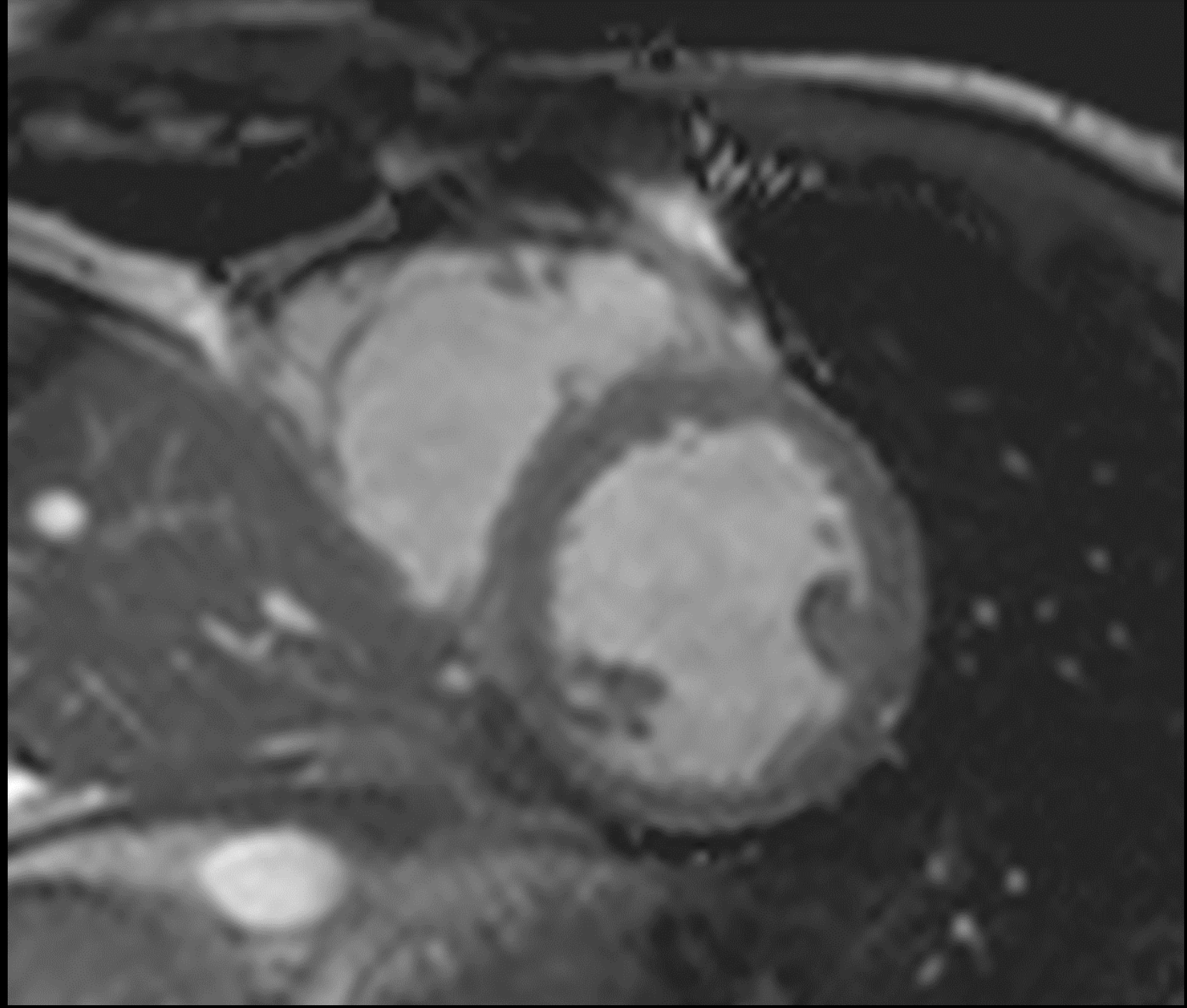
The corresponding annualized event rates were 0.45% per year for MPI and 0.54% per year for echocardiography. In subgroup analyses, annualized event rates were <1% for each MPI isotope, and were similar for women and men. For secondary events, MPI and echocardiography had annualized event rates of 1.25% and 0.95%, respectively

Metz et al. JACC Vol41. January 16, 2007:227–37 Prognostic Value of Exercise MPI and Echocardiography

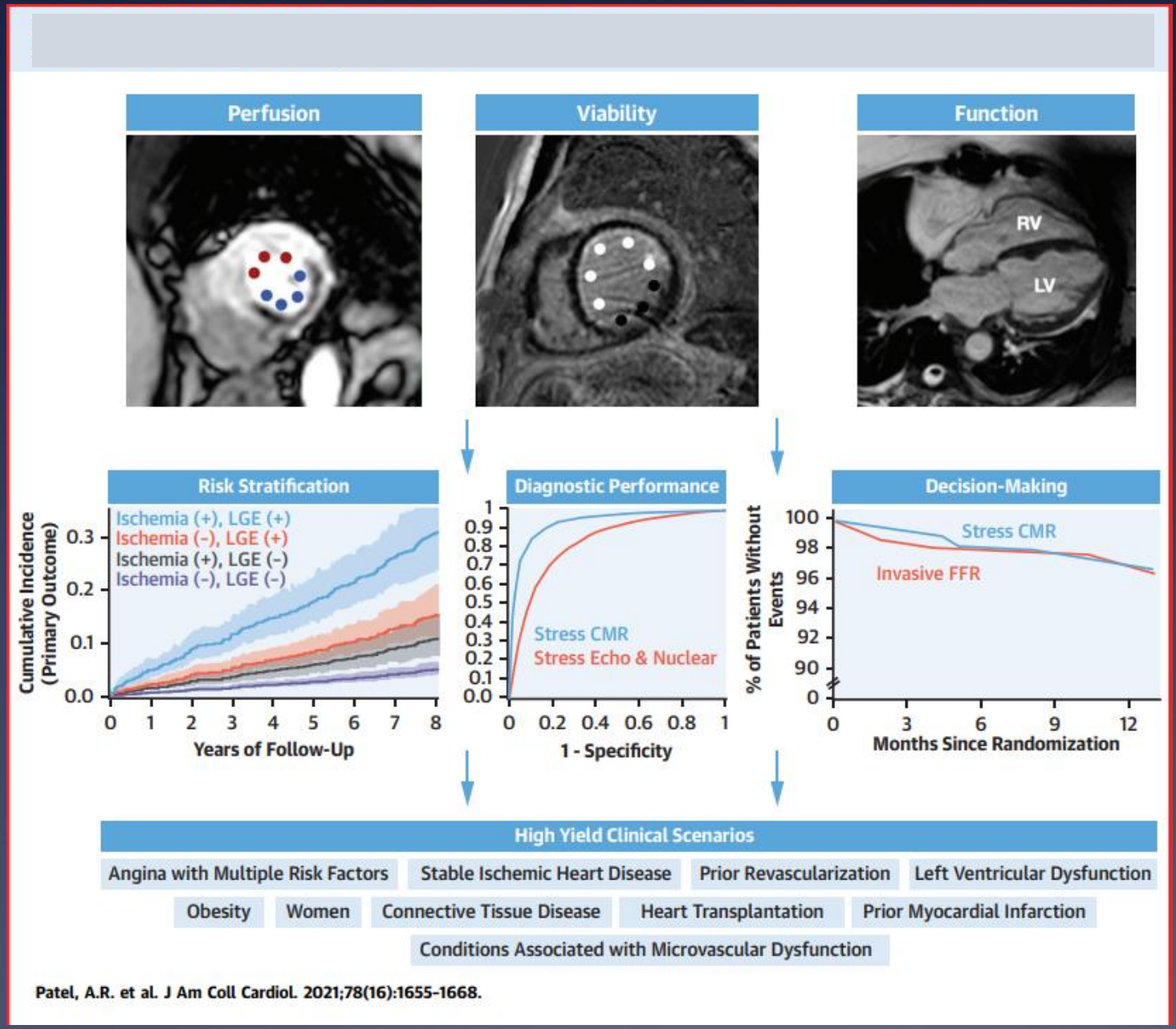


Cardiac MRI Imaging

* CMR reported high sensitivity 89% and specificity of 87%.
* CMR also has a g high spatial and temporal resolution in detecting subendocardial ischemia or infarction, freedom from soft tissue attenuation or the requirement of an acoustic window, sensitive tissue characterization for silent myocardial infarction and myocardial viability.
* Excellent safety profile, and lack of ionizing radiation or iodinated contrast exposure.



The Key Elements of A Stress Cardiac Magnetic Resonance Imaging Examination Include Assessment of Ischemia, Viability, and Function



Patel, A.R. et al. J Am Coll Cardiol. 2021;78(16):1655-1668.

LGE: Late gadolinium enhancement

Cardiac MRI Imaging limitations

* Stress CMR cannot readily be combined with exercise at present.
* Claustrophobic and obese patients may not be able to tolerate the study.
* Patients with implantable devices including ferromagnetic materials may not be ideal candidates for stress CMR due to device-related imaging artifacts that limit interpretability of the images.
* The utilization of stress CMR is also hampered by cost and expertise.

JACC REVIEW TOPIC OF THE WEEK

JACC VOL. 78, NO. 16, OCTOBER 19, 2021:1655 – 166

Stress Cardiac Magnetic Resonance Myocardial Perfusion Imaging

JACC Review Topic of the Week

Amit R. Patel, MD,[a,b] Michael Salerno, MD, PhD, MS,[c,d,e] Raymond Y. Kwong, MD, MPH,[f] Amita Singh, MD,[a] Bobak Heydari, MD,[g] Christopher M. Kramer, MD[c,d]

ABSTRACT

Stress cardiovascular magnetic resonance imaging (CMR) is a cost-effective, noninvasive test that accurately assesses myocardial ischemia, myocardial viability, and cardiac function without the need for ionizing radiation. There is a large body of literature, including randomized controlled trials, validating its diagnostic performance, risk stratification capabilities, and ability to guide appropriate use of coronary intervention. Specifically, stress CMR has shown higher diagnostic sensitivity than single-photon emission computed tomography imaging in detecting angiographically significant coronary artery disease. Stress CMR is particularly valuable for the evaluation of patients with moderate to high pretest probability of having stable ischemic heart disease and for patients known to have challenging imaging characteristics, including women, individuals with prior revascularization, and those with left ventricular dysfunction. This paper reviews the basics principles of stress CMR, the data supporting its clinical use, the added-value of myocardial blood flow quantification, and the assessment of myocardial function and viability routinely obtained during a stress CMR study.

(J Am Coll Cardiol 2021;78:1655-1668)

diagnostics

MDPI

Review

Qualitative and Quantitative Stress Perfusion Cardiac Magnetic Resonance in Clinical Practice: A Comprehensive Review

Wenli Zhou [1], Jason Sin [2], Andrew T. Yan [3], Haonan Wang [4], Jing Lu [1], Yuehua Li [1], Paul Kim [5], Amit R. Patel [6] and Ming-Yen Ng [7,8,*]

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5 Department of Medicine, University of California San Diego, San Diego, CA 92093, USA
6 Department of Cardiovascular Medicine, University of Virginia, Charlottesville, VA 22903, USA
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* Correspondence: myng2@hku.hk

Abstract: Stress cardiovascular magnetic resonance (CMR) imaging is a well-validated non-invasive stress test to diagnose significant coronary artery disease (CAD), with higher diagnostic accuracy than other common functional imaging modalities. One-stop assessment of myocardial ischemia, cardiac function, and myocardial viability qualitatively and quantitatively has been proven to be a cost-effective method in clinical practice for CAD evaluation. Beyond diagnosis, stress CMR also provides prognostic information and guides coronary revascularisation. In addition to CAD, there is a large body of literature demonstrating CMR's diagnostic performance and prognostic value in other common cardiovascular diseases (CVDs), especially coronary microvascular dysfunction (CMD). This review focuses on the clinical applications of stress CMR, including stress CMR scanning methods, practical interpretation of stress CMR images, and clinical utility of stress CMR in a setting of CVDs with possible myocardial ischemia.

Keywords: stress imaging; cardiac magnetic resonance imaging; myocardial ischemia; coronary artery disease; coronary microvascular dysfunction

Citation: Zhou, W.; Sin, J.; Yan, A.T.; Wang, H.; Lu, J.; Li, Y.; Kim, P.; Patel, A.R.; Ng, M.-Y. Qualitative and Quantitative Stress Perfusion Cardiac Magnetic Resonance in Clinical Practice: A Comprehensive Review. *Diagnostics* **2023**, *13*, 524. https://

This Issue | Views 4,591 | Citations 0 | Altmetric 50

Original Investigation

June 7, 2023

Diagnostic and Prognostic Value of Stress Cardiovascular Magnetic Resonance Imaging in Patients With Known or Suspected Coronary Artery Disease

A Systematic Review and Meta-analysis

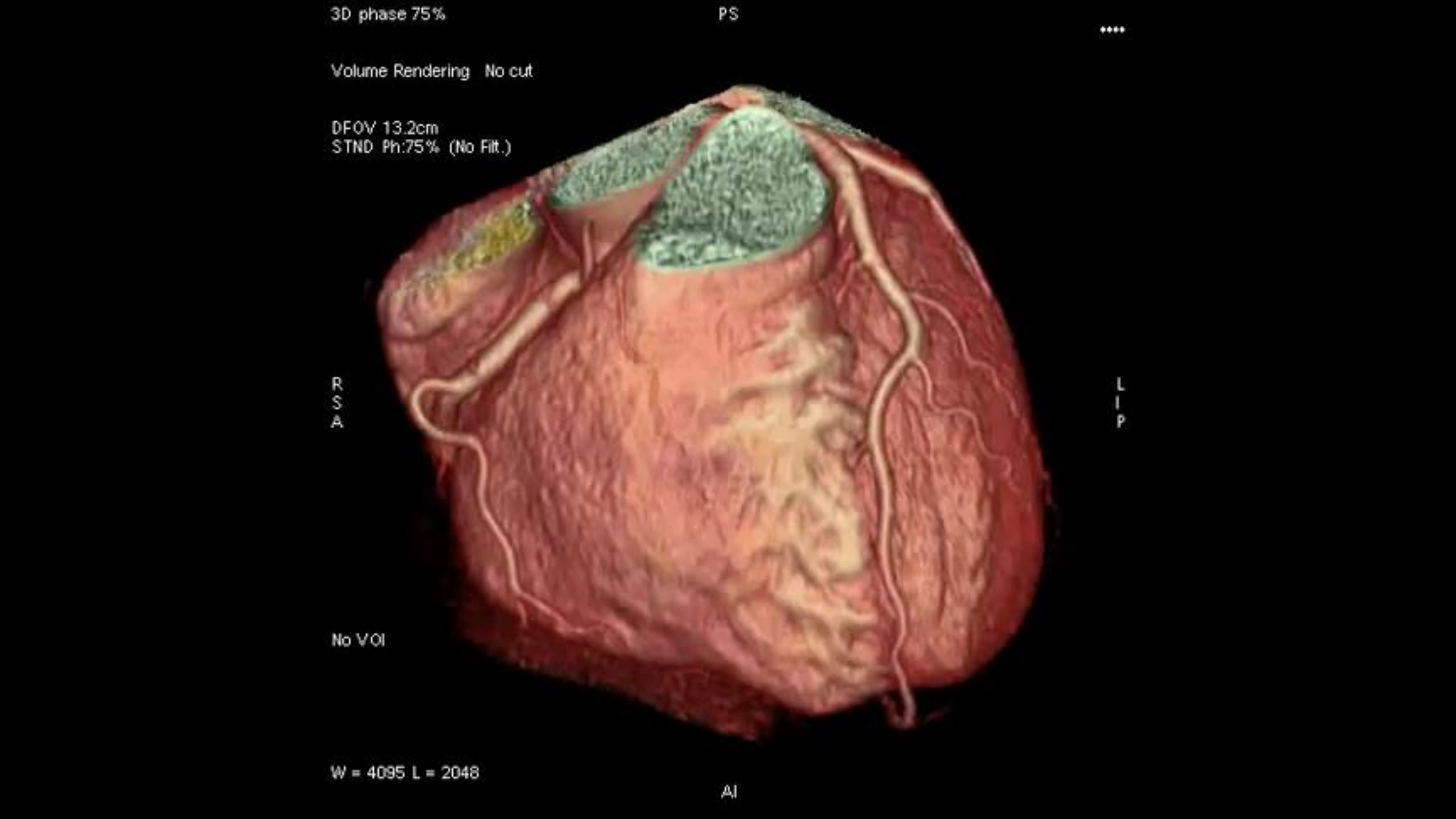
Fabrizio Ricci, MD, PhD, MSc[1,2,3]; Mohammed Y. Khanji, MBBCh, PhD[3,4,5]; Giandomenico Bisaccia, MD[1]; et al

» Author Affiliations

JAMA Cardiol. 2023;8(7):662-673. doi:10.1001/jamacardio.2023.1290

This systematic review and meta-analysis pooling 74,470 patients with stable chest pain over 381,357 person-years of follow-up, stress CMR yielded high diagnostic accuracy and accurate risk stratification in patients with known or suspected coronary artery disease, particularly when 3-T imaging was used.

The presence of stress-inducible ischemia and late gadolinium enhancement was associated with higher mortality and likelihood of cardiovascular events, while normal stress CMR results were associated with a lower likelihood of cardiovascular events for at least 3.5 years.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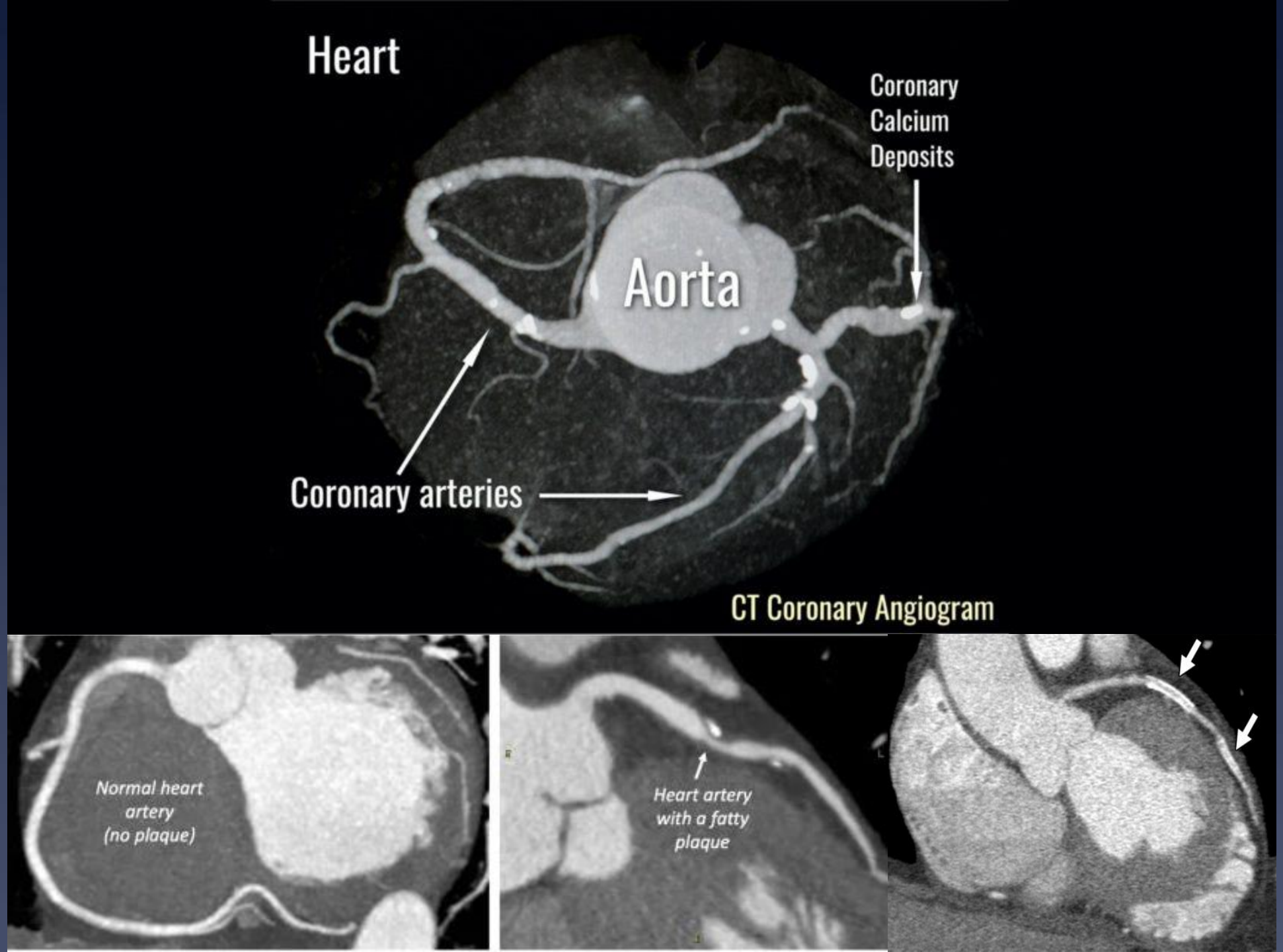
AI

CT coronary angiogram study

* Sensitivity is about 85-90% and the specificity is 64-90%
* Advantage : High negative predictive value (especially in low to intermediate risk subjects)
* Disadvantage : Radiation (12-20 mSv) and Functional effect of stenosis not usually assessed, nor exercise capacity

Coronary artery calcium score CT radiation is about 1–3 mSv


Heart
Coronary
Calcium
Deposits
Aorta
Coronary arteries
CT Coronary Angiogram
Normal heart
artery
(no plaque)
Heart artery
with a fatty
plaque

Article published online: 2022-03-01

Review

Thieme

Update for the Performance of CT Coronary Angiography

Evidence-Based Application and Technical Guidance According to Current Consensus Guidelines and Practical Advice from the Clinical Routine

Update zur Durchführung der CT-Koronarangiografie

Evidenzbasierter Einsatz und technische Anleitung entsprechend den aktuellen Empfehlungen sowie praktische Tipps aus der Routine am eigenen Standort

Authors

Martin Soschynski[1], Muhammad Taha Hagar[1], Jana Taron[1,2], Tobias Krauss[1], Philipp Ruile[3], Manuel Hein[3], Thomas Nührenberg[3], Maximilian Frederik Russe[1], Fabian Bamberg[1], Christopher L Schlett[1]

* cCTA is recommended in the current guidelines of the ESC primarily in the case of low and intermediate clinical probability of coronary artery disease.
* This study and the consensus recommendations of the Society of Cardiovascular Computed Tomography (SCCT) can be used as an orientation guide for the practical workflow for cCTA preparation and acquisition.
* Image quality and radiation dose still depend on the examination preparation and the selection of the scan protocol.

Soschynski M et al. Fortschr Röntgenstr 2022; 194: 613–624 | © 2022. Thieme.

CT coronary angiography in patients with suspected angina due to coronary heart disease (SCOT-HEART): an open-label, parallel-group, multicentre trial

*The SCOT-HEART investigators**

Summary

Background The benefit of CT coronary angiography (CTCA) in patients presenting with stable chest pain has not been systematically studied. We aimed to assess the effect of CTCA on the diagnosis, management, and outcome of patients referred to the cardiology clinic with suspected angina due to coronary heart disease.

Methods In this prospective open-label, parallel-group, multicentre trial, we recruited patients aged 18–75 years referred for the assessment of suspected angina due to coronary heart disease from 12 cardiology chest pain clinics across Scotland. We randomly assigned (1:1) participants to standard care plus CTCA or standard care alone. Randomisation

……the PROMISE and SCOT-HEART trials — that compared CT with functional testing in patients with stable symptoms …..The investigators found that CT was as good as functional testing as a preliminary evaluation before possible ICA.

Findings Between Nov 18, 2010, and Sept 24, 2014, we randomly assigned 4146 (42%) of 9849 patients who had been referred for assessment of suspected angina due to coronary heart disease. 47% of participants had a baseline clinic diagnosis of coronary heart disease and 36% had angina due to coronary heart disease. At 6 weeks, CTCA reclassified the diagnosis of coronary heart disease in 558 (27%) patients and the diagnosis of angina due to coronary heart disease in 481 (23%) patients (standard care 22 [1%] and 23 [1%]; p<0·0001). Although both the certainty (relative risk [RR] 2·56, 95% CI 2·33–2·79; p<0·0001) and frequency of coronary heart disease increased (1·09, 1·02–1·17; p=0·0172), the certainty increased (1·79, 1·62–1·96; p<0·0001) and frequency seemed to decrease (0·93, 0·85–1·02; p=0·1289) for the diagnosis of angina due to coronary heart disease. This changed planned investigations (15% *vs* 1%; p<0·0001) and treatments (23% *vs* 5%; p<0·0001) but did not affect 6-week symptom severity or subsequent admittances to hospital for chest pain. After 1·7 years, CTCA was associated with a 38% reduction in fatal and non-fatal myocardial infarction (26 *vs* 42, HR 0·62, 95% CI 0·38–1·01; p=0·0527), but this was not significant.

Interpretation In patients with suspected angina due to coronary heart disease, CTCA clarifies the diagnosis, enables targeting of interventions, and might reduce the future risk of myocardial infarction.

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This online publication has been corrected. The corrected version first appeared at

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The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Coronary CT Angiography and 5-Year Risk of Myocardial Infarction

The use of CTA in addition to standard care in patients with stable chest pain resulted in a significantly lower rate of death from coronary heart disease or nonfatal myocardial infarction at 5 years than standard care alone, without resulting in a significantly higher rate of coronary angiography or coronary revascularization.

The 5-year rate of the primary end point was lower in the CTA group than in the standard-care group (2.3% [48 patients] vs. 3.9% [81 patients]; hazard ratio, 0.59; 95% confidence interval [CI], 0.41 to 0.84; P=0.004).

METHODS

In an open-label, multicenter, parallel-group trial, we randomly assigned 4146 patients with stable chest pain who had been referred to a cardiology clinic for evaluation to standard care plus CTA (2073 patients) or to standard care alone (2073 patients). Investigations, treatments, and clinical outcomes were assessed over 3 to 7 years of follow-up. The primary end point was death from coronary heart disease or nonfatal myocardial infarction at 5 years.

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 28, 2022 VOL. 386 NO. 17

CT or Invasive Coronary Angiography in Stable Chest Pain

The DISCHARGE Trial Group

ABSTRACT

- Pragmatic, randomized trial comparing CT with ICA as initial diagnostic imaging strategies for guiding the treatment of patients with stable chest pain.
- 3561 patients followed up for 3.5 years. The primary outcome was major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke)

Among patients referred for ICA because of stable chest pain and intermediate pretest probability of CAD, the risk of major adverse cardiovascular events was similar in the CT group and the ICA group.

JACC: CARDIOVASCULAR IMAGING
VOL. 12, NO. 7, 2019

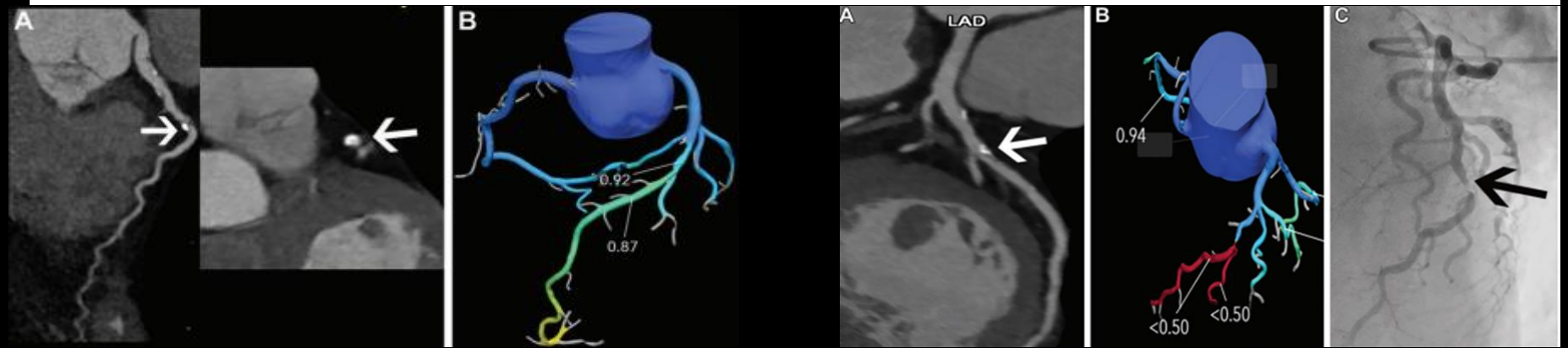
PUBLISHED BY ELSEVIER

ORIGINAL RESEARCH

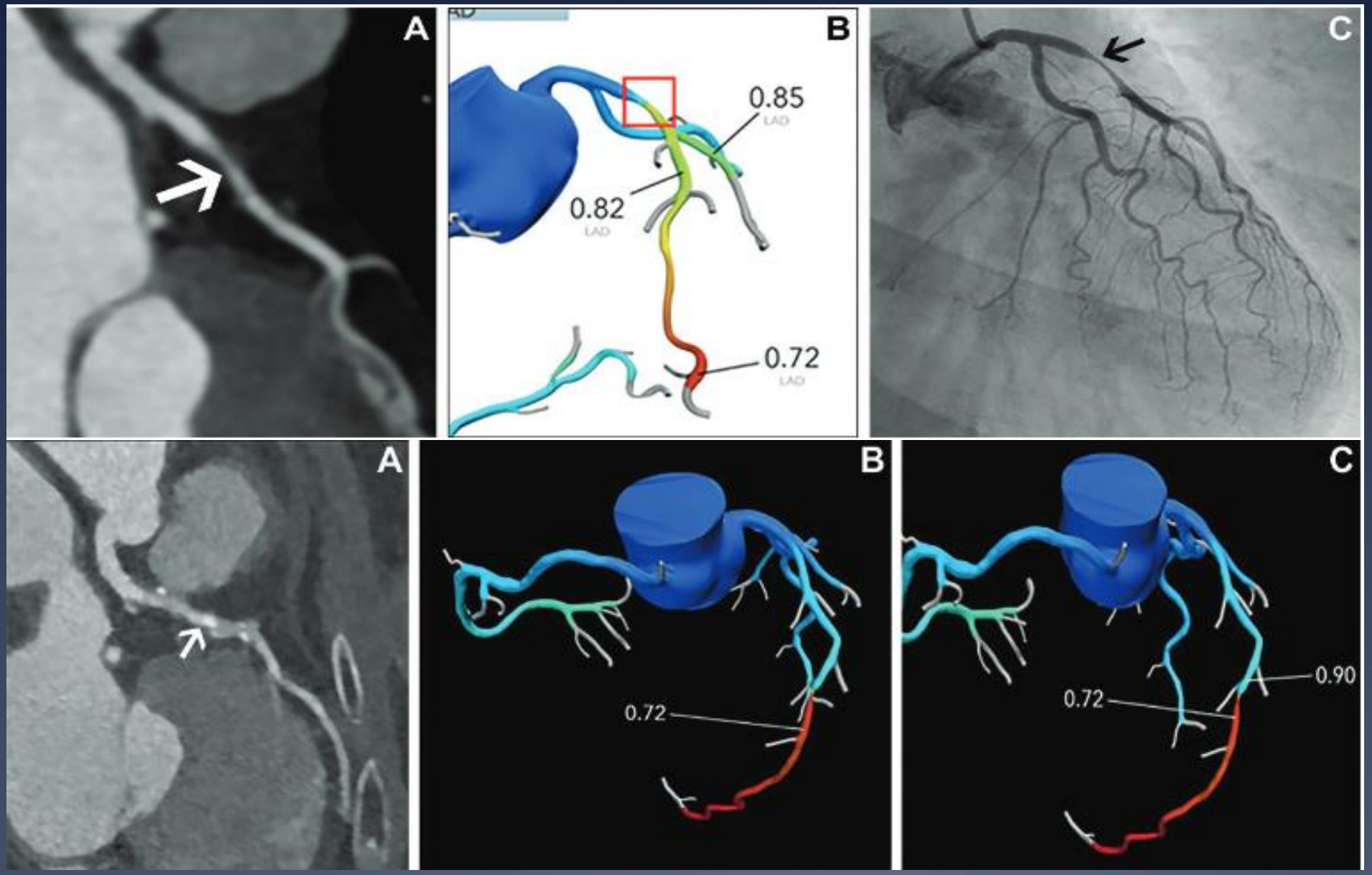
Anatomical and Functional Computed Tomography for Diagnosing Hemodynamically Significant Coronary Artery Disease

A Meta-Analysis

Csilla Celeng, MD, PhD,[a] Tim Leiner, MD, PhD,[a] Pál Maurovich-Horvat, MD, PhD, MPH,[b] Béla Merkely, MD, PhD,[b] Pim de Jong, MD, PhD,[a] Jan W. Dankbaar, MD, PhD,[a] Hendrik W. van Es, MD, PhD,[c] Brian B. Ghoshhajra, MD, MBA,[d] Udo Hoffmann, MD, MPH,[d] Richard A.P. Takx, MD, PhD, MSc[a,c,d]



CT FFR (FFR_{CT})



CT Fractional Flow Reserve: A Practical Guide to Application, Interpretation, and Problem Solving

Prabhakar Rajiah, MBBS, MD, FRCR
Kristopher W. Cummings, MD
Eric Williamson, MD
Phillip M. Young, MD

Abbreviations: ACS = acute coronary syndrome, CAD = coronary artery disease, CTA = CT angiography, FFR_{CT} = fractional flow reserve CT, ICA = invasive coronary angiography, LAD = left anterior descending artery, LCx = left circumflex artery, MACE = major adverse cardiovascular events, MPR = multiplanar reconstruction, OMT = optimal medical therapy, PCI = percutaneous coronary intervention, TAVR = transcatheter aortic valve replacement, 3D = three dimensional

RadioGraphics 2022; 42:340–358

https://doi.org/10.1148/rg.210097

Content Codes: CA CT

From the Department of Radiology, Mayo Clinic, 200 1st St SW, Rochester, MN 55905 (P.R., E.W., P.M.Y.); and Department of Radiology, Mayo Clinic, Phoenix, Ariz (K.W.C.). Recipient of a Cum Laude award for an education exhibit at the 2020 RSNA Annual Meeting. Received March 29, 2021; revision requested April 30 and received June 22; accepted July 2. For this journal-based SA-CME activity, the author P.R. has provided disclosures (see end of article); all other authors, the editor, and the reviewers have disclosed no relevant relationships. **Address correspondence to** P.R. (e-mail: *radpr73@gmail.com*).

CT fractional flow reserve (FFR_{CT}) is a physiologic simulation technique that models coronary flow from routine coronary CT angiography (CTA). To evaluate lesion-specific ischemia, FFR_{CT} is measured 2 cm distal to a stenotic lesion. FFR_{CT} greater than 0.8 is normal, 0.76–0.8 is borderline, and 0.75 or less is abnormal. FFR_{CT} should always be interpreted in correlation with clinical and anatomic coronary CTA findings. FFR_{CT} increases the specificity of coronary CTA in the evaluation of coronary artery disease, decreases the prevalence of nonobstructive disease in invasive coronary angiography (ICA), and helps with revascularization decisions and planning. Patients with intermediate-risk coronary anatomy at CTA and abnormal FFR_{CT} can undergo ICA and revascularization, whereas those with normal FFR_{CT} can be safely deferred from ICA. In borderline FFR_{CT} values, management is decided in the context of the clinical scenario, but many cases could be safely managed with medical treatment. There are some limitations and pitfalls of FFR_{CT}. Abnormal FFR_{CT} values can be seen in mild stenosis, and normal FFR_{CT} values can be seen in severe stenosis. Gradually decreasing or abnormal low FFR_{CT} values at the distal vessel without a proximal focal lesion could be due to diffuse atherosclerosis. Coronary stents, bypass grafts, coronary anomalies, coronary dissection, transcatheter aortic valve replacement, unstable angina, and acute or recent myocardial infarction are situations in which FFR_{CT} has not been validated and should not be used at this time. The authors provide a practical guide to the applications and interpretation of FFR_{CT}, focusing on common pitfalls and challenges.

Online supplemental material is available for this article.

Coronary angiogram study

* Sensitivity is about 100% and the specificity is 100%
* Advantage : Gold standard.
* Disadvantage : Invasive, Radiation (8 to 10 mSv) and Functional effect of stenosis not routinely.

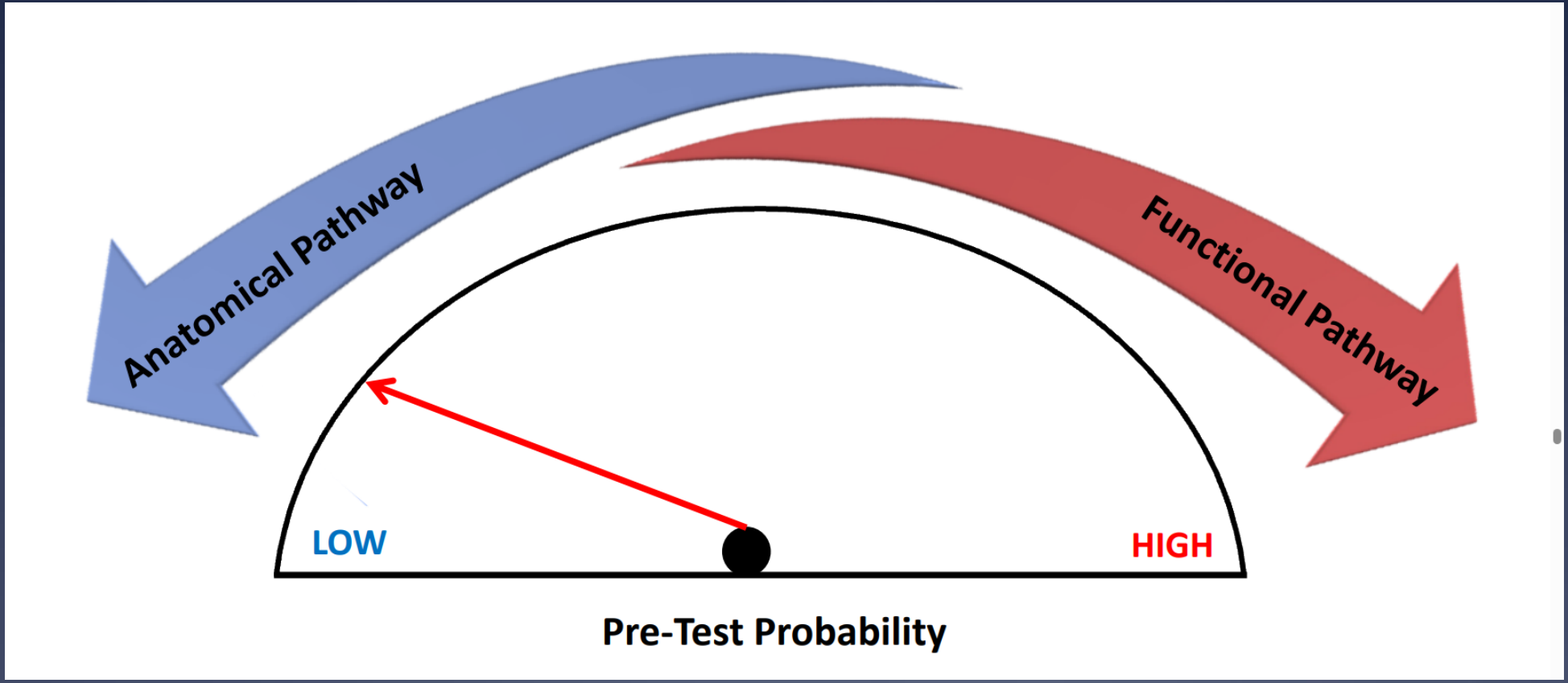
Coronary angiography	5.6 mSv
PTCA	6.9 mSv
Coronary angiography with PTCA	9.3 mSv
Coronary Angiography + PTCA + Stent	13 mSv

100 mSv	Above about 100 mSv, the probability of cancer (rather than the severity of illness) increases with dose. The estimated risk of fatal cancer is 5 of every 100 persons exposed to a dose of 1000 mSv (ie. if the normal incidence of fatal cancer were

10,000 mSv (10 sieverts)	As a short-term and whole-body dose would cause immediate illness, such as nausea and decreased white blood cell count, and subsequent death within a few weeks. Between 2 and 10 sieverts in a short-term dose would cause severe radiation sickness with increasing likelihood that this would be fatal.
1,000 mSv (1 sievert)	In a short term dose is about the threshold for causing immediate radiation sickness in a person of average physical attributes, but would be unlikely to cause death. Above 1000 mSv, severity of illness increases with dose. If doses greater than 1000 mSv occur over a long period they are less likely to have early health effects but they create a definite risk that cancer will develop many years later.
100 mSv	Above about 100 mSv, the probability of cancer (rather than the severity of illness) increases with dose. The estimated risk of fatal cancer is 5 of every 100 persons exposed to a dose of 1000 mSv (ie. if the normal incidence of fatal cancer were 25%, this dose would increase it to 30%).

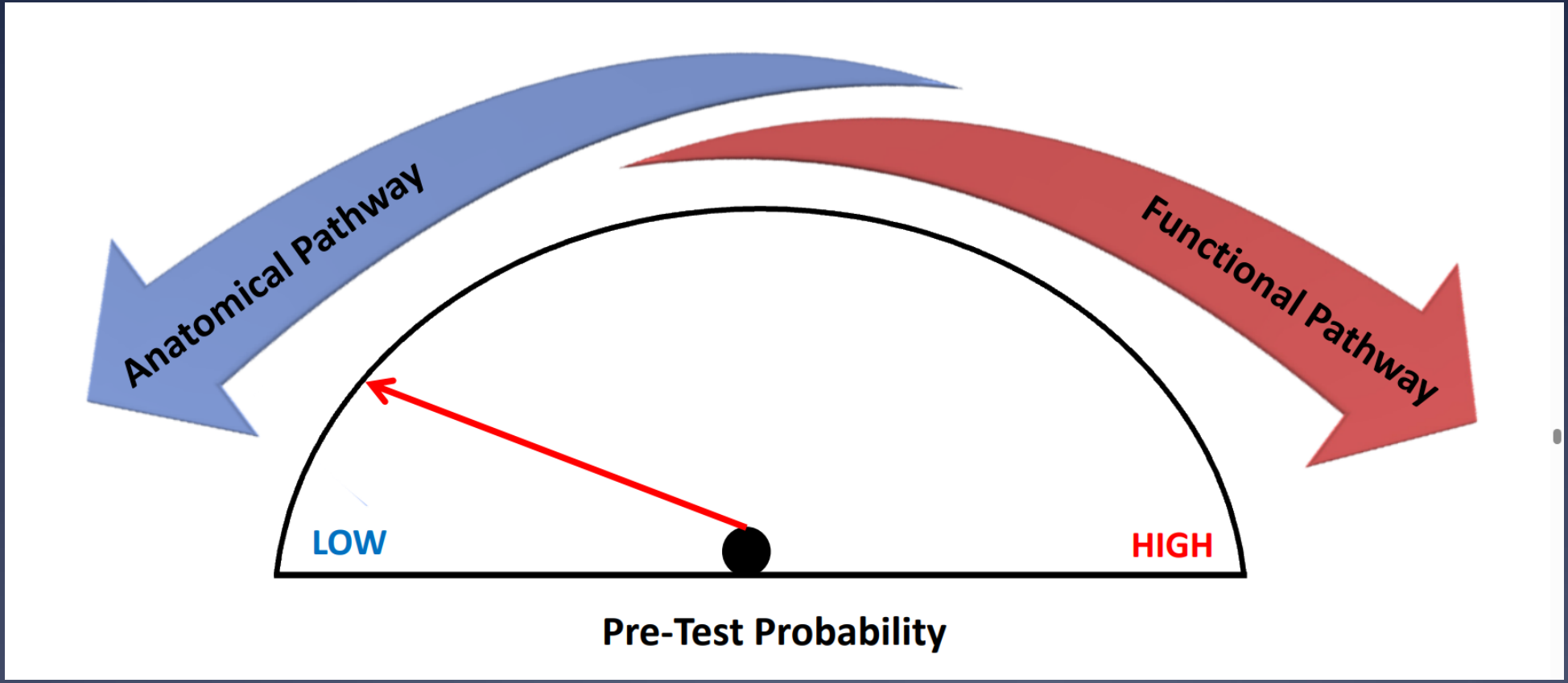
0.05 mSv/yr	A very small fraction of natural background radiation, is the design target for maximum radiation at the perimeter fence of a nuclear electricity generating station. In practice the actual dose is less.

Non-invasive imaging in Chronic Coronary Syndrome



Luca Bergamaschi et al. Diagnostics 2023, 13, 2083.

Non-invasive imaging in Chronic Coronary Syndrome



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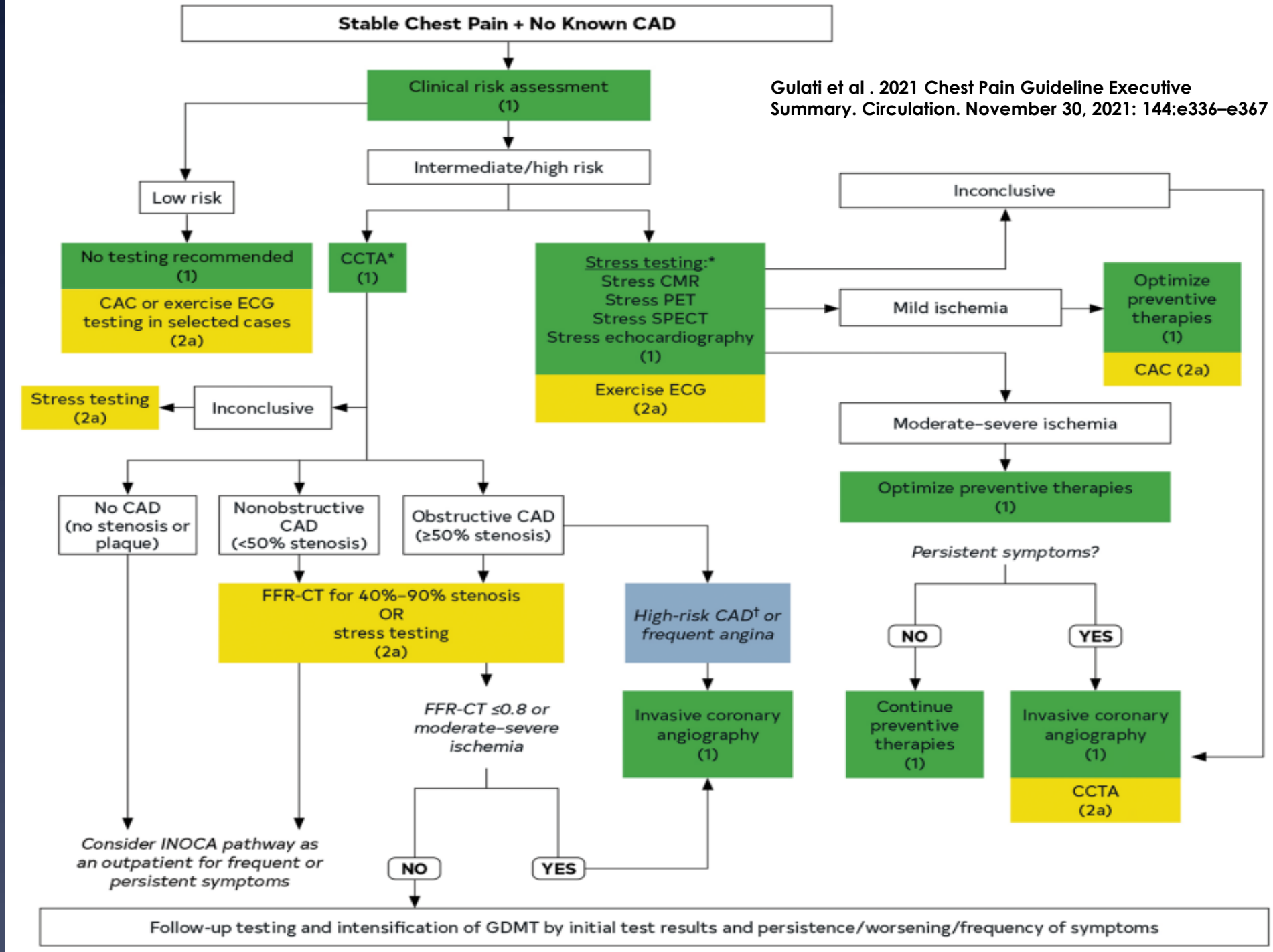
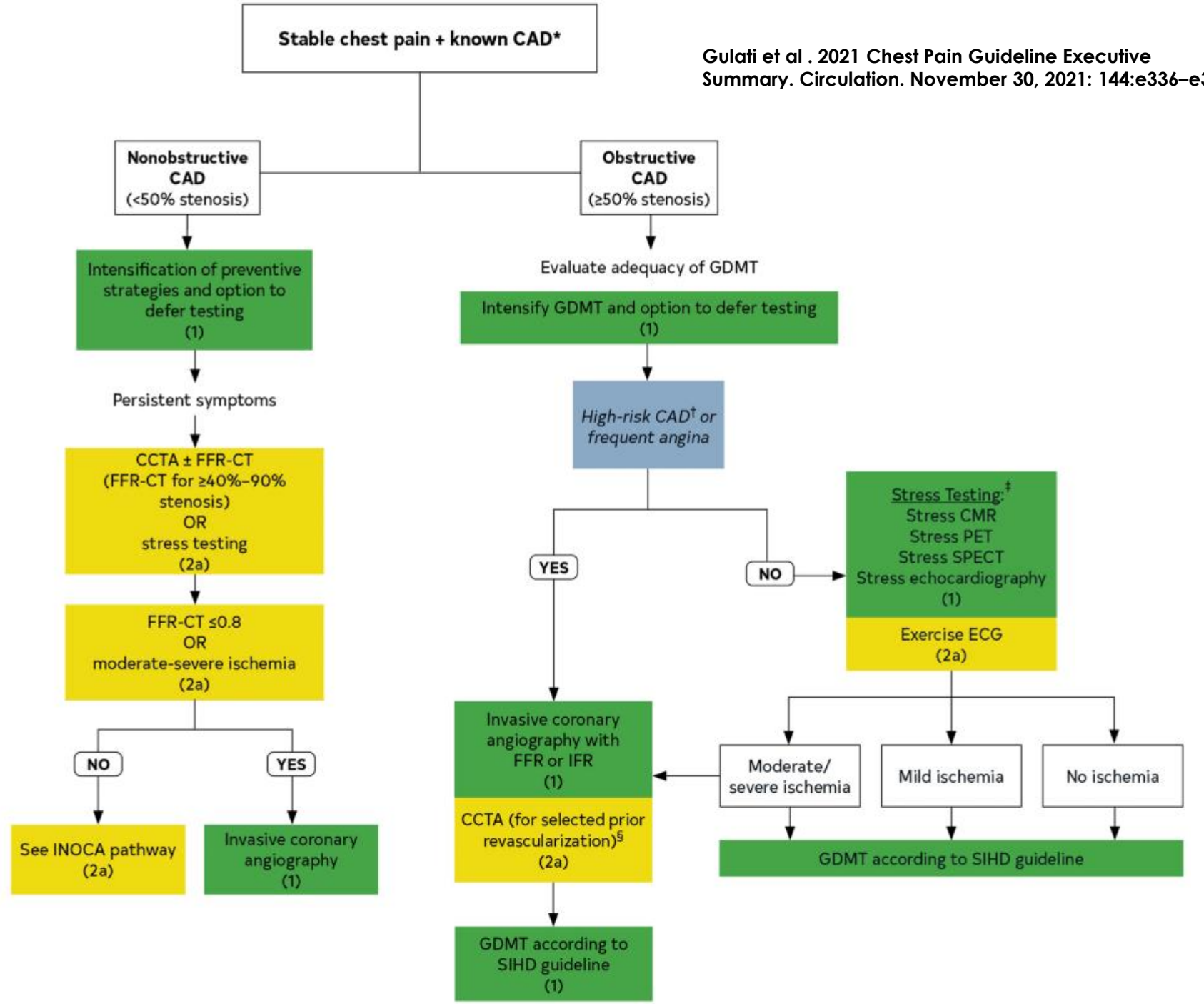


Gulati et al . 2021 Chest Pain Guideline Executive Summary. Circulation. November 30, 2021: 144:e336–e367

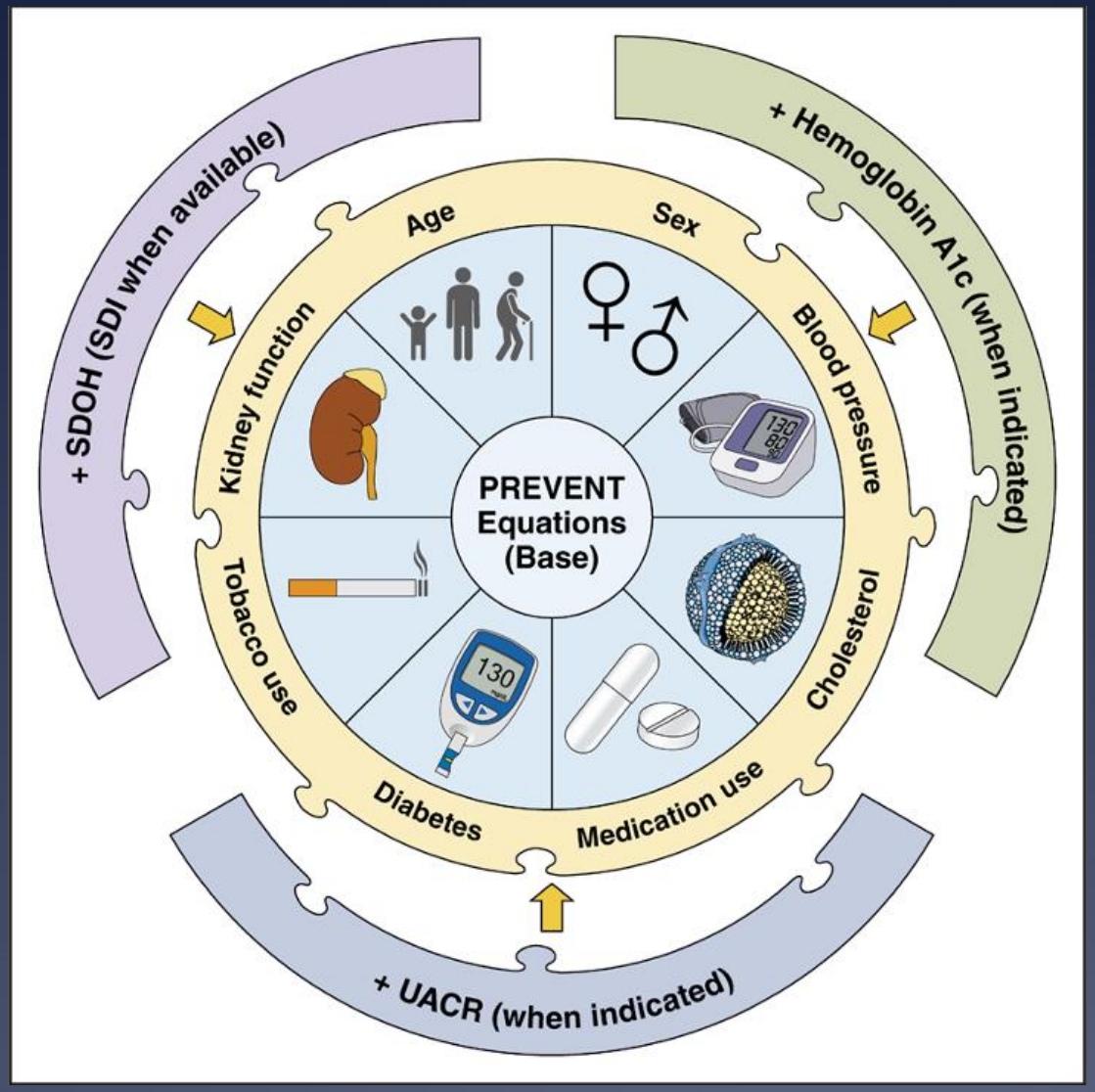


Gulati et al . 2021 Chest Pain Guideline Executive Summary. Circulation. November 30, 2021: 144:e336–e367

Conclusion

* Which test to prescribe can be sometimes difficult to decide. Both anatomic and functional imaging techniques have strengths and limitations.
* CCTA is the preferred test in patients with a lower range of clinical likelihood of CAD….. Hence rule-out power.
* Non-invasive functional tests for ischemia have a better rule-in power and should be therefore preferred in those with higher clinical risk of coronary atherosclerosis.

PREVENT base and additional equations.



CVD indicates cardiovascular disease; PREVENT, AHA Predicting Risk of CVD Events; SDI, social deprivation index; SDOH, social determinants of health; and UACR urine albumin-to-creatinine ratio.

Khan et al . Risk of Cardiovascular Disease Incorporating CKM Health. Circulation. December 12. 2023;148:1982–2004.

Clinical background and CV Risk Factors

Medical history (%)	2007-2009 (n=10,709)	2010-2012 (n=13,750)	2013-2014 (n=14,136)	2015-2016 (n=19,494)	2017-2018 (n=21,618)	2019-2020 (n=24,309)
Smoking status						
Former (quit > 30 days)	28.2	27.8	21.8	22.5	21.8	22.1
Current (any tobacco use within last 30 days)	18.8	23.0	27.8	26.8	25.4	25.9
New Onset of Angina (<2 weeks)	24.6	22.9	28.6	41.2	31.4	37.4
Family history of premature CVD	19.0	15.4	10.6	14.3	11.1	12.8
History of heart failure	4.0	3.4	4.2	4.2	4.0	4.7
Chronic renal failure (include all pts with creatinine >200micromol/l)	6.6	5.4	4.8	4.9	4.8	5.4

W.A. Wan Azman (Ed). Annual Report of the NCVD-PCI Registry, Year 2019-2020. Kuala Lumpur, Malaysia: National Cardiovascular Disease Database, 2023.

* Obesity, diabetes, and chronic kidney disease (CKD) are each associated with a high burden of cardiovascular disease (CVD) morbidity and mortality.

* They commonly co-occur and disproportionately affect disenfranchised populations (eg, underrepresented racial and ethnic groups).

* Absolute risk assessment for CVD remains the corner stone of clinical primary prevention efforts.

Some patients without CVD are automatically determined as high risk

- Age >60 years
- Diabetes with microalbuminuria (20 micrograms/min or urinary albumin : creatinine ratio; 2.5 mg/mmol for males, 3.5 mg/mmol for females)
- Moderate or severe chronic kidney disease (eGFR 45 mL/min/1.73 m2)
- Previous diagnosis of familial hypercholesterolaemia
- Systolic BP ≥180 mm Hg; or diastolic BP ≥ 110 mm Hg
- Serum total cholesterol 7.5 mmol/L

Risk assessment for most asymptomatic men is recommended from the age of 45 (or from the age of 35 if they have risk factors). Risk assessment for most asymptomatic women is recommended from the age of 55 (or from the age of 45 if they have risk factors).

Guidelines for the management of Absolute cardiovascular disease risk National Vascular Disease Prevention Alliance

Some patients without CVD are automatically determined as high risk

- Diabetes and age 60 years
- Diabetes with microalbuminuria (20 micrograms/min or urinary albumin : creatinine ratio; 2.5 mg/mmol for males, 3.5 mg/mmol for females)
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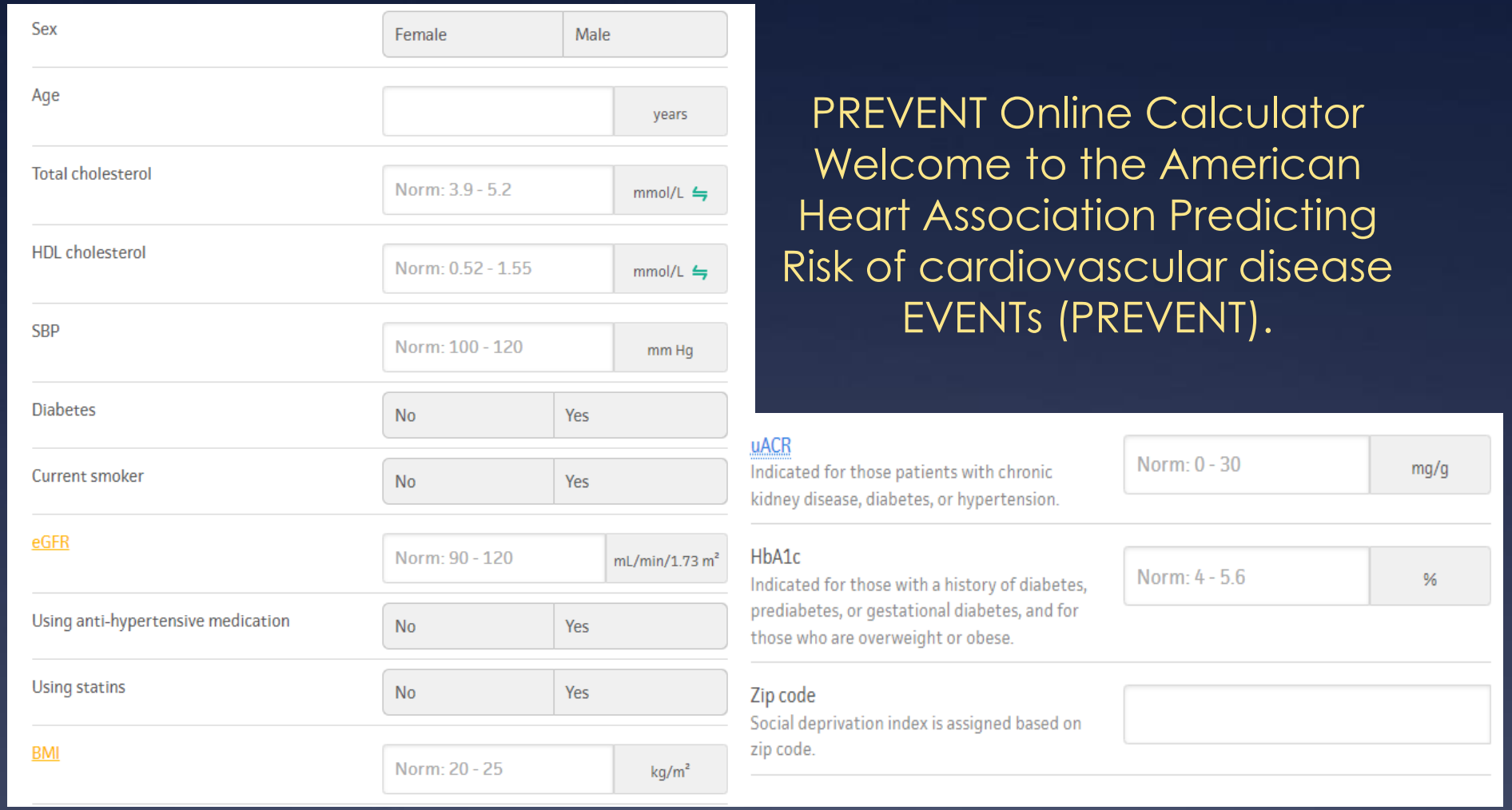
Guidelines for the management of Absolute cardiovascular disease risk
National Vascular Disease Prevention Alliance

PREVENT Online Calculator Welcome to the American Heart Association Predicting Risk of cardiovascular disease EVENTs (PREVENT).



Interpretation of Risk Estimates: 10-year risk for CVD is categorized as:

- Low risk (<5%)
- Borderline risk (5% to 7.4%)
- Intermediate risk (7.5% to 19.9%)
- High risk (≥20%)

Patients with risk factor values outside the validated ranges of this tool require individualized assessment and management

Importance of major risk factors for coronary heart disease

* In an analysis of 3 large prospective studies, nearly all individuals (92% of men and 87% of women) who experienced a nonfatal CHD event had at least 1 clinically elevated major risk factor (which was defined as elevated total cholesterol [≥6.22 mmol/L], systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, current cigarette smoking, or diabetes) before the event. Similar estimates were observed for fatal CHD events.

* VIRGO study (Variation in Recovery: Role of Gender on Outcomes of Young AMI Patients), a prospective observational cohort of individuals 18 to 55 years of age who presented with premature onset myocardial infarction, the population-attributable fraction for traditional risk factors was 85%.

Greenland P, Knoll MD, Stamler J, Neaton JD, Dyer AR, Garside DB, Wilson PW. Major risk factors as antecedents of fatal and nonfatal coronary heart .disease events. JAMA. 2003;290:891–897

Importance of major risk factors for coronary heart disease

* InterHeart study…. INTERHEART global case-control study including 27 098 participants from 52 countries, 6787 of whom were women.

* Nine modifiable risk factors were associated with MI in women and men. Hypertension, diabetes, , physical activity, moderate alcohol use, association of abnormal lipids, current smoking, abdominal obesity, high risk diet, and psychosocial stress factors.

* The population attributable risk (PAR) of all nine risk factors exceeded 94%, and was similar among women and men

Anand SS, Islam S, Rosengren A, Franzosi MG, Steyn K, Yusuf ali AH, Keltai M, Diaz R, Rangarajan S, Yusuf S; INTERHEART Investigators. Risk factors for myocardial infarction in women and men: insights from the INTERHEART study. Eur Heart J. 2008;29:932–940.

Circulation

Circulation. March 26th 2019;139:1603–1611.

ORIGINAL RESEARCH ARTICLE

Quantifying Importance of Major Risk Factors for Coronary Heart Disease

BACKGROUND: To optimize preventive strategies for coronary heart disease (CHD), it is essential to understand and appropriately quantify the contribution of its key risk factors. Our objective was to compare the associations of key modifiable CHD risk factors—specifically lipids, systolic blood pressure (SBP), diabetes mellitus, and smoking—with incident CHD events based on their prognostic performance, attributable risk fractions, and treatment benefits, overall and by age.

Michael J. Pencina, PhD
Ann Marie Navar, MD, PhD
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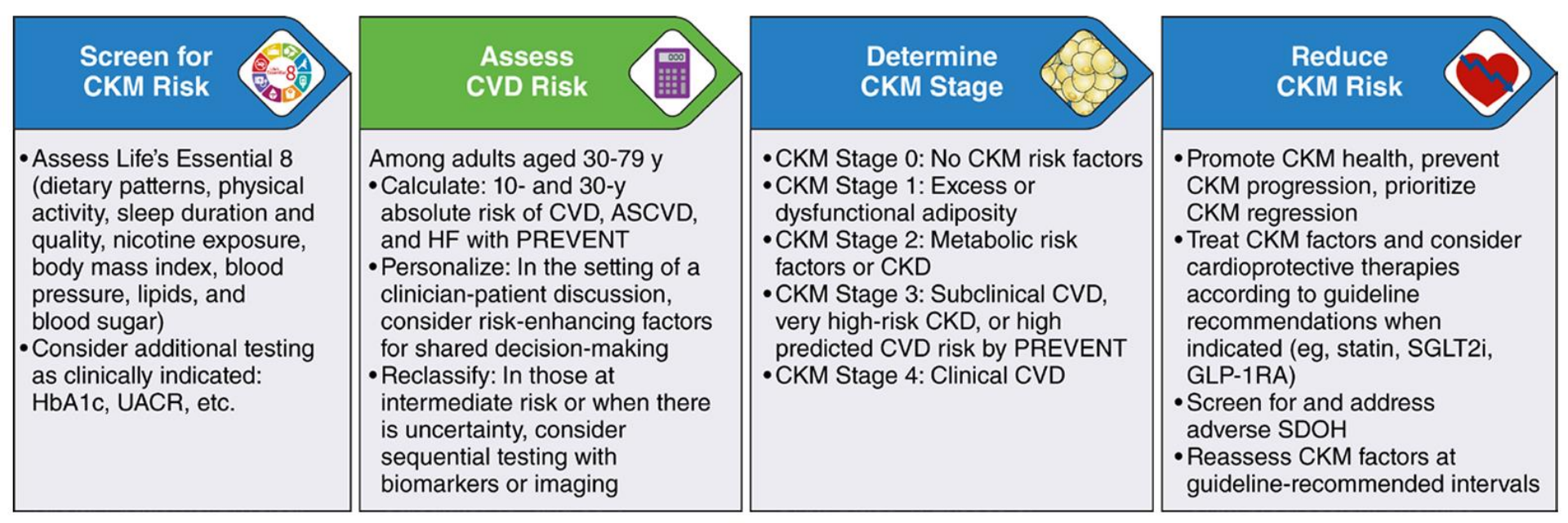
Concluding……that Our models indicate by eliminating or controlling these individual factors would lead to substantial reductions in total population CHD events.

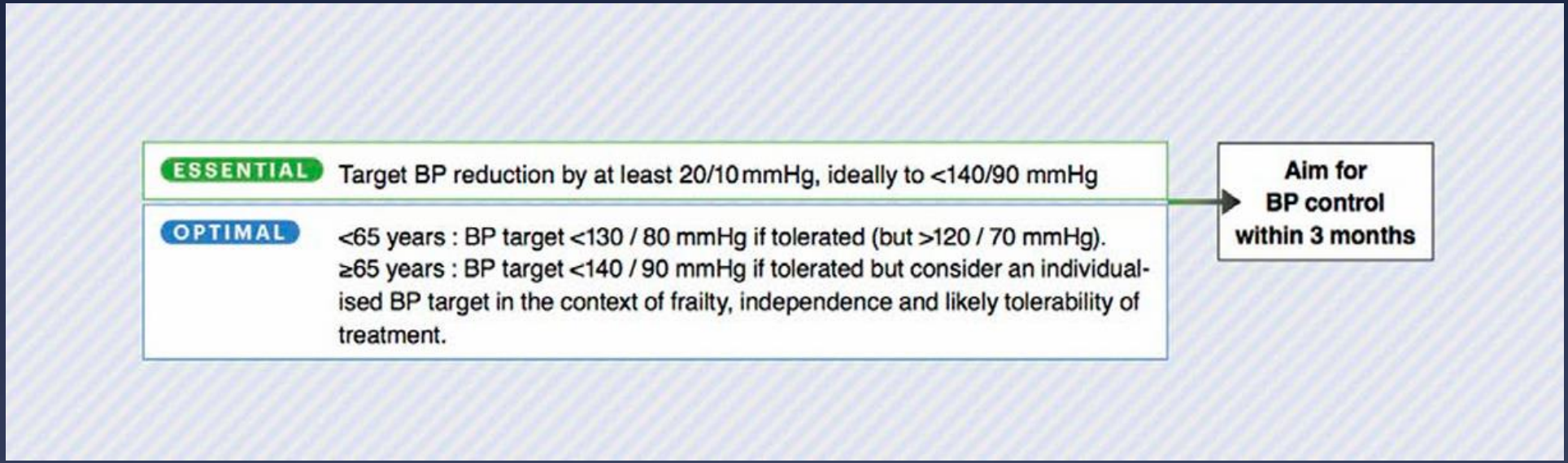
attributable fractions for SBP, non–high-density lipoprotein cholesterol (non-HDL-C), diabetes mellitus, and smoking. Expected absolute risk reductions for antihypertensive and lipid-lowering treatment were assessed.

Conceptual framework for risk-based prevention of cardiovascular disease integrating risk assessment with PREVENT and cardiovascular-kidney-metabolic health staging



R. Khan et al. isk of Cardiovascular Disease Incorporating CKM Health. Circulation. December 12, 2023;148:1982–2004

Office blood pressure targets for treated hypertension



1. Treatments should be evidence-based in relation to morbidity/mortality prevention.
2. Use a once-daily regimen which provides 24-hour blood pressure control.
3. Treatment should be affordable and/or cost-effective relative to other agents.
4. Treatments should be well-tolerated.
5. Evidence of benefits of use of the medication in populations to which it is to be applied

Unger et al. Hypertension. 2020;75:1334-1357. ISH Global Hypertension Practice Guidelines

Targets Blood Pressure to achieve

* Previous stroke subjects : BP should be lowered if ≥140/90 mm Hg and treated to a target.
* Heart failure subjects: Treating hypertension has a major impact on reducing the risk of incident HF and HF hospitalization. BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80mmHg but >120/70 mm Hg.
* CAD subjects : BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80mmHg.
* Diabetes subjects : BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80mmHg
* Renal impairment subjects : BP should be lowered if ≥140/90 mm Hg and treated to a target <130/80mmHg

Decoding the Rhythm of your Heart: A Personalised Cardiovascular Risk Assessment.

6th Myanmar Cardiac Society Conference.
23rd -24th November 2024

Dr K.H. Lam
MRCP. FNHAM. FASPIC. FAsCC. FESC. FACC
Assunta Hospital. Malaysia

Criteria defining prediabetes in non pregnant individuals

A1C 5.7–6.4% (39–47 mmol/mol)
OR
FPG 100 mg/dL (5.6 mmol/L) to 125 mg/dL (6.9 mmol/L) (IFG)
OR
2-h PG during 75-g OGTT 140 mg/dL (7.8 mmol/L) to 199 mg/dL (11.0 mmol/L) (IGT)

The most important management in prediabetes is a lifestyle change and promotion of intense weight loss. Reducing weight by 7% through a low-fat diet, in addition to an exercise regimen of about 30 minutes per day, is the overall goal of management.

Approximately 70% of people with prediabetes will go on to be diagnosed with diabetes mellitus. However, this is not inevitable. Prediabetes managed appropriately can prevent diabetes mellitus and lower the risk of cardiovascular disease.

Some patients will need to take some medications. These patients include those that have failed to maintain adequate lifestyle therapy or are at high-risk for developing type 2 diabetes. The most common medications used for prediabetes are metformin and acarbose, which will help prevent the development of diabetes mellitus. These two drugs have minimal side effects and work well in prediabetic patients.

Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024 Diabetes Care 2024;47(Suppl. 1):S20–S42

Criteria for the diagnosis of diabetes in non pregnant individuals

A1C ≥6.5% (≥48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP certified and standardized to the DCCT assay.*

OR

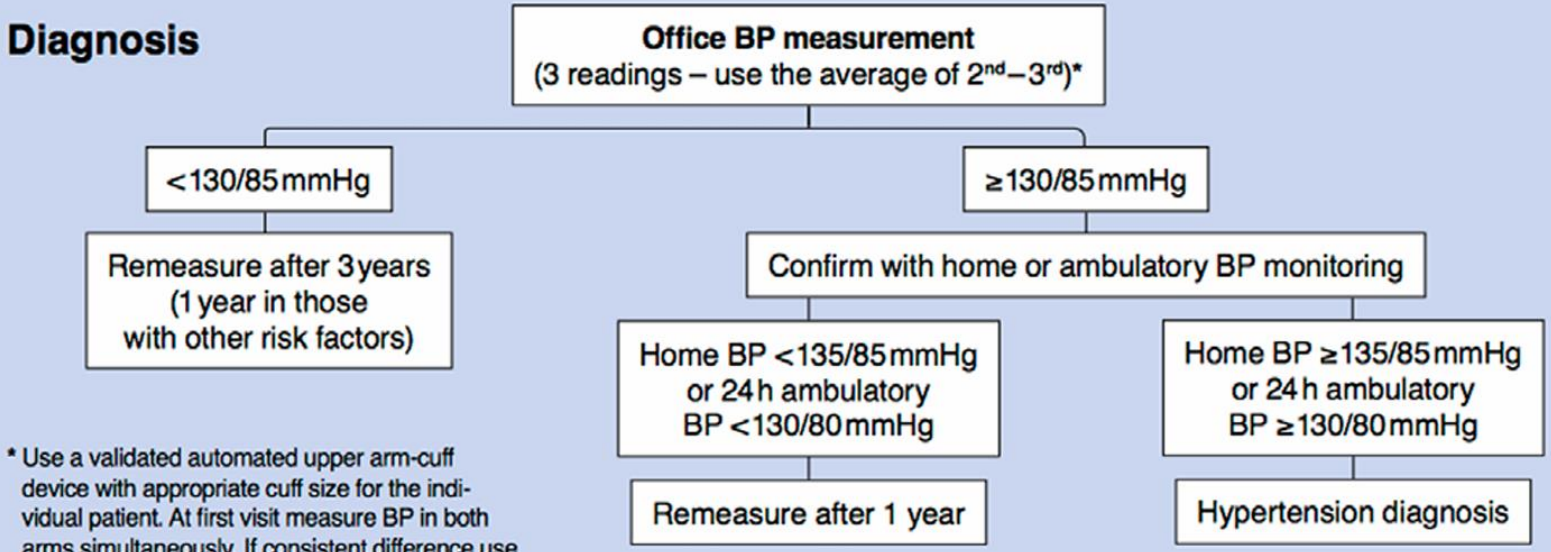
Individualised HbA_{1c} targets based on patient profile

≤6.5 % (Tight)	6.6%-7.0%	7.1%-8.0% (Less tight)
• Newly and recently diagnosed • Younger age • Healthier (no complications) • Low risk of hypoglycaemia	• All others	• Elderly patients • Presence of co-morbidities • High risk of severe hypoglycaemia; hypo unawareness • Short life expectancy

In an individual with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (≥11.1 mmol/L). Random is any time of the day without regard to time since previous meal.

Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2024 Diabetes Care 2024;47(Suppl. 1):S20–S42 |

Diagnosis



* Use a validated automated upper arm-cuff device with appropriate cuff size for the individual patient. At first visit measure BP in both arms simultaneously. If consistent difference use the arm with the higher BP.

Treatment

Grade 1 Hypertension:
140–159/90–99 mmHg
1. Start lifestyle interventions
2. Start drug treatment:
- ***Immediately:*** In high-risk patients (CVD, CKD, diabetes or organ damage)
- ***After 3–6 months of lifestyle intervention:*** In low-moderate risk patients with persistent BP elevation

Grade 2 Hypertension:
≥160/100 mmHg
1. Start drug treatment immediately
2. Start lifestyle intervention

Lifestyle Interventions
- Stop smoking
- Regular exercise
- Lose weight
- Salt reduction
- Healthy diet and drinks
- Lower alcohol intake
- Lower stress
- Reduce exposure to air pollution

Drug Therapy Steps
Simplify regimen with once daily dosing and single pill combinations.
Consider monotherapy in low-risk grade 1 hypertension and in patients aged >80 years or frail

Non-Black Patients
1. Low dose ACEI/ARB* + DHP-CCB
2. Increase to full dose
3. Add thiazide-like diuretic
4. Add spironolactone or, if not tolerated or contraindicated, amiloride, doxazosin, eplerenone, clonidine or beta-blocker

Black Patients
1. Low dose ARB* + DHP-CCB or DHP-CCB + thiazide-like diuretic
2. Increase to full dose
3. Add diuretic or ACEI/ARB
4. Add spironolactone or, if not tolerated or contraindicated, amiloride, doxazosin, eplerenone, clonidine or beta-blocker

* No ACEI/ARB in women with or planning pregnancy

Target Blood Pressure in the elderly

* Geriatric medicine proposes taking into account the function/frailty/autonomy status of older people.
* The 2017 American College of Cardiology/American Heart Association guidelines indicate that a BP <130/80 mm Hg should be targeted after the age of 65 years.
* The 2018 ESC /ESH guidelines propose a BP goal of <140/90 mm Hg for individuals older than 65 years.
* Finally, the 2017 American College of Physicians/ American Association of Family Physicians guidelines propose to target a BP <150/90 mm Hg.

Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:1269–1324.

Williams B, Mancia G, Spiering W, et al; ESC Scientific Document Group. 2018 ESC/ESH Guidelines for the management of arterial hypertension. Eur Heart J. 2018;39:3021–3104.

Qaseem A, Wilt TJ, Rich R, Humphrey LL, Frost J, Forciea MA; Clinical Guidelines Committee of the American College of Physicians and the Commission on Health of the Public and Science of the American Academy of Family Physicians. Pharmacologic treatment of hypertension in adults aged 60 years or older to higher versus lower blood pressure targets: a clinical practice guideline from the American College of Physicians and the American Academy of Family Physicians. Ann Intern Med. 2017;166:430–437

CLINICAL PRACTICE GUIDELINES

Management of Hypertension

Older Adult Population	Target SBP (mmHg)
>80 years old	<150
65-80 years old	<140
Multiple comorbidities Functional and cognitive impairment Frail Institutionalized Experiencing ADRs	Consider less strict targets Limit number of antihypertensive agents

For fit* 65-80 years old patients consider target SBP <130 mmHg.

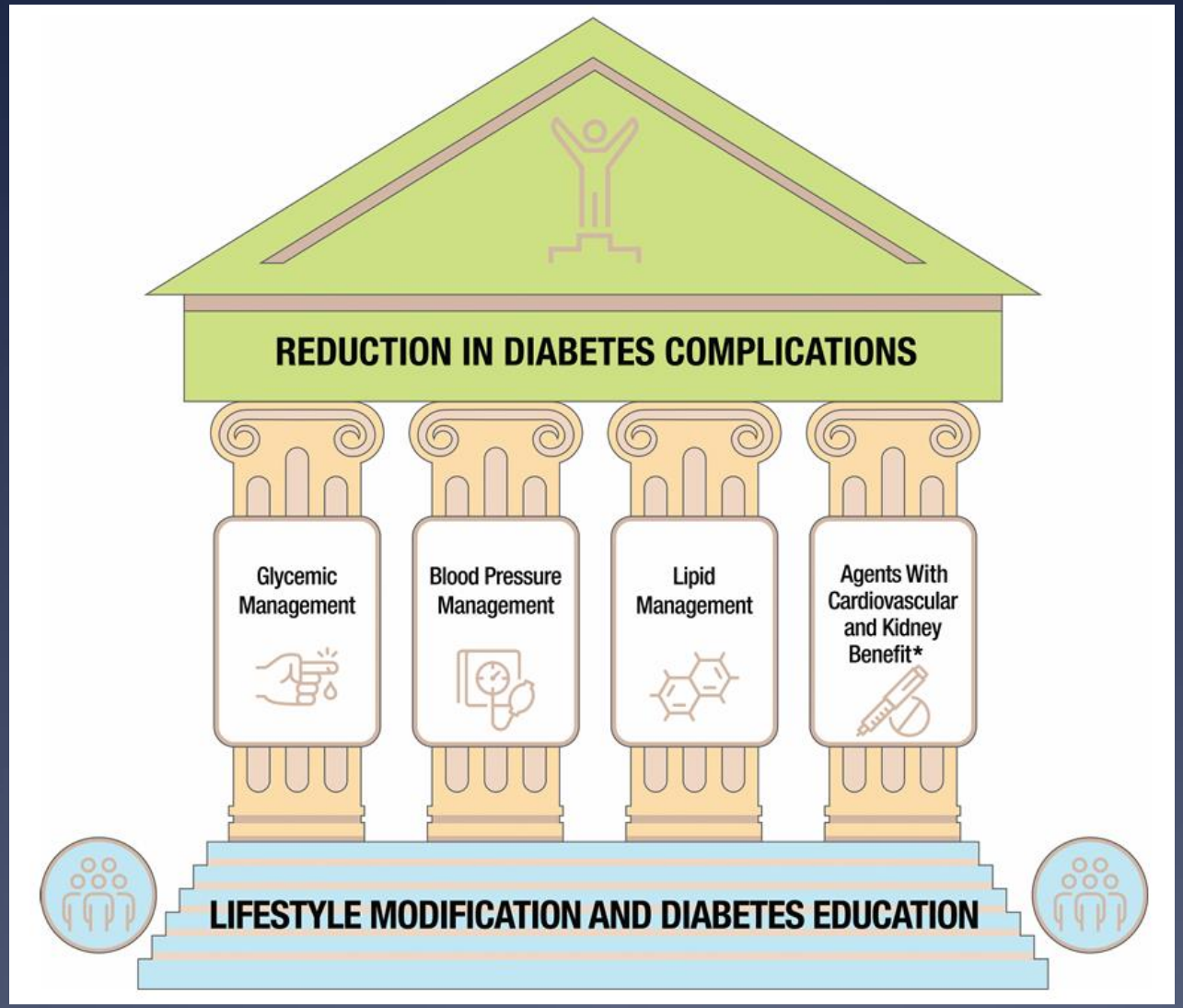
* free from health conditions that limit mobility and/or functional ability with good nutrition and cognitive status.

Malaysian Society of Hypertension

Ministry of Health Malaysia

Academy of Medicine of Malaysia

Multifactorial approach to reduction in risk of diabetes complications



Diabetes Care Volume 47, Supplement 1, January 2024.Diabetes Care Volume 47, Supplement 1, January 2024

Definition of Hypertension and the Target to achieved in Diabetic

1. Hypertension is defined as a systolic blood pressure >130mmHg or a diastolic blood pressure >80 mmHg .

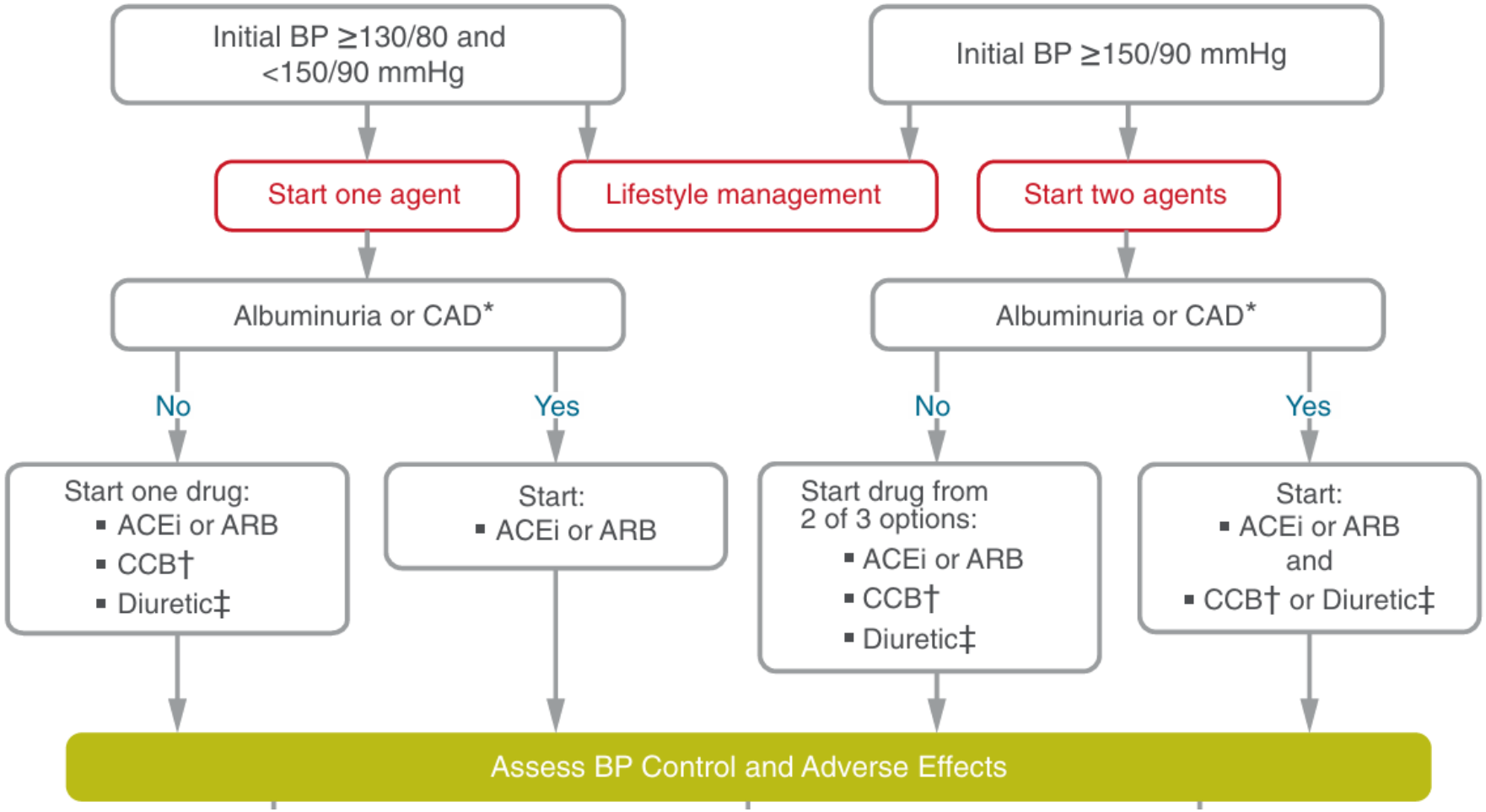
2. The recommendation to support a blood pressure goal of <130/80 mmHg in people with diabetes is consistent with guidelines from the American College of Cardiology and American Heart Association , the International Society of Hypertension , and the European Society of Cardiology .

De Boer IH, Bangalore S, Benetos A, et al. Diabetes and hypertension: a position statement by the American Diabetes Association. Diabetes Care 2017;40:1273–1284

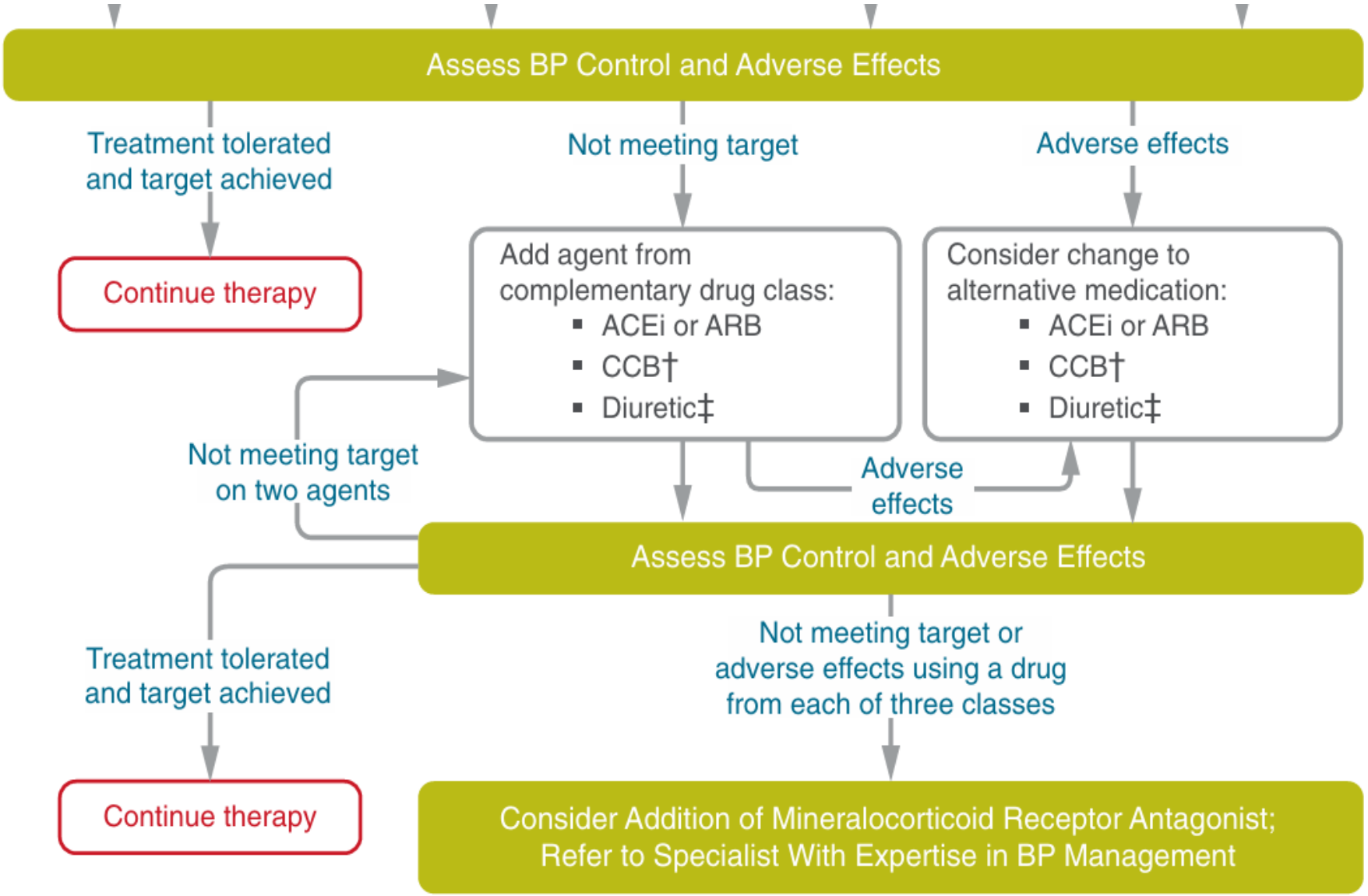
Unger T, Borghi C, Charchar F, et al. 2020 International Society of Hypertension global hypertension practice guidelines. Hypertension 2020;75:1334–1357

Williams B, Mancia G, Spiering W, et al.; ESC Scientific Document Group. 2018 ESC/ESH guidelines for the management of arterial hypertension. Eur Heart J 2018;39:3021–3104

Recommendations for the Treatment of Confirmed Hypertension in Nonpregnant People With Diabetes



Diabetes Care Volume 47, Supplement 1, January 2024.Diabetes Care Volume 47, Supplement 1, January 2024



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Hyperlipidemia and Diabetes

* For people with diabetes aged 40–75 years without ASCVD, use moderate-intensity statin therapy in addition to lifestyle therapy.

* For people with diabetes aged 20–39 years with additional ASCVD risk factors, it may be reasonable to initiate statin therapy in addition to lifestyle therapy.

* For people with diabetes aged 40–75 years at higher cardiovascular risk, including those with one or more ASCVD risk factors, it is recommended to use high-intensity statin therapy to *reduce LDL cholesterol by >50% of baseline and to target an LDL cholesterol goal of <1.8mmol/L.*

* For people of all ages with diabetes and ASCVD, high-intensity statin therapy should be added to lifestyle therapy. It is recommended to *target an LDL cholesterol reduction of >50% from baseline and an LDL cholesterol goal of <1.4mmol/L*

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Screening Asymptomatic Individuals for Atherosclerotic Cardiovascular Disease

* The screening of asymptomatic individuals with high ASCVD risk is not recommended, in part because these high-risk people should already be receiving intensive medical therapy.. an approach that provides benefits similar to those of invasive revascularization.

* The ultimate balance of benefit, cost, and risk of such an approach in asymptomatic individuals re mains controversial, particularly in the modern setting of aggressive ASCVD risk factor control.

Bax JJ, Young LH, Frye RL, Bonow RO, Steinberg HO; ADA. Screening for coronary artery disease in patients with diabetes. Diabetes Care 2007;30:2729–2736 192.

Boden WE, O'Rourke RA, Teo KK, et al.; COURAGE Trial Research Group. Optimal medical therapy with or without PCI for stable coronary disease. N Engl J Med2007;356:1503–1516 193.

Frye RL, August P, Brooks MM, et al.; BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. NEngl J Med2009;360:2503–2515

Diabetes and Heart failure

The recommendations for screening and treatment of heart failure in people with diabetes are consistent with the ADA consensus report on heart failure and with current American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for the management of heart failure .

- ✓ Many people with diabetes have stage BHF, defined as asymptomatic with at least one of the following: 1) evidence of structural heart disease, 2) abnormal cardiac function, or 3) elevated natriuretic peptide levels or elevated cardiac troponin levels.
- ✓ Early diagnosis of HF could enable targeted treatment to prevent adverse outcomes.
- ✓ Measurement of a natriuretic peptide or high-sensitivity cardiac troponin on at least a yearly basis is recommended to identify the presence of stage B HF and to determine risk for progression to symptomatic HF.
- ✓ Useful cutoff values for BNP (50 pg/mL), NT-proBNP (125 pg/mL), or high sensitivity cardiac troponin (>99th per centile upper reference limit) to determine HF risk are based on population-based data and/or clinical trials.

Pop-Busui R, Januzzi JL, Bruemmer D, et al. Heart failure: An underappreciated complication of diabetes. A consensus report of the American diabetes association. Diabetes Care 2022;45: 1670–1690

Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation 2022;145:e895–e1032

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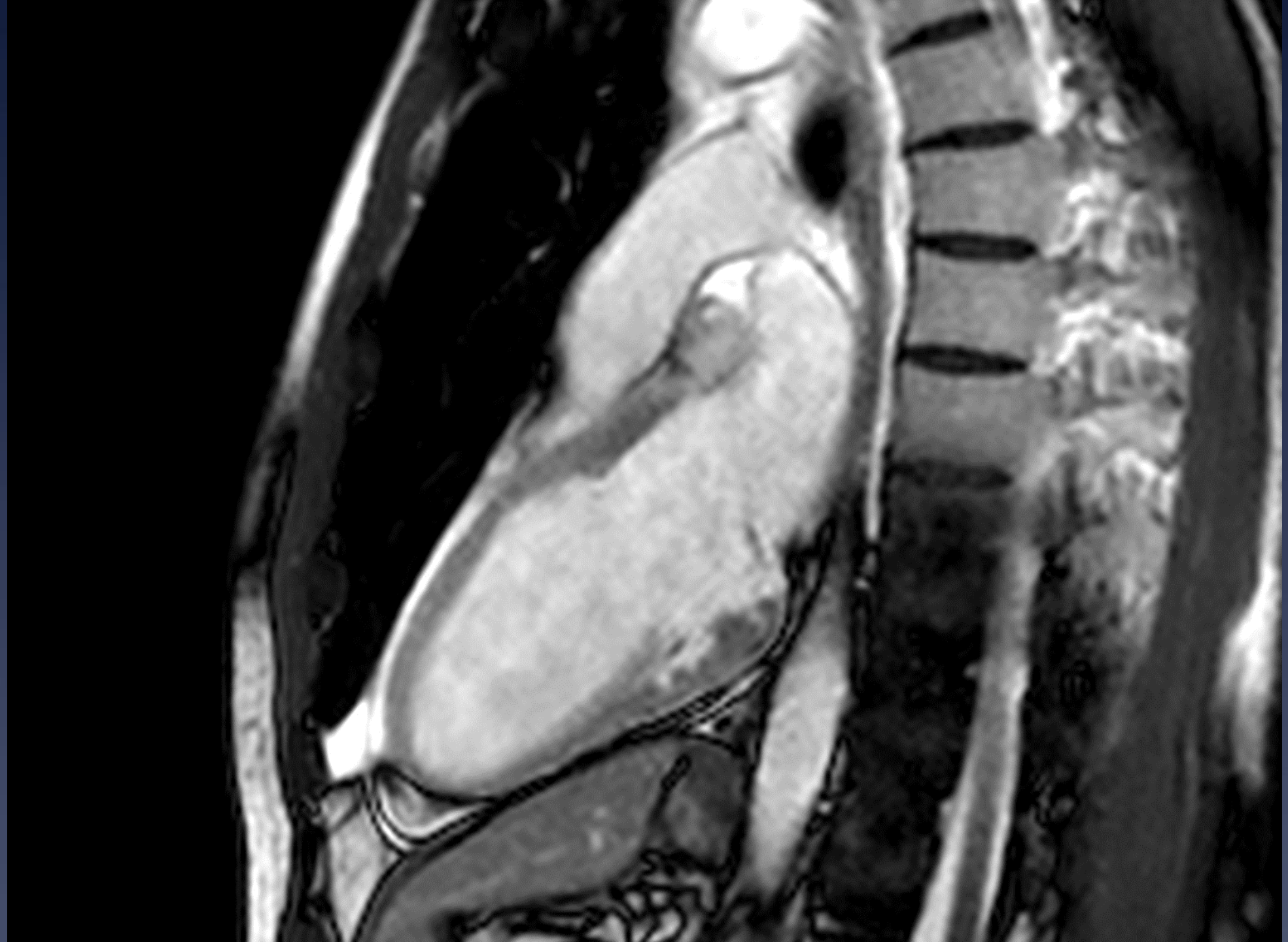
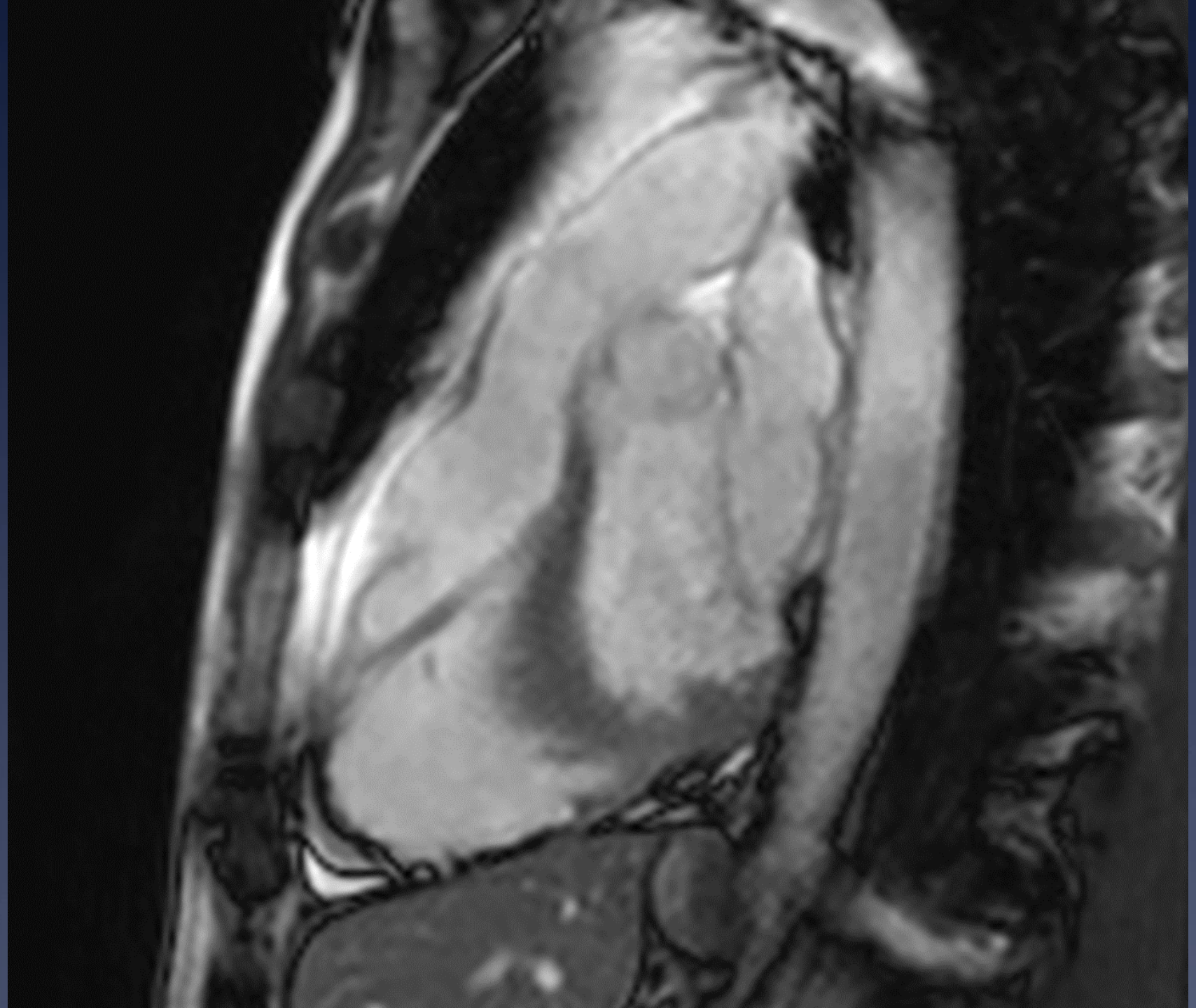
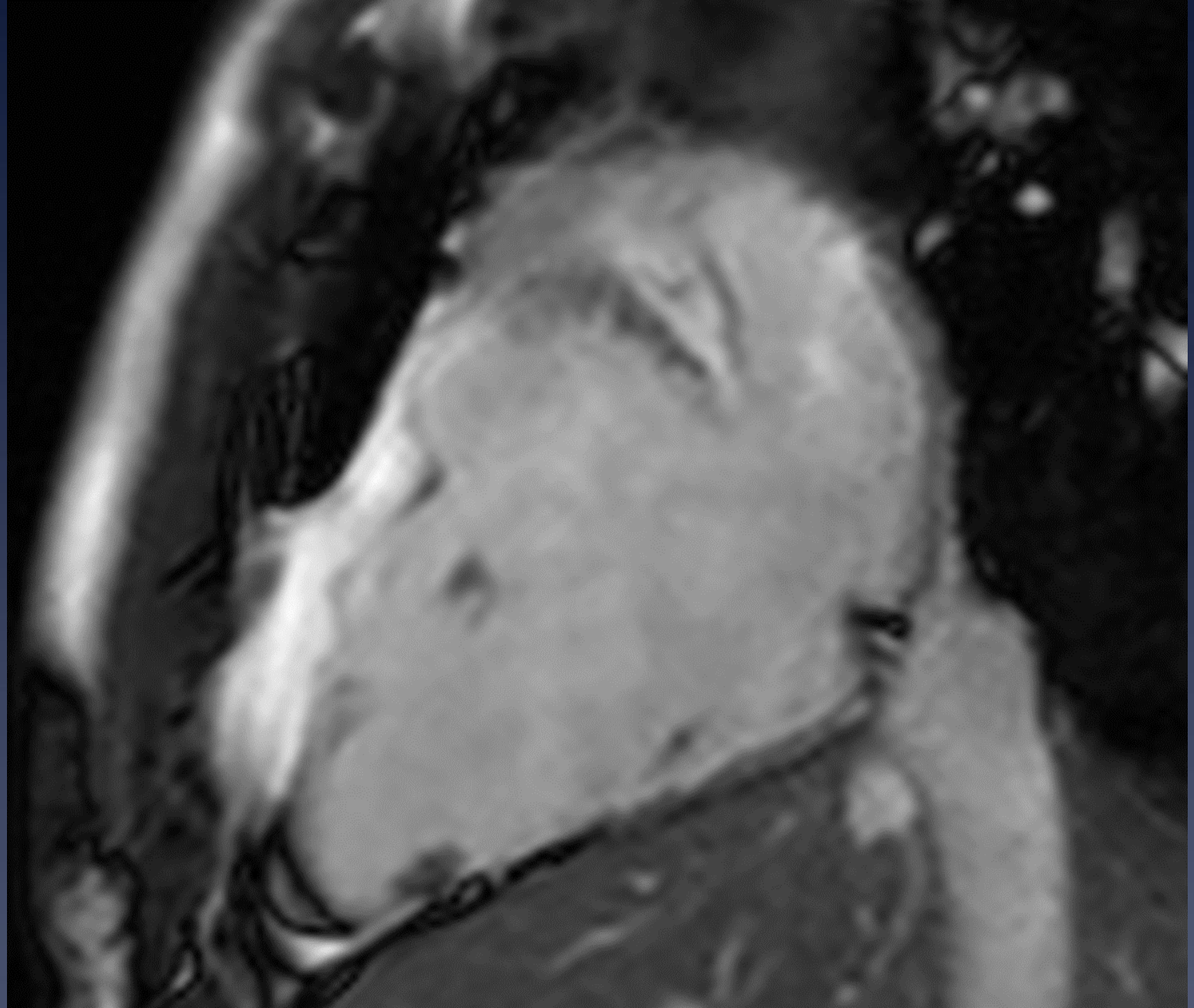
* The identification of an abnormal natriuretic peptide or high-sensitivity cardiac troponin should be part of individualized management decision plans (







Case study

* 68 yr old Malay lady. Active lady
* Known hypertension and hyperlipidemia 10 year.
* Current medications:

Cardiprin	100 mg daily
Felodipine	5 mg daily
Simvastatin	20 mg on

Case study

* Angina on exertion 1 month. On and off. Height 155 cm, Weight 69 kg (BMI 28.7).
* The BP is 140/80 mmHg and the is pulse 84 bpm. Clinical examination normal
* Blood: Total cholesterol 4.7 mmol/L , LDL 2.6 mmol/L , HDL 1.0 mmol/L, TG 2.0 mmol/L FBS 8.0 mmol/L, HbA1c 8.0%. Renal profile and urine normal.
* ECG normal. Echocardiography was done and it showed a normal cardiac anatomy with no regional LV wall abnormalities seen at rest.
* Positive stress Echo for ischeamia at High work load mainly at the inferior and posterior territory.

What is Optimal Medical treatment

* The combination of intensive, evidence-based pharmacologic intervention with life-saving interventions comprises optimal medical therapy (OMT).

* OMT is recommended by guidelines for all stable IHD patients, regardless of whether revascularization is performed.

* Optimal medical therapy consisted of antiplatelet therapy, anti-ischemic therapy, and aggressive lipid and blood pressure control.

* Based on the strength of the evidence, recommending more-aggressive medical therapy for patients with moderate-to-severe angina, and PCI or CABG for many patients in whom symptoms persist

Case study : How would You managed her

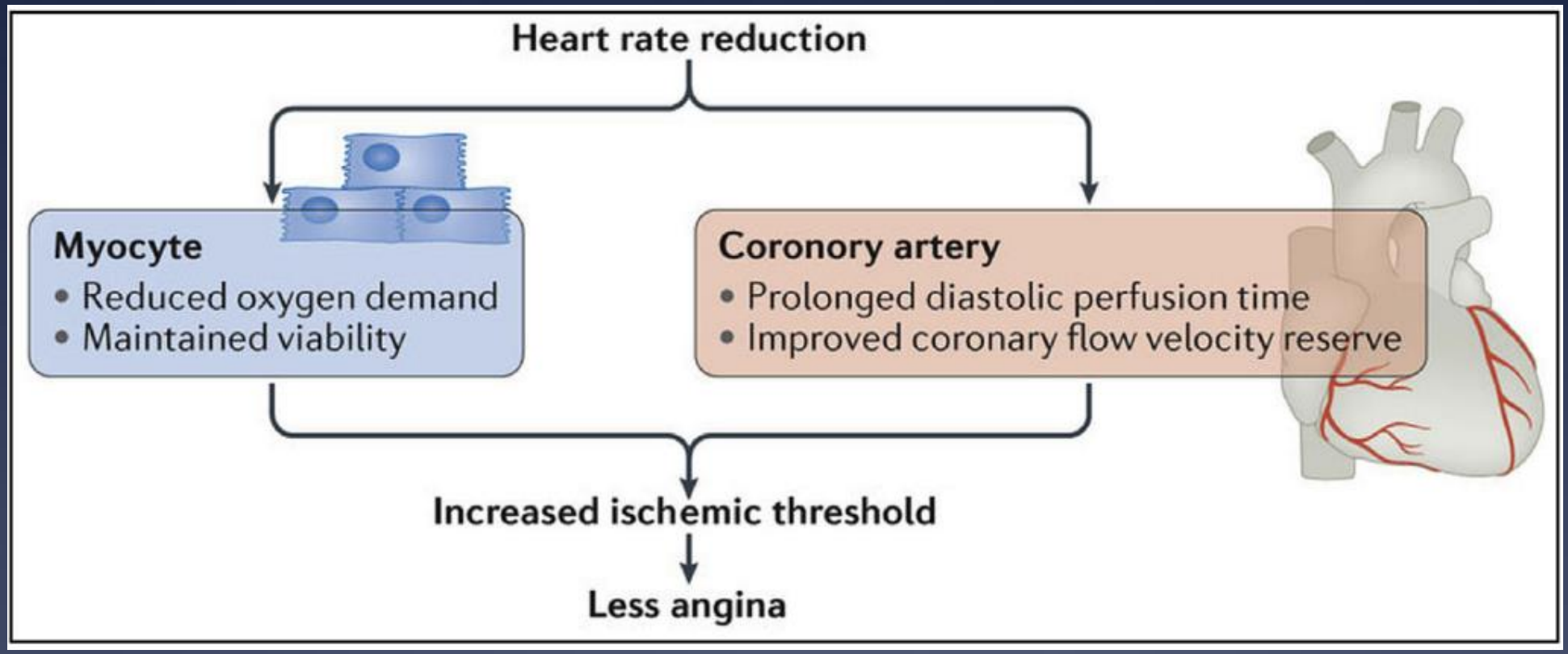
* Risk factor modification and go on medical treatment.
* Do other test like MSCT angiogram.
* Counselled patient for Invasive coronary angiogram.

That the Diabetic need to be address with Metformin in combination with SGLT2 inhibitor and the Felodipine was replace with ACEI and for the angina I started with Bisoprolol and Trimetazidine

* Ultimately the goal of using non-invasive testing is to guide further non-invasive medical or invasive therapy.

* Anatomical testing is recommended for patients with low to intermediate risk for future events, while stress testing is preferred in higher risk patients due to its greater rule in power

Beneficial effects of heart rate reduction in angina



DiFrancesco D, Borer JS. The funny current. Drugs. 2007;67:15e24.

Problems with Guidelines

* All guidelines take into consideration evidence provided by published trial data and meta-analysis of the different studies.

* However, in absence of these data which unfortunately is not uncommon, the recommendations are made according to previously reported guidelines, tradition-driven beliefs, and opinion of the experts on the guideline committees.

* Some guideline suggestions are inevitably, therefore, not evidence-based. The lack of reliable, objective data is indicated by providing a lower class to the recommendation.

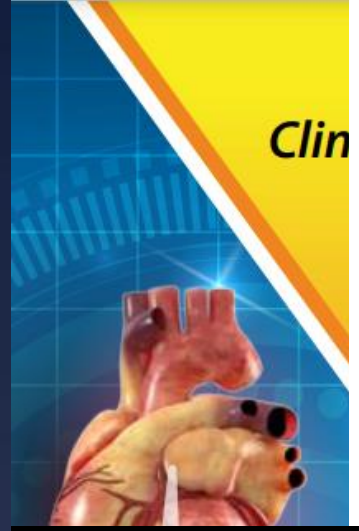
Angina Guidelines

* The absence of objective data is particularly relevant to the guidelines for antianginal drug therapy. The AHA/ACC , ESC , and NICE recommendations suggest a first-choice therapy with sublingual or short-acting nitroglycerin, β-blockers, and calcium-channel blockers.

* *Ivabradine, nicorandil, ranolazine, and trimetazidine are reserved for patients who have contraindications to the first-choice agents, do not tolerate them, or remain symptomatic, even though more evidence-based clinical data that are more contemporary are available for them than for the first-choice drugs.*

* No head-to-head comparisons between first-choice and second-choice treatments are available that demonstrate superiority of one over any other in terms of antianginal effects.

* Sometimes double and sometimes triple therapy with different classes of antianginal drugs is often needed, and the guidelines do not provide an indication of the optimal combination.



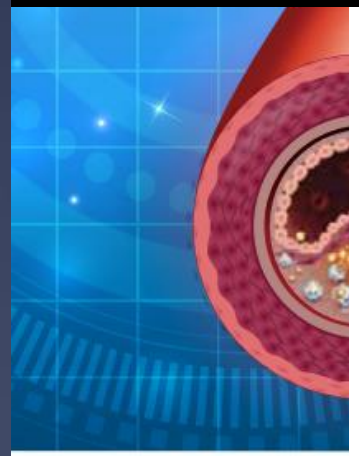
8.2.2. Management of symptoms - Anti-ischemic therapy (Fig 2, pg 25)

Anti-ischemic therapy is used to treat the symptoms of angina. While these medications have been shown to reduce symptoms, none have been shown to prevent MI or death in patients with stable CAD.

These medications prevent attacks of angina by:

- decreasing myocardial oxygen consumption (lowering heart rate, blood pressure, myocardial loading, or myocardial contractility) and/or
- increasing myocardial oxygen supply (increasing coronary blood flow)

.....That the Diabetic need to be address with Metformin in combination with SGLT2 inhibitor and the Felodipine was replace with ACEI and for the angina I started with Bisoprolol and Trimetazidine……



- Ivabradine
- Ranolazine
- Nicorandil

The choice of anti-ischemic therapy should be individualised depending upon:

- presence of co-morbidities (such as asthma) and/or
- physiological parameters such as resting heart rate, blood pressure, LV function and/or
- Cost and availability

Combination of anti-ischemic therapy may be necessary to control symptoms.

CONSENSUS STATEMENT

Nature Reviews | Cardiology. 15| February 2018

OPEN

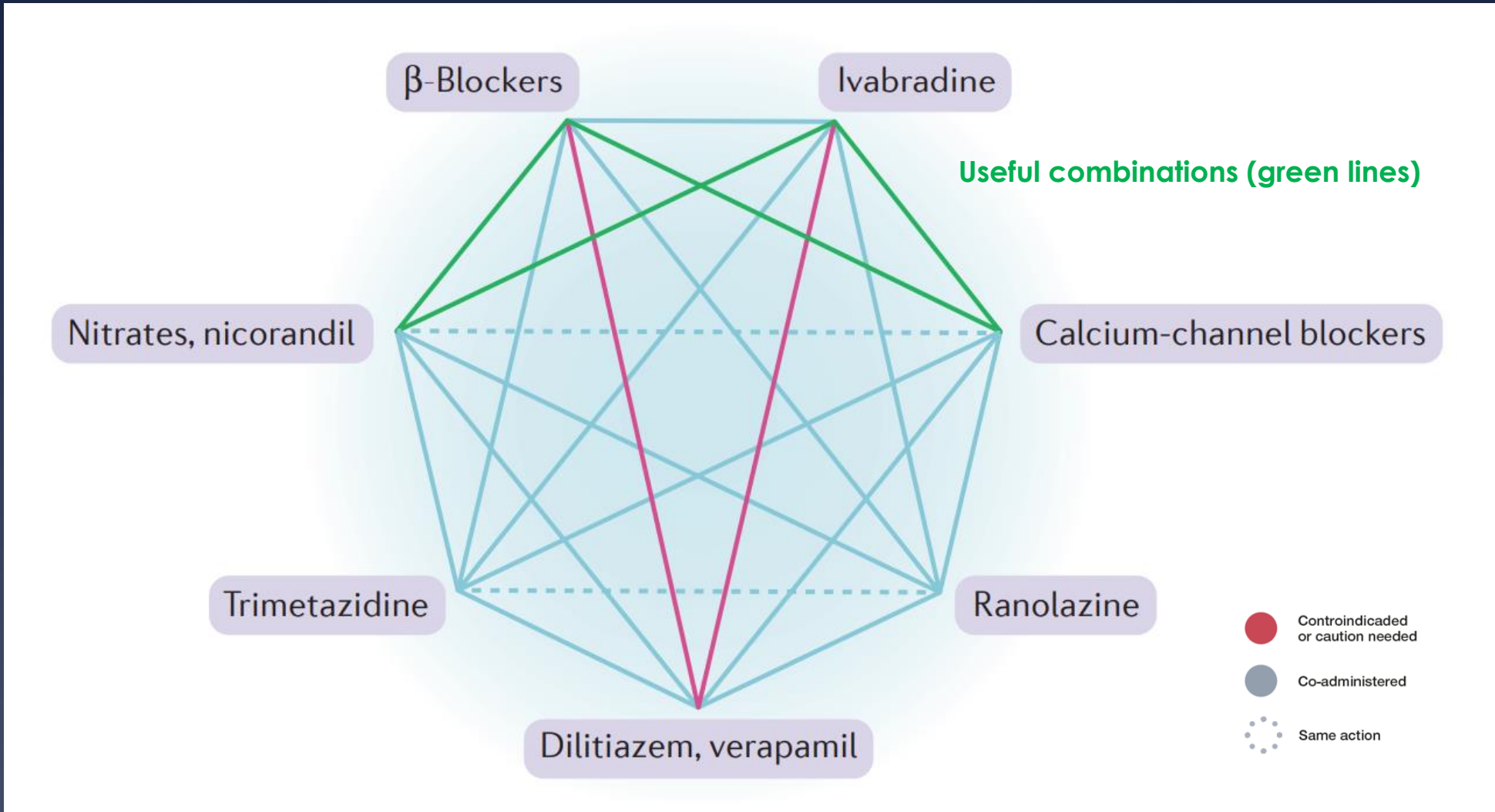
EXPERT CONSENSUS DOCUMENT

A ‘diamond’ approach to personalized treatment of angina

Roberto Ferrari[1,2], Paolo G. Camici[3], Filippo Crea[4], Nicolas Danchin[5], Kim Fox[6], Aldo P. Maggioni[7], Athanasios J. Manolis[8], Mario Marzilli[9,10], Giuseppe M. C. Rosano[11,12] and José L. Lopez-Sendon[13]

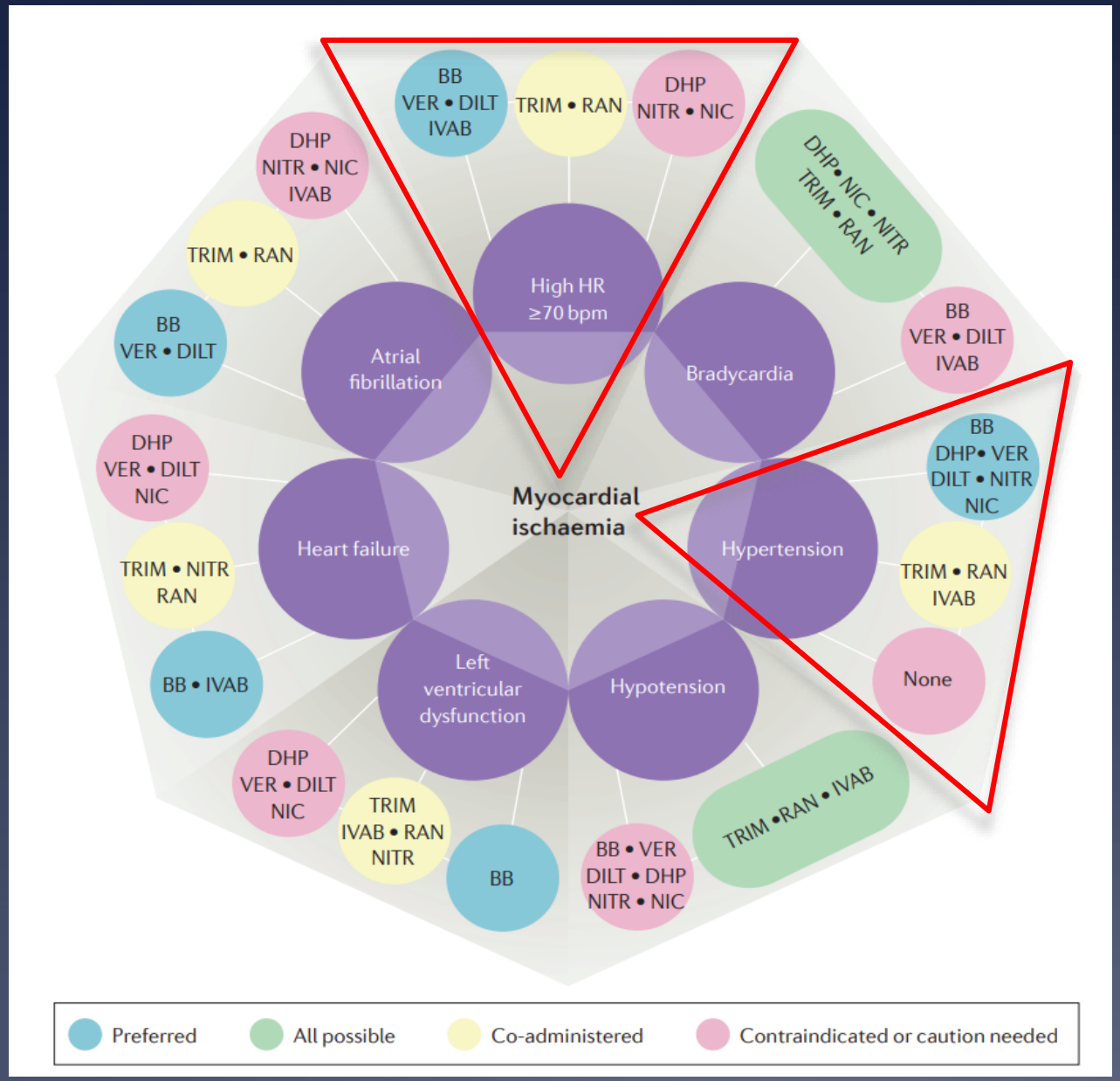
Abstract | In clinical guidelines, drugs for symptomatic angina are classified as being first choice (β-blockers, calcium-channel blockers, short-acting nitrates) or second choice (ivabradine, nicorandil, ranolazine, trimetazidine), with the recommendation to reserve second-choice medications for patients who have contraindications to first-choice agents, do not tolerate them, or remain symptomatic. No direct comparisons between first-choice and second-choice treatments have demonstrated the superiority of one group of drugs over the other. Meta-analyses show that all antianginal drugs have similar efficacy in reducing symptoms, but provide no evidence for improvement in survival. The newer, second-choice drugs have more evidence-based clinical data that are more contemporary than is available for traditional first-choice drugs. Considering some drugs, but not others, to be first choice is, therefore, difficult. Moreover, double or triple therapy is often needed to control angina. Patients with angina can have several comorbidities, and symptoms can result from various underlying pathophysiologies. Some agents, in addition to having antianginal effects, have properties that could be useful depending on the comorbidities present and the mechanisms of angina, but the guidelines do not provide recommendations on the optimal combinations of drugs. In this Consensus Statement, we propose an individualized approach to angina treatment, which takes into consideration the patient, their comorbidities, and the underlying mechanism of disease.

Possible combinations of different classes of antianginal drugs



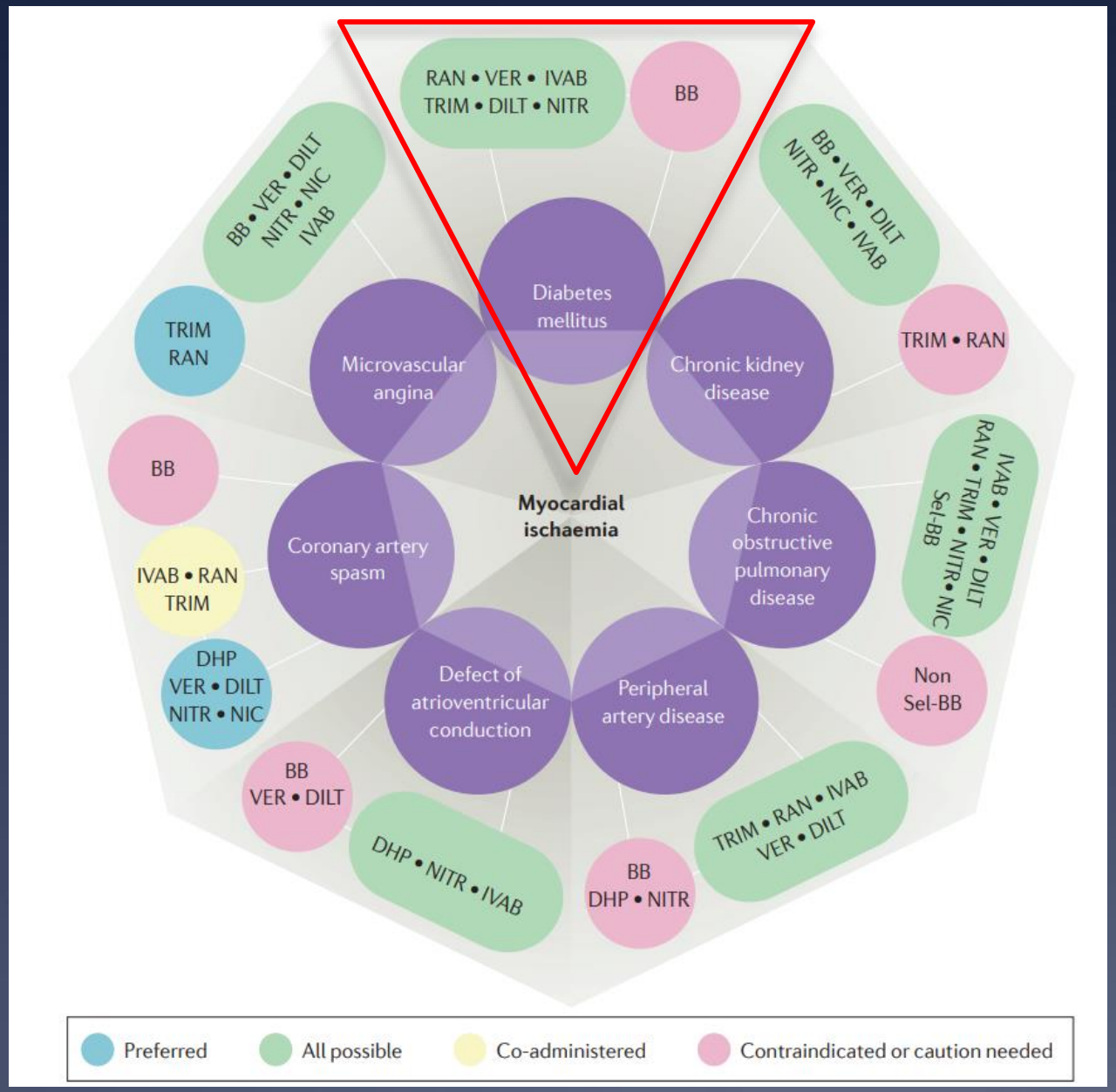
Expert Consensus Document. A 'diamond' approach to personalized treatment of angina. Roberto Ferrari et al. Nature Reviews | Cardiology. 15| February 2018

Possible combinations of classes of antianginal drugs according to different comorbidities



Expert Consensus Document. A 'diamond' approach to personalized treatment of angina. Roberto Ferrari et al. Nature Reviews | Cardiology. 15| February 2018

Possible combinations of classes of antianginal drugs according to different comorbidities



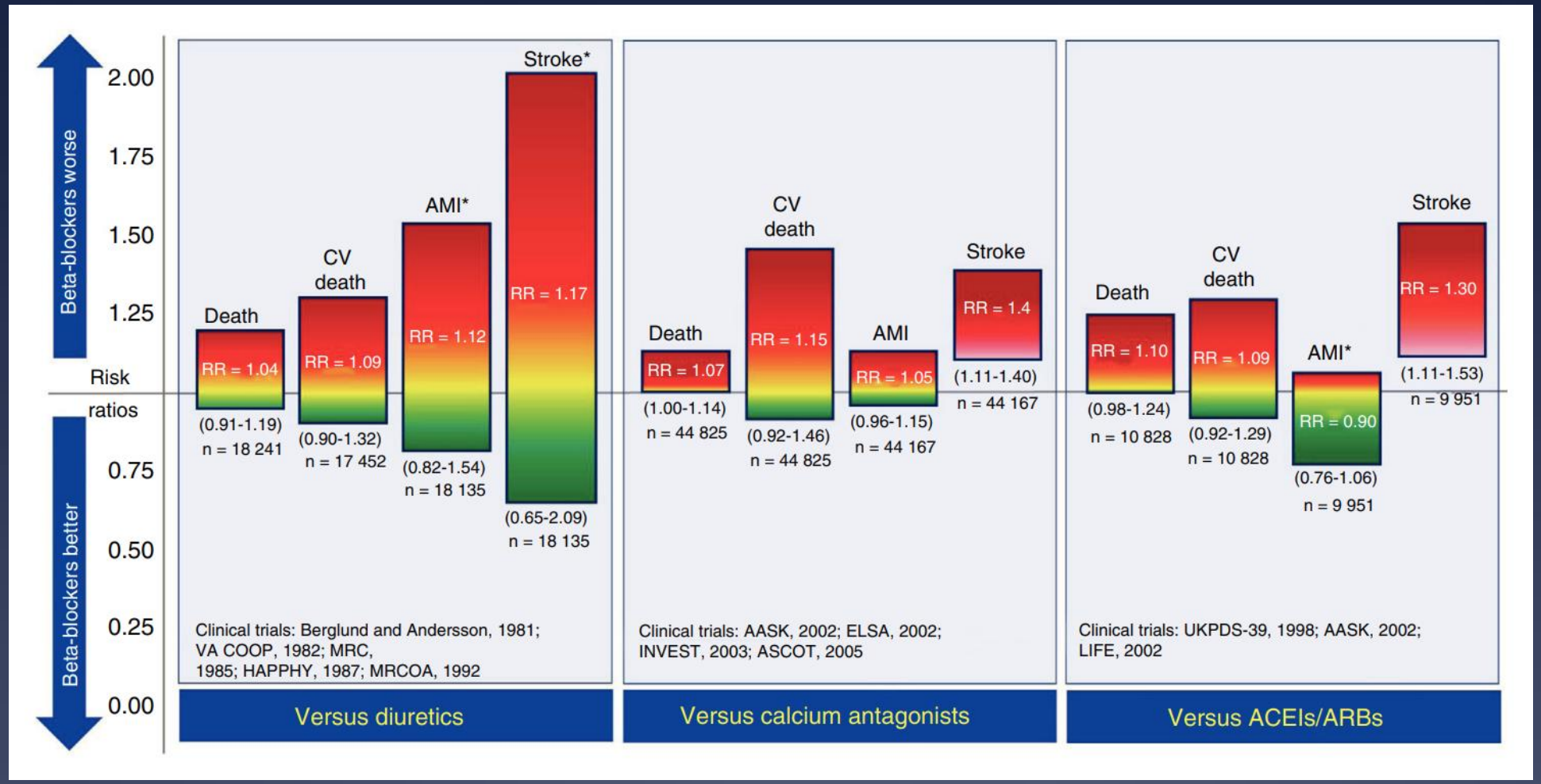
Expert Consensus Document. A 'diamond' approach to personalized treatment of angina. Roberto Ferrari et al. Nature Reviews | Cardiology. 15| February 2018

Case Study

* Came back earlier to see me because she felt fatigue and “Mengah” .
* The BP is 130/80 mmHg and the is pulse 74 bpm. Clinical examination normal.
* Stopped Bisoprolol and started Ivabradine at 5 mg Bid

Have been with me for the last 5 years with no cardiac events with fairly good control of the Risk factors and a pulse rate between 60-70 bpm with Ivabradine 7.5 mg bd

Beta Blockers in Hypertension



Compared with placebo, BBs have not been shown to reduce all-cause or cardiovascular mortality in patients with uncomplicated essential hypertension but there was reduction of stroke. Compared with diuretics, CCB and ACEi/ARB , BBs do not reduce cardiovascular events and may even be associated with a higher incidence of stroke.

The new European guidelines on hypertension rule out BBs as first-line drug therapy for uncomplicated hypertension.

J. Martınez-Milla et al. / Rev Esp Cardiol. 2019;72(10):844–852

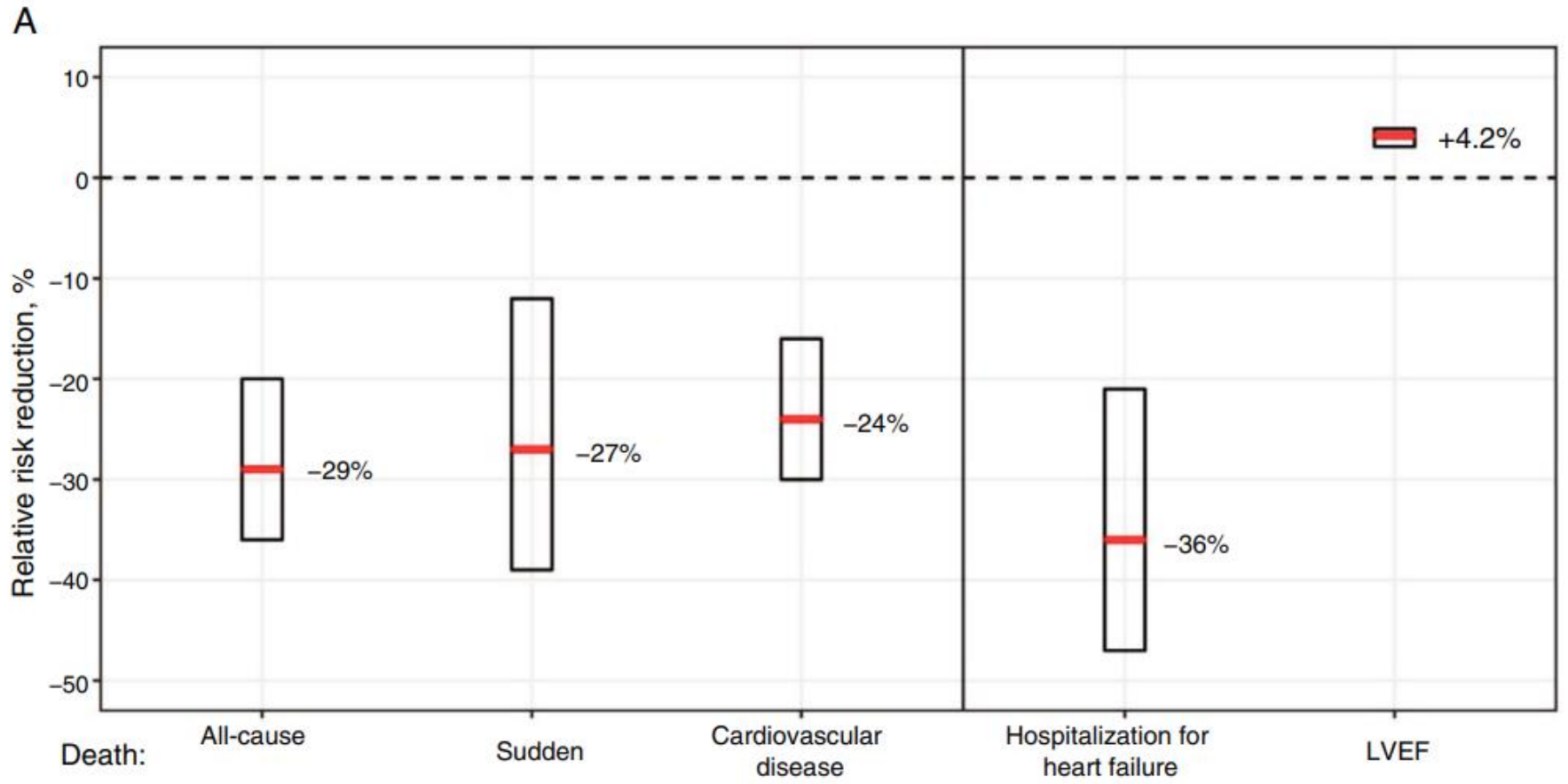
Main clinical studies analyzing beta-blockers in the treatment of essential hypertension

Study	Population	Beta-blocker	Comparison	Result
Berglund and Andersson[30]	47-54 y	Propranolol	Thiazide	No difference in mortality
VA COOP[31]	21-65 y	Propranolol	Thiazide	No difference in mortality, AMI, or stroke
MRC[32]	35-64 y	Propranolol	Thiazide Placebo	Lower risk of stroke vs placebo; no difference in AMI or mortality Higher risk of stroke vs thiazide
Coope and Warrender[33]	60-79 y	Atenolol ± thiazide	Placebo	Lower risk of stroke vs placebo; no difference in AMI or mortality
HAPPHY[34]	40-65 y (only men)	Metoprolol Atenolol	Thiazide	Tendency for less stroke vs diuretics No difference in mortality or AMI
MAPHY[35]	40-64 y (only white men)	Metoprolol	Thiazide	Reduction in total mortality, AMI, and stroke
STOP-Hypertension[36]	70-84 y	Pindolol Metoprolol Atenolol	Placebo	Reduction in cardiovascular mortality, AMI, and stroke
MRCOA[37]	65-74 y	Atenolol Diuretics	Placebo	No difference in cardiovascular death, stroke, or AMI vs placebo (diuretic vs placebo did reduce such events)
UKPDS[38]	Diabetic patients	Atenolol	Captopril	No difference in total mortality, AMI, or stroke
STOP-2[39]	70-84 y	Pindolol Metoprolol Atenolol	Enalapril Lisinopril Felodipine Isradipine	No difference in mortality, AMI, or stroke
CAPPP[40]	20-66 y	Metoprolol Atenolol	Captopril	Tendency for higher cardiovascular mortality No difference in AMI Lower risk of stroke
ELSA[41]	Carotid atherosclerosis	Atenolol	Lacidipine	Increased atherosclerotic plaque progression
LIFE[42]	55-80 y	Atenolol	Losartan	Same cardiovascular mortality Same risk of AMI More stroke More DM
INVEST[43]	≥50 y Ischemic heart disease	Atenolol ± thiazide	Verapamil ± trandolapril	No difference in mortality, AMI, or stroke
CONVINCE[44]	≥ 55 years with 1 CVRF	Atenolol	Verapamil	No difference in mortality, AMI, or stroke
ASCOT-BPLA[45]	40-79 y High cardiovascular risk	Atenolol ± thiazide	Amlodipine ± perindopril	Tendency for higher risk of AMI Higher risk of stroke Higher cardiovascular mortality Higher risk of DM

Beta Blockers in Heart failure

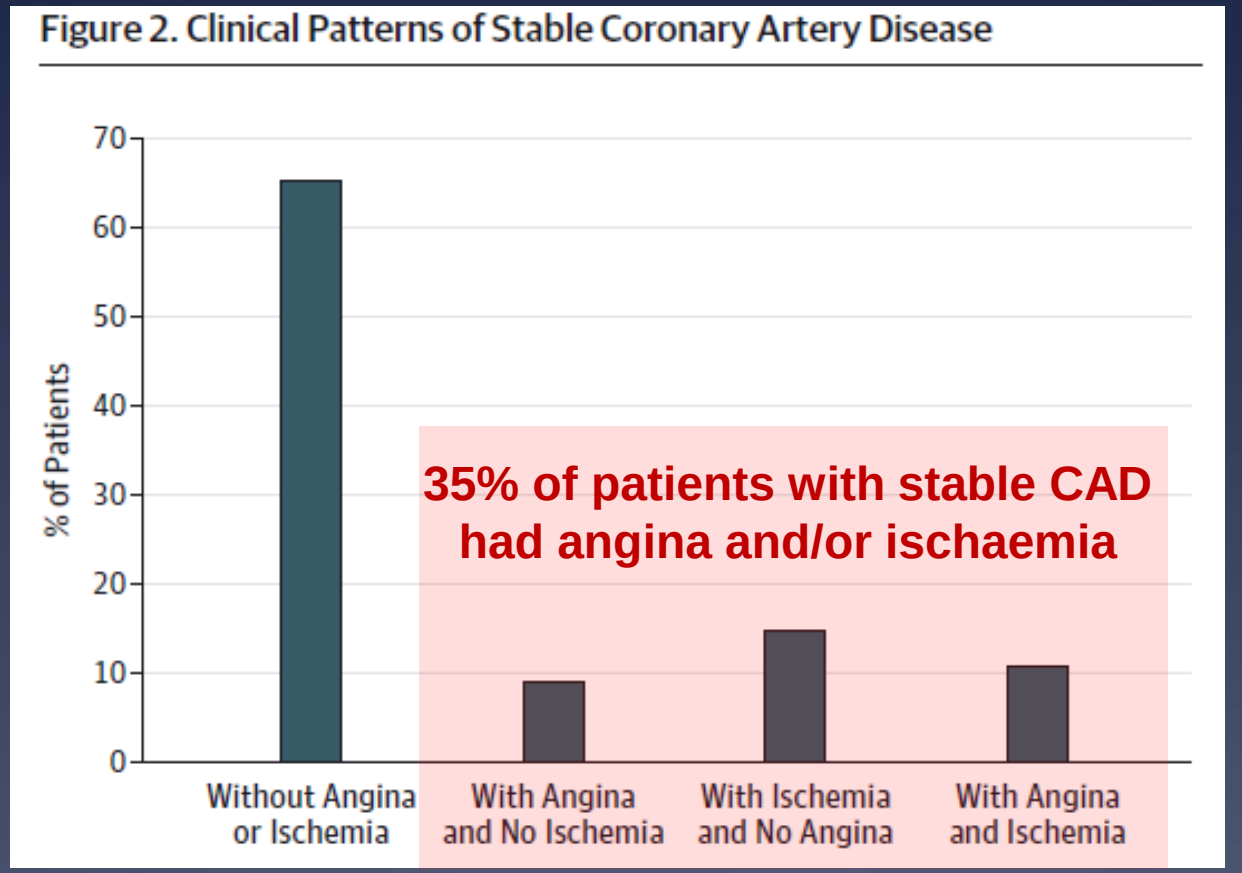
Design and results of the main clinical trials of beta-blockers in heart failure

Study (y, patients)	Drug, mean (mg/d)	NYHA	LVEF	Ischemic	Mean follow-up, mo	NYHA class III/IV	NNT 1 life 1 y	Reduction in risk of death				Reduction in risk of hospitalization	
								Total	CV	Sudden	Due to HF	Total	Due to HF
CIBIS-II[6] (1999, n = 2647)	Bisoprolol 7.5 mg/d	III-IV	≤35%	50%	15	100%	23	34%	29%	44%	26%	20%	36%
MERIT-HF[7] (1999, n = 3991)	Metoprolol 159 mg/d	II-IV	≤40%	65%	12	59%	27	34%	38%	41%	49%	18%	35%



CLARIFY

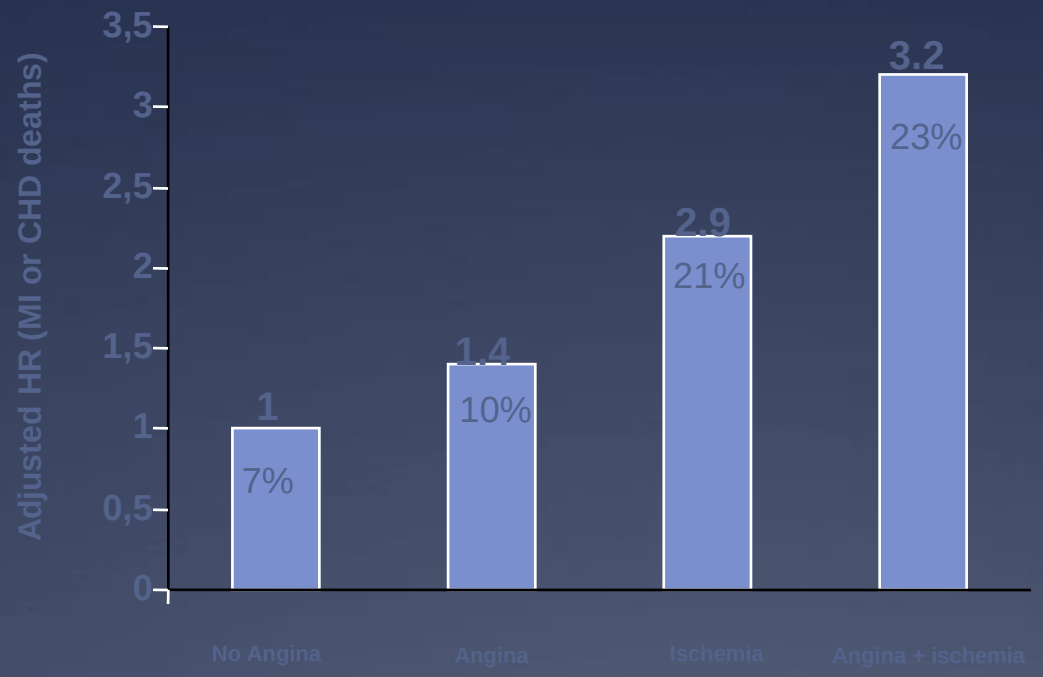
ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease



Steg PA et al. JAMA Intern Med. 2014;174:1651-59

myocardial ischaemia increases the risk of coronary events

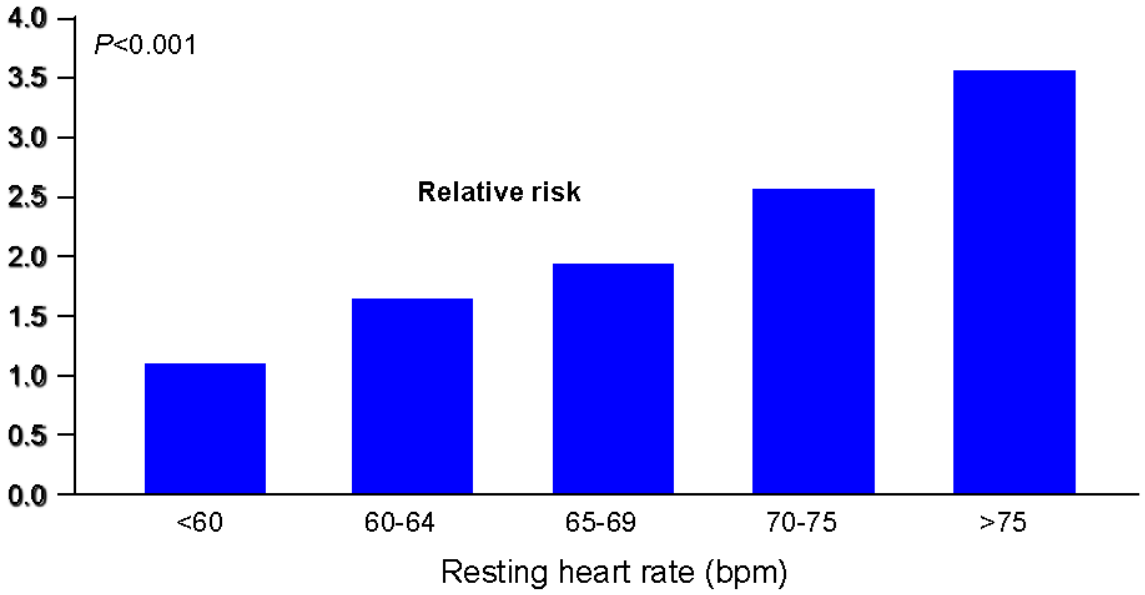
The Heart and Soul Study; 937 outpatients with stable CHD, 3.9 years of follow-up



Gehi AK et al. Arch Intern Med. 2008;168(13):1423-1428

Sudden death risk increases progressively with resting heart rate in the general population

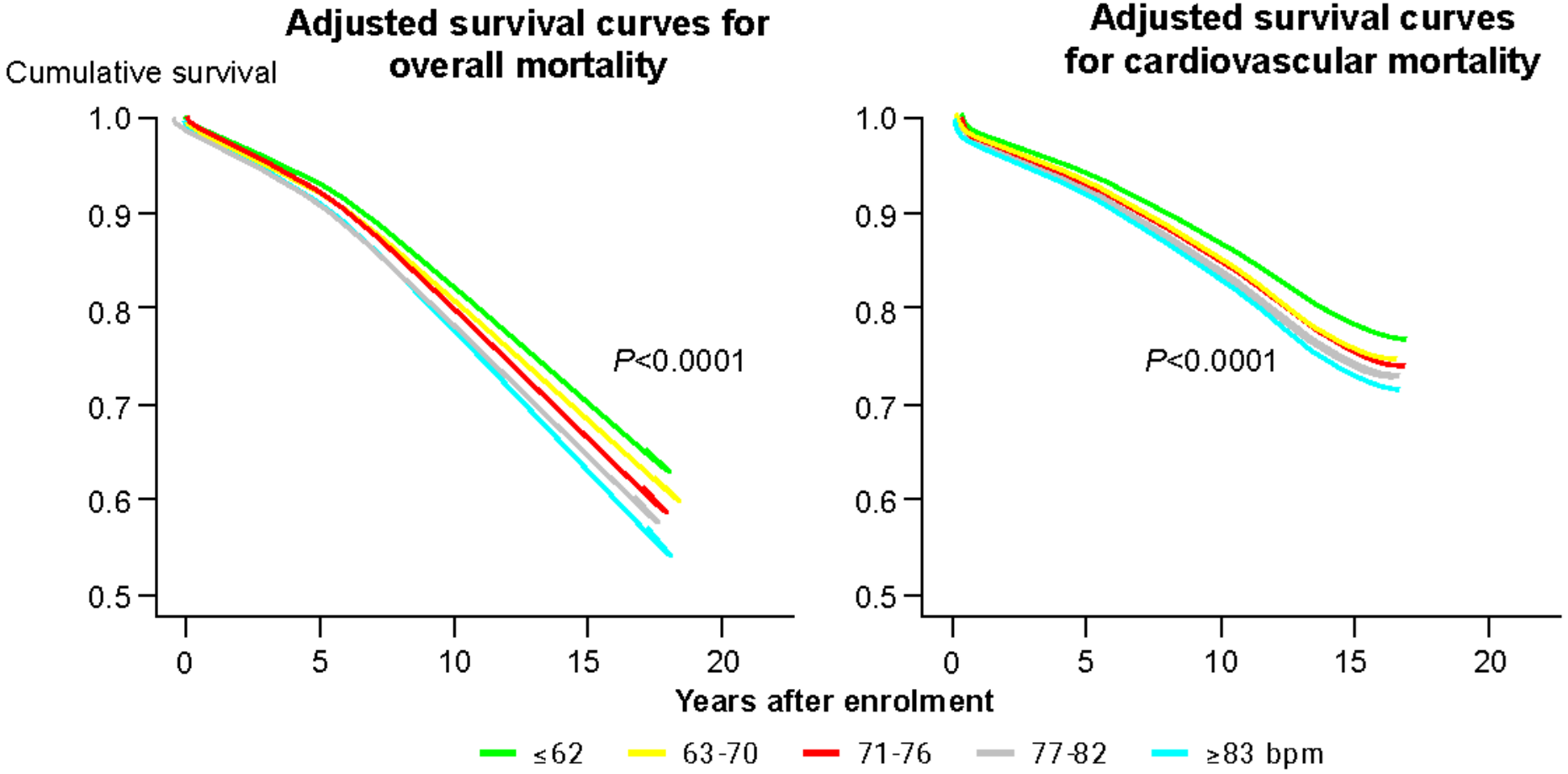
The Paris Prospective Study I, general population, 5713 men; 23-year follow-up



Jouven X, et al., *N Engl J Med*. 2005;352:1951-1958.

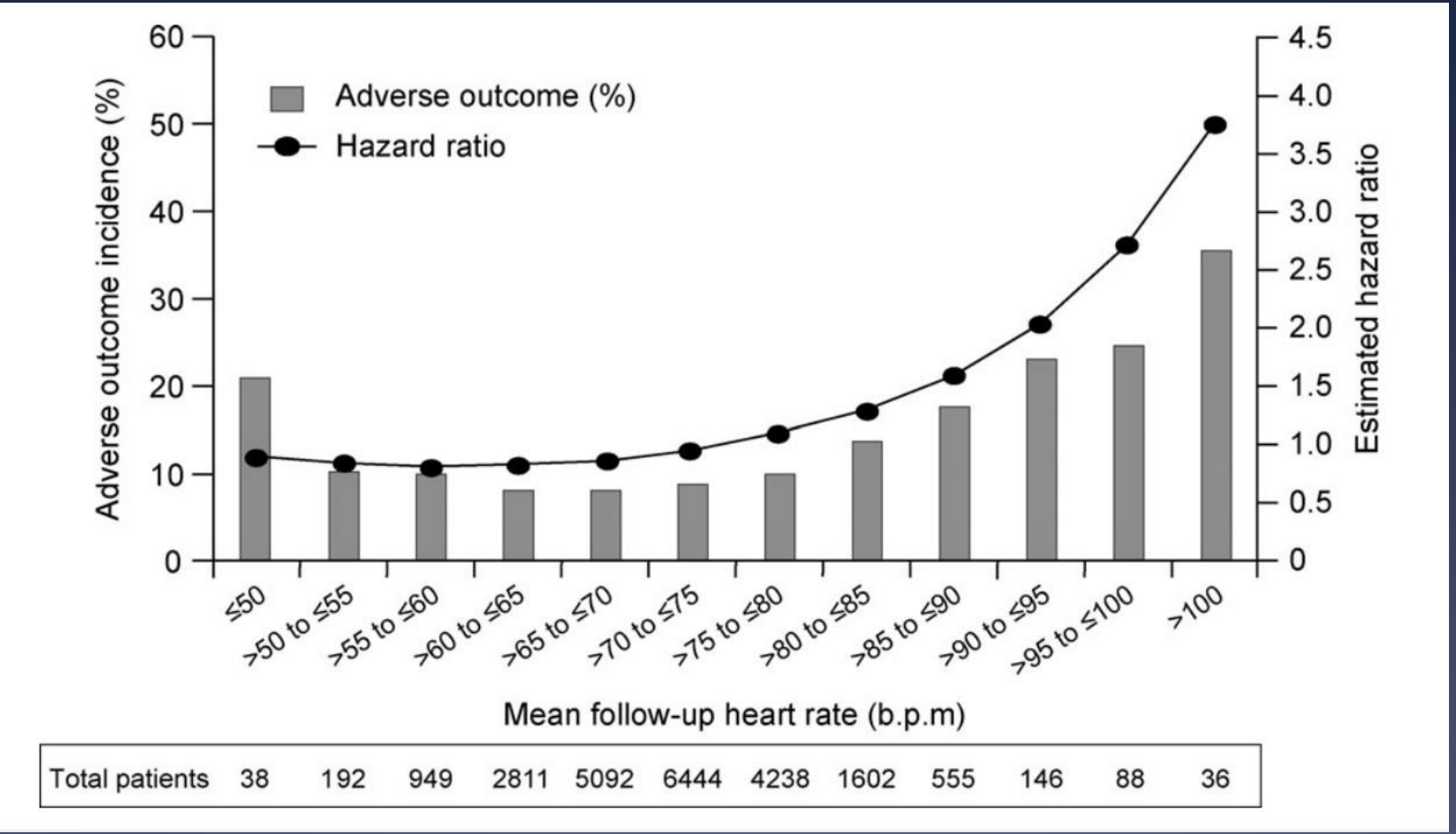
Resting heart rate is an independent predictor of mortality in patients with CAD

The Coronary Artery Surgery Study (CASS) registry; 24 913 CAD patients; 14.1-year follow-up



Diaz A, et al. *Eur Heart J.* 2005;26:967-974.

Impact of resting heart rate on outcomes in hypertensive patients with CAD



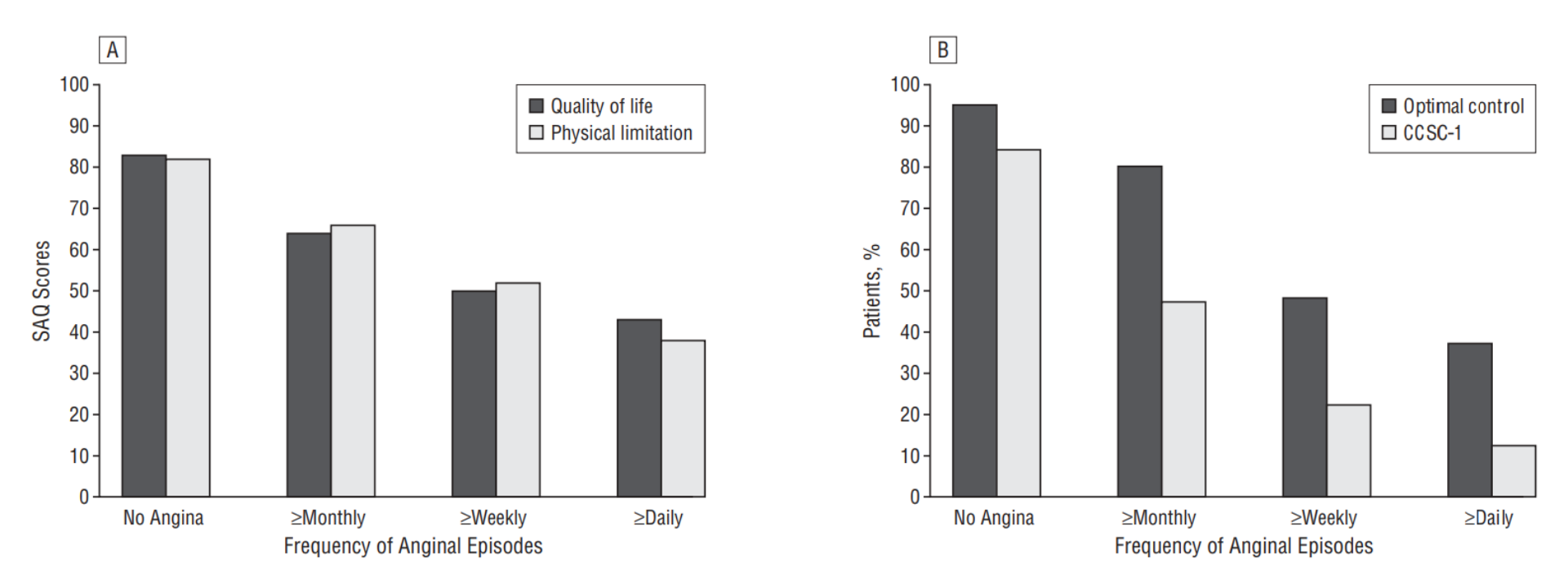
Relationship between follow-up resting heart rate for all patients and incidence of adverse outcomes (left axis, bars) and risk (right axis –†–, hazard ratio) derived from a stepwise Cox proportional hazards model. Among all patients, the nadir for follow-up resting heart rate was 59 b.p.m

INVEST Study : Population is 22,576 followed up for 24 months

R. Kolloch et al. European Heart Journal (2008) 29, 1327–1334

Prevalence of angina increases with age in both sexes

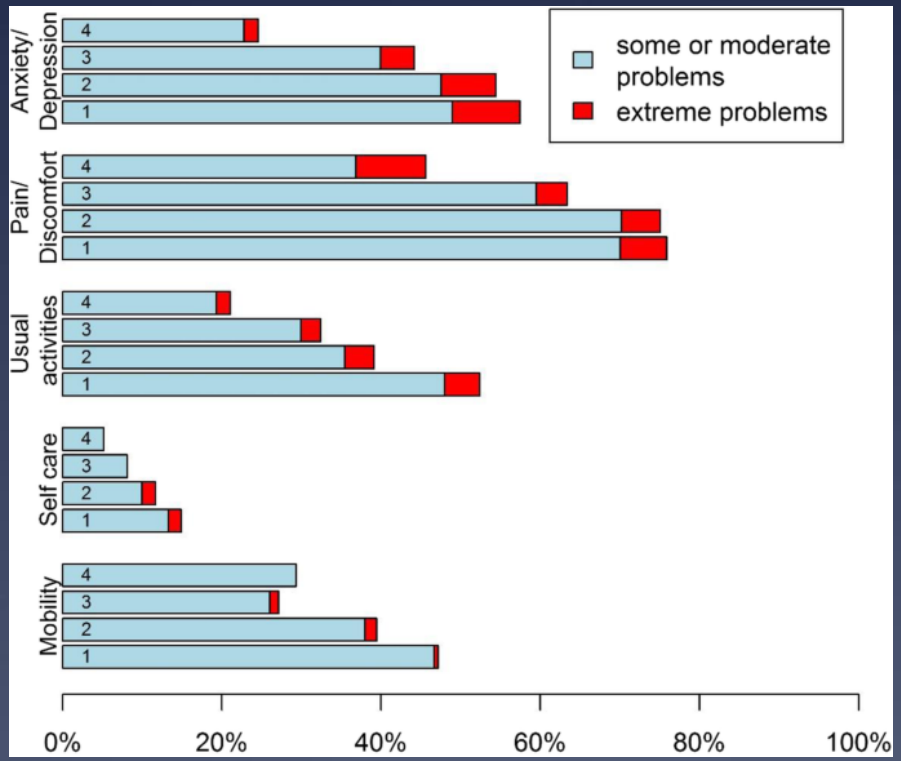
Angina associated with greater physical limitation and poorer quality of life



Relationship between angina frequency and patient-assessed quality-of-life indices and general practitioner (GP) perception. Relationship between the frequency of anginal episodes (over the preceding 4 weeks) and (A) patient-assessed Seattle Angina Questionnaire (SAQ) quality-of-life indices or (B) GP-perceived physical limitation by angina (Canadian Cardiovascular Society Classification 1 [CCSC-1]) and optimal therapeutic control.

Beltrame JF et al. The Coronary Artery Disease in General Practice (CADENCE) Study . J Arch Intern Med. 2009;169(16):1491-1499.

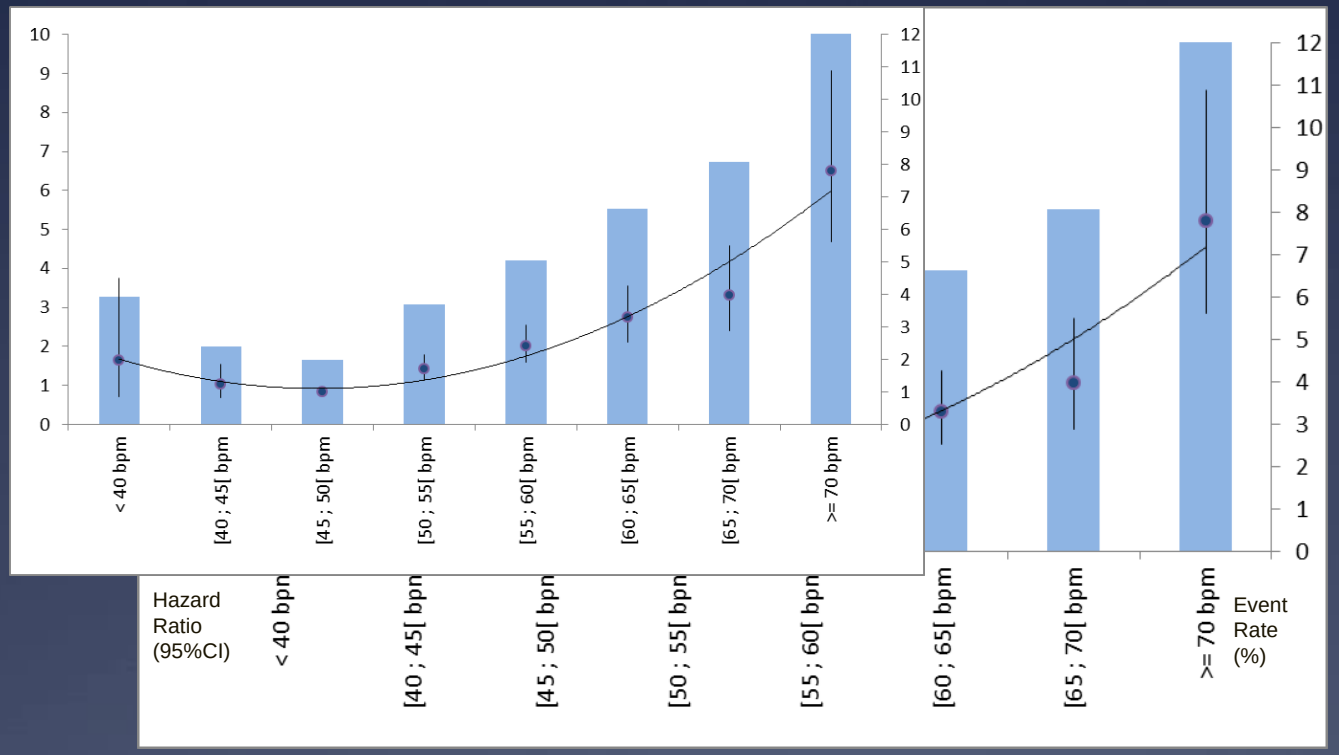
Angina impacts patient mobility, self-care, usual activities, pain/discomfort, and anxiety/depression



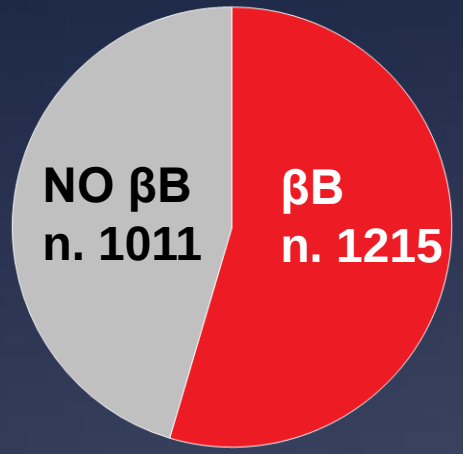
1. Typical angina
2. Atypical angina
3. Non-anginal chest discomfort
4. Other chest discomfort

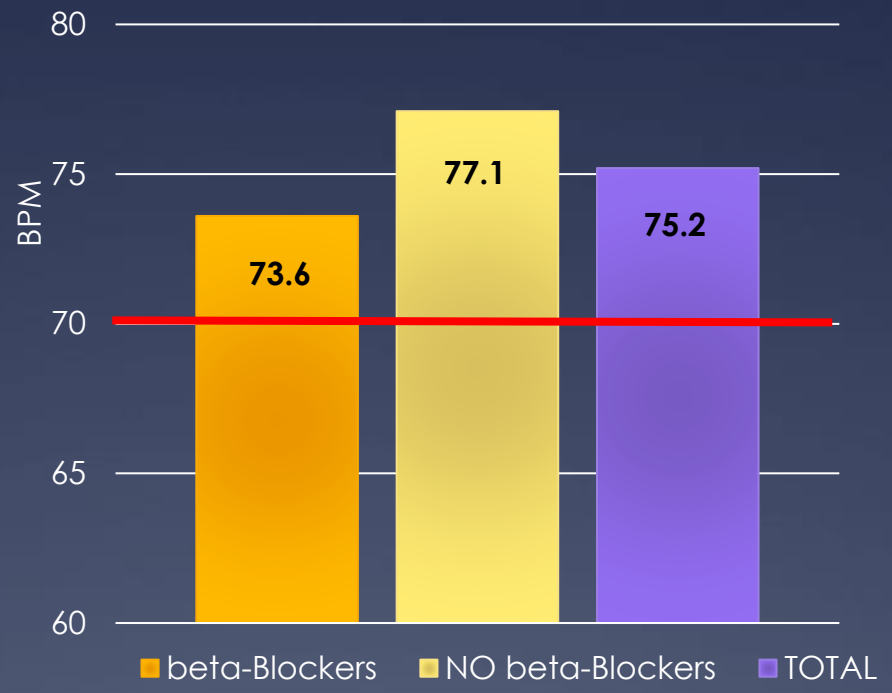
Rieckmann N et al. Health Qual Life Outcomes. 2020;18(140):e2112800.

Shifting the paradigm from threshold to target HR in patients receiving HR lowering drugs



Heart rate control and β-Blocker use in patients with CAD





This observational, cross-sectional, multicenter survey patients with chronic CAD attending outpatient clinics. N = 2226 . F/U 6 months

Vitale C et al Ann Int Med 2010

Beta-blockers in CAD without LVD

* Beta-blockers have been approved on the basis of small studies that are not adequate according to current standards
* No real evidence exists from the small and relatively old (1979–2003) randomized trials in patients with chronic angina that β-blockers reduce mortality

Beta-blockade in post-MI patients with preserved LV function

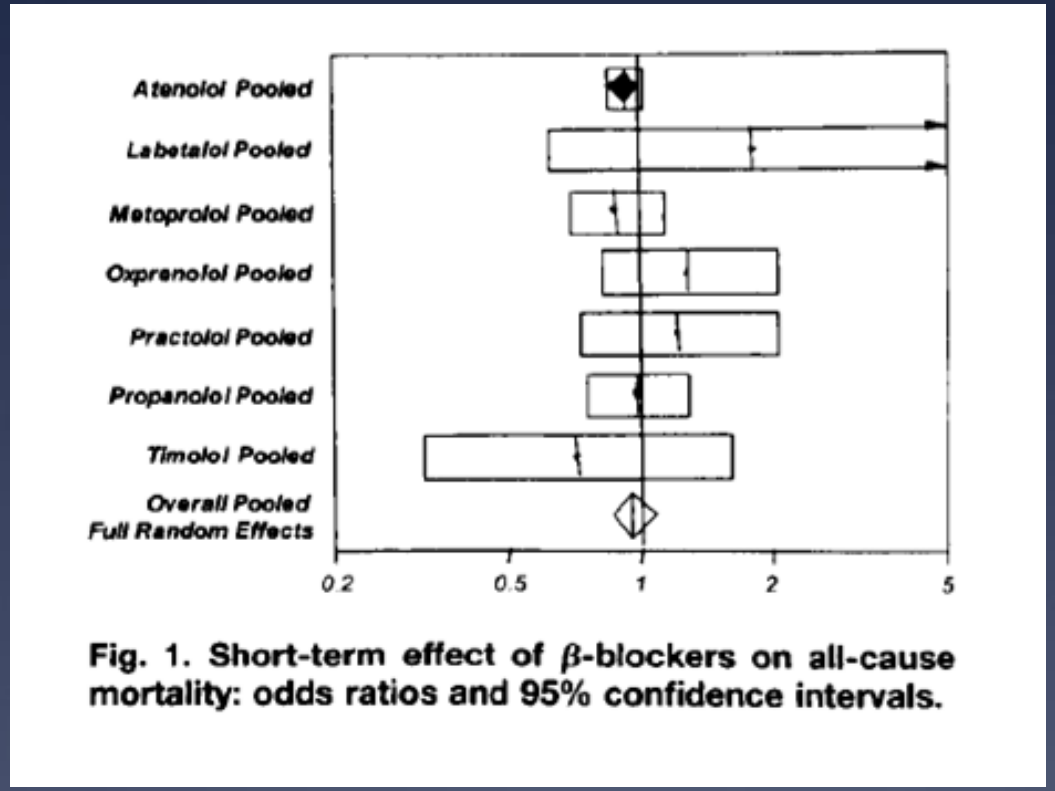
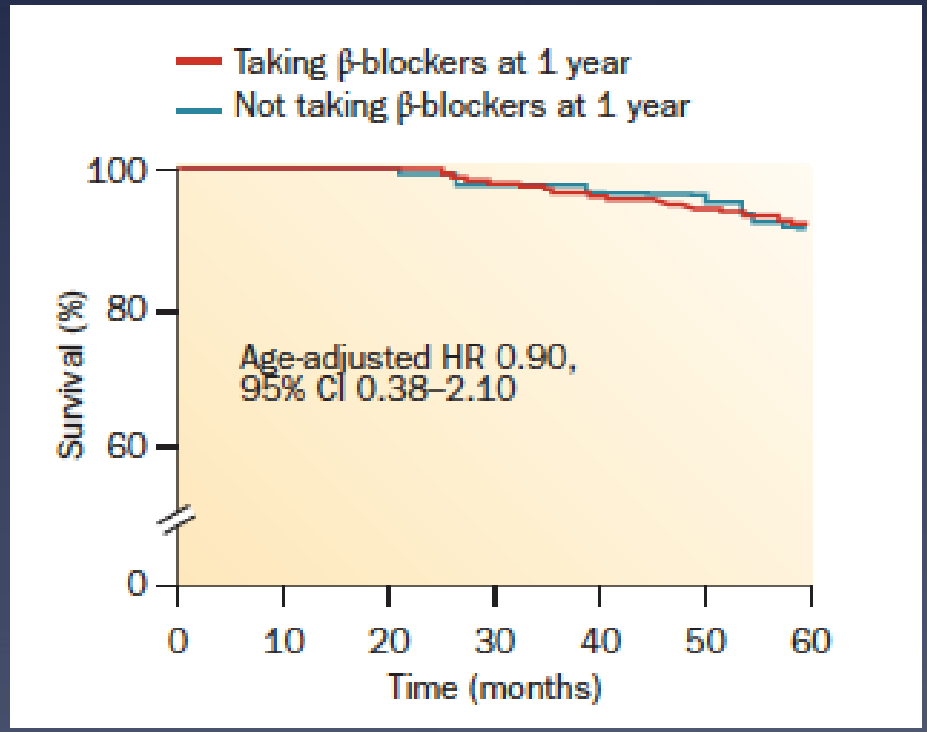


Fig. 1. Short-term effect of β-blockers on all-cause mortality: odds ratios and 95% confidence intervals.

Freemantle N, et al. Prog Cardiovasc Dis 2002;44:243-250.

Beta Blockers at 1 year after MI
The FAST-MI 2005 registry



http://www.escardio.org/congresses/esc-2012/congress-reports/Pages/707-5

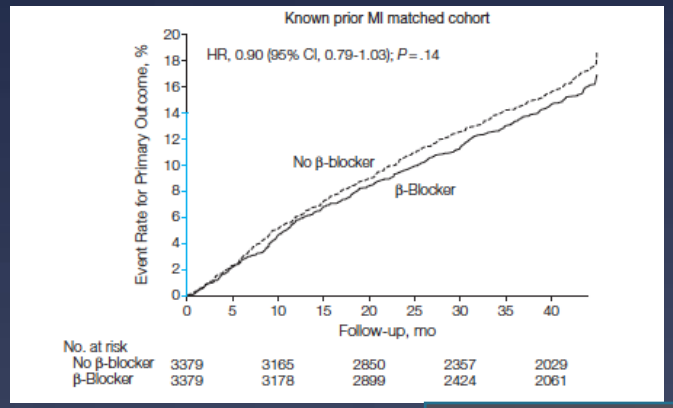
Lack of Effect of Oral Beta-Blocker Therapy at Discharge on Long-Term Clinical Outcomes of ST-Segment Elevation Acute Myocardial Infarction After Primary Percutaneous Coronary Intervention

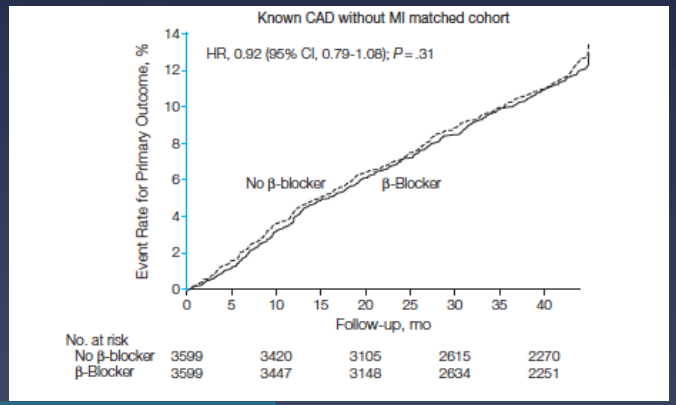
Neiko Ozasa, MD[a], Takeshi Kimura, MD[a,*], Takeshi Morimoto, MD, MPH[b], Heigen Hou, MD[a], Toshihiro Tamura, MD[a], Satoshi Shizuta, MD[a], Yoshihisa Nakagawa, MD[c], Yutaka Furukawa, MD[d], Yasuhiko Hayashi, MD[e], Koichi Nakao, MD[f], Masunori Matsuzaki, MD[g], Masakiyo Nobuyoshi, MD[h], and Kazuaki Mitsudo, MD[i], on behalf of the j-Cypher Registry Investigators

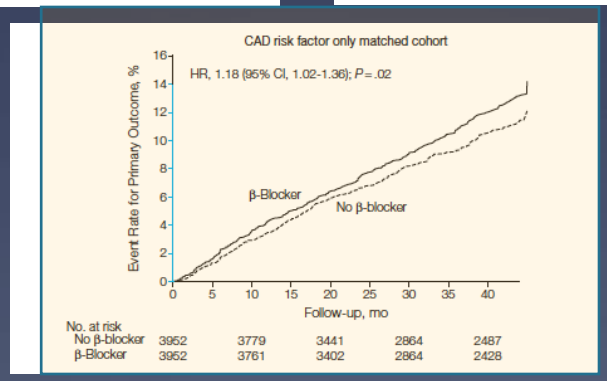
Am J Cardiol 2010;106:1225–1233

- 12,824 consecutive patients
- 910 patients who underwent PCI within 24 hours from onset of STEMI

β-blocker use and clinical outcomes
The REACH registry - CV death, MI, Stroke





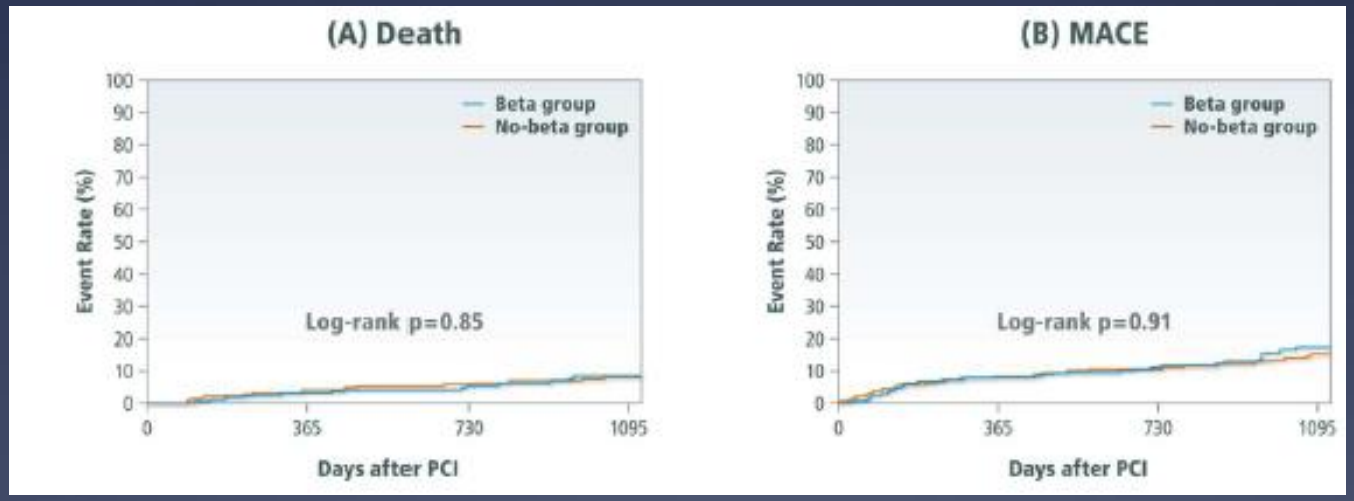


Am J Cardiol 2010;106:1225–1233

Long term effect of BB administered at discharge after primary-PCI

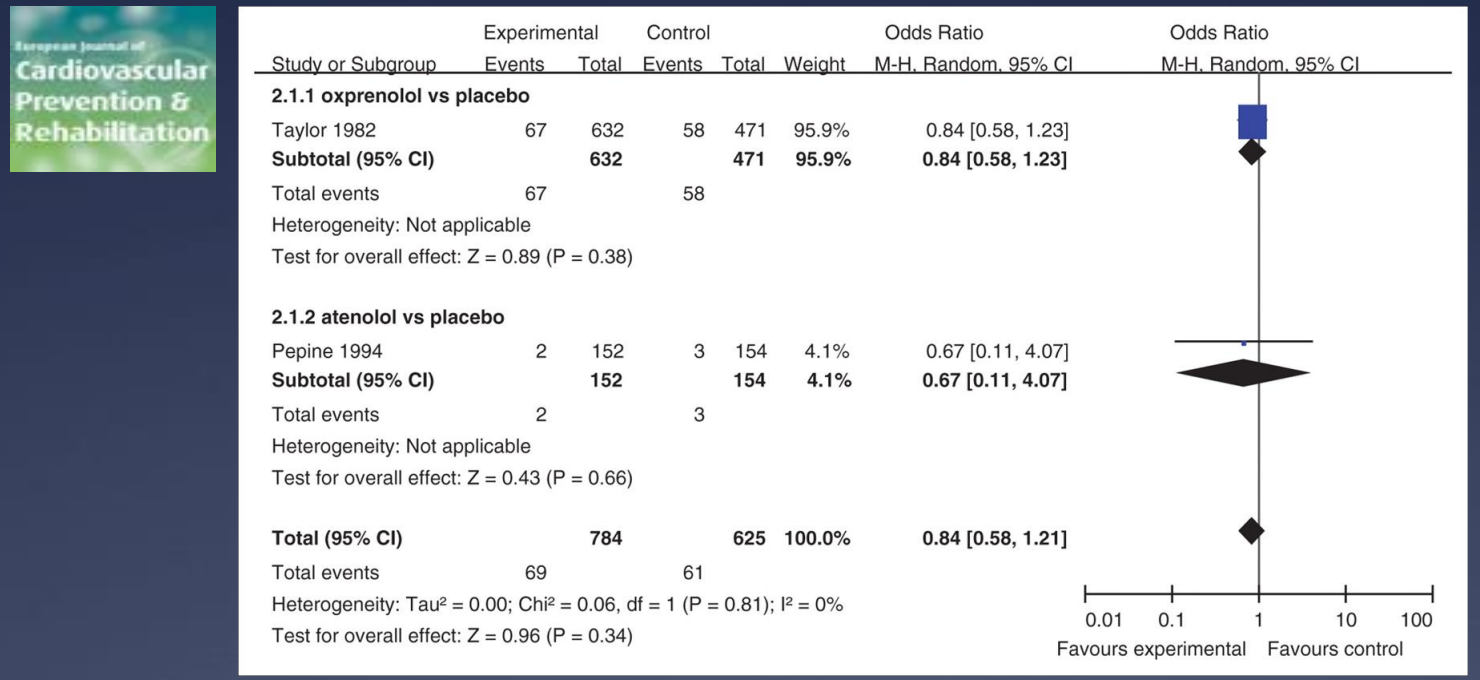
The j-cypher Registry

- 12,824 consecutive patients
- 910 patients who underwent PCI within 24 hours from onset of STEMI



Ozasa N et al. *Am J Cardiol*. 2010;106:1225-33

Long-term beta blockers for stable angina: systematic review and meta-analysis



Shu de F et al. *Eur J Prev Cardiol*. 2012;19:330-41

therapy trials: Chronic angina/stable CAD (1992-2014)

Trial	Mortality	Prevent MI	Short-Term Anginal Relief	Short-Term QoL ↑	Long-Term QoL ↑
RITA-2	No diff	No diff	PCI	PCI	No diff
ACME	No diff	No diff	PCI	PCI	N/A
ACME-2	No diff	No diff	PCI	No diff	N/A
MASS	No diff	No diff	PCI	N/A	N/A
MASS-II	No diff	No diff	PCI	PCI	N/A
AVERT	No diff	No diff	PCI	No diff	No diff
TIME	No diff	No diff	PCI	PCI	No diff
COURAGE	No diff	No diff	PCI*	PCI	No diff
BARI-2D	No diff	No diff	PCI	PCI	No diff
FAME 2	No diff	No diff	PCI	N/A	N/A

*No difference at 5 years

Approach to the treatment of CAD/Angina

- In patients with angina OMT is able to control symptoms in most patients, improves QoL, at a very low cost compared with PCI
- Evidence shows that OMT is equal to PCI in controlling symptoms and it is superior in reducing events
- PCI is not one off but often leads to repetite procedures with increasing costs (in EU the mean cost of PCI is between 3K and 8K/procedure. This cost is increased by the need of double anti-platelet therapy

Treatment approach of Angina in 2021

- Best initial management strategy for patients with Angina?

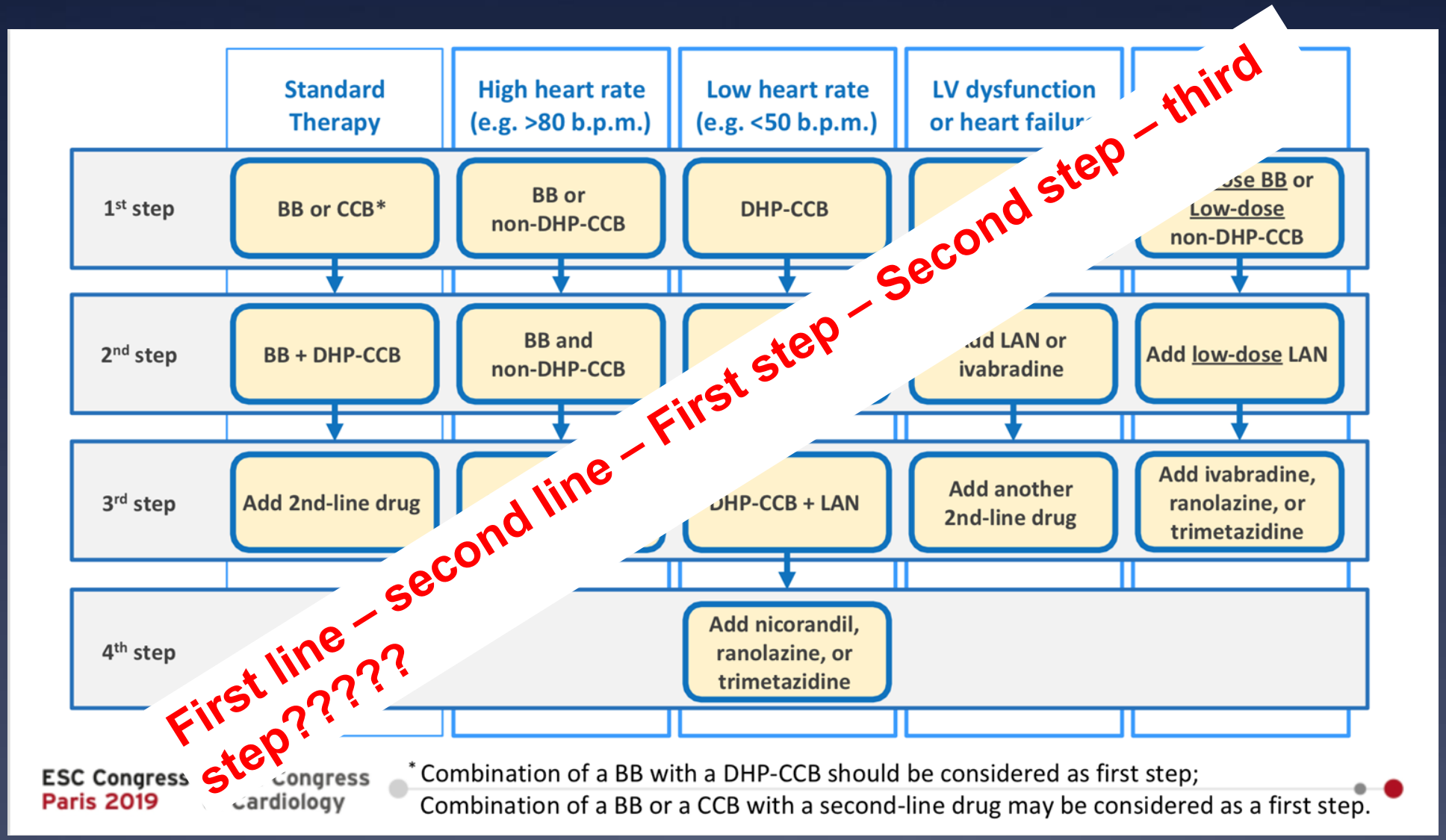
  ESC and ACC/AHA Guidelines Recommend an "OMT First" Treatment Approach

- Does early revascularization improve prognosis compared to OMT in CCS?

  In the past 25 years not one single trial has demonstrated any additional benefit of PCI

- Is PCI superior to OMT for durable angina relief?

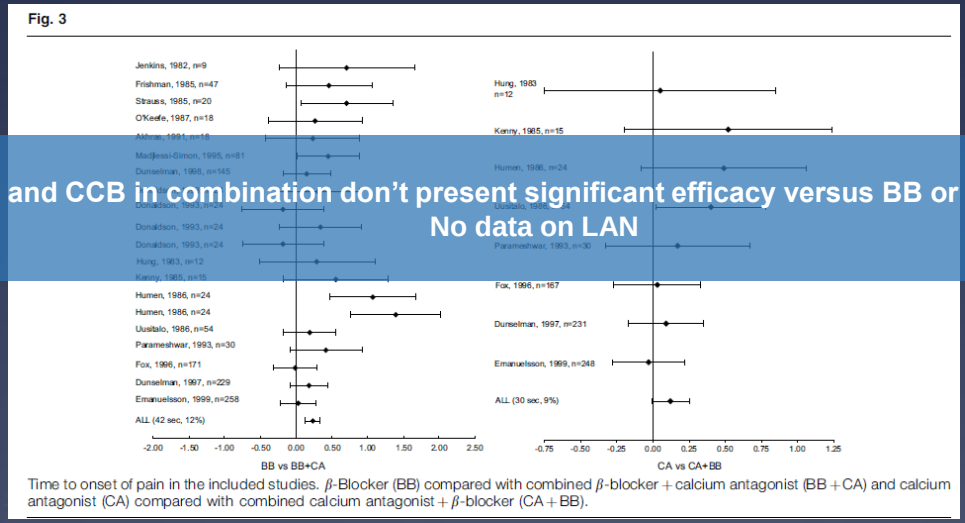
  Results of early studies, the ORBITA and ISCHEMIA Trials demonstrate that most patients remain symptomatic after PCI


Standard Therapy
High heart rate (e.g. >80 b.p.m.)
Low heart rate (e.g. <50 b.p.m.)
LV dysfunction or heart failu
1st step
BB or CCB*
BB or non-DHP-CCB
DHP-CCB
se BB or Low-dose non-DHP-CCB
2nd step
BB + DHP-CCB
BB and non-DHP-CCB
d LAN or ivabradine
Add low-dose LAN
3rd step
Add 2nd-line drug
HP-CCB + LAN
Add another 2nd-line drug
Add ivabradine, ranolazine, or trimetazidine
4th step
Add nicorandil, ranolazine, or trimetazidine
First line – second line – First step – Second step – third step?????
ESC Congress
Paris 2019
Congress
Cardiology
* Combination of a BB with a DHP-CCB should be considered as first step;
Combination of a BB or a CCB with a second-line drug may be considered as a first step.

CCS 2019 Guidelines acknowledge the unconvincing data of combining first-line anti-anginal therapy - BB and CCB

22 studies

BB and CCB in combination don't present significant efficacy versus BB or CCB alone
No data on LAN



Time to onset of pain in the included studies. β-Blocker (BB) compared with combined β-blocker + calcium antagonist (BB + CA) and calcium antagonist (CA) compared with combined calcium antagonist + β-blocker (CA + BB).

Meta-analysis in angina pectoris Klein et al. Coronary Artery Disease 2002, Vol 13 No 8

Knuuti J, Wijns W, Saraste A, et al. 2019 ESC guidelines for the diagnosis and management of chronic coronary syndromes. *Eur Heart J.* 2020;41(3):407-477.

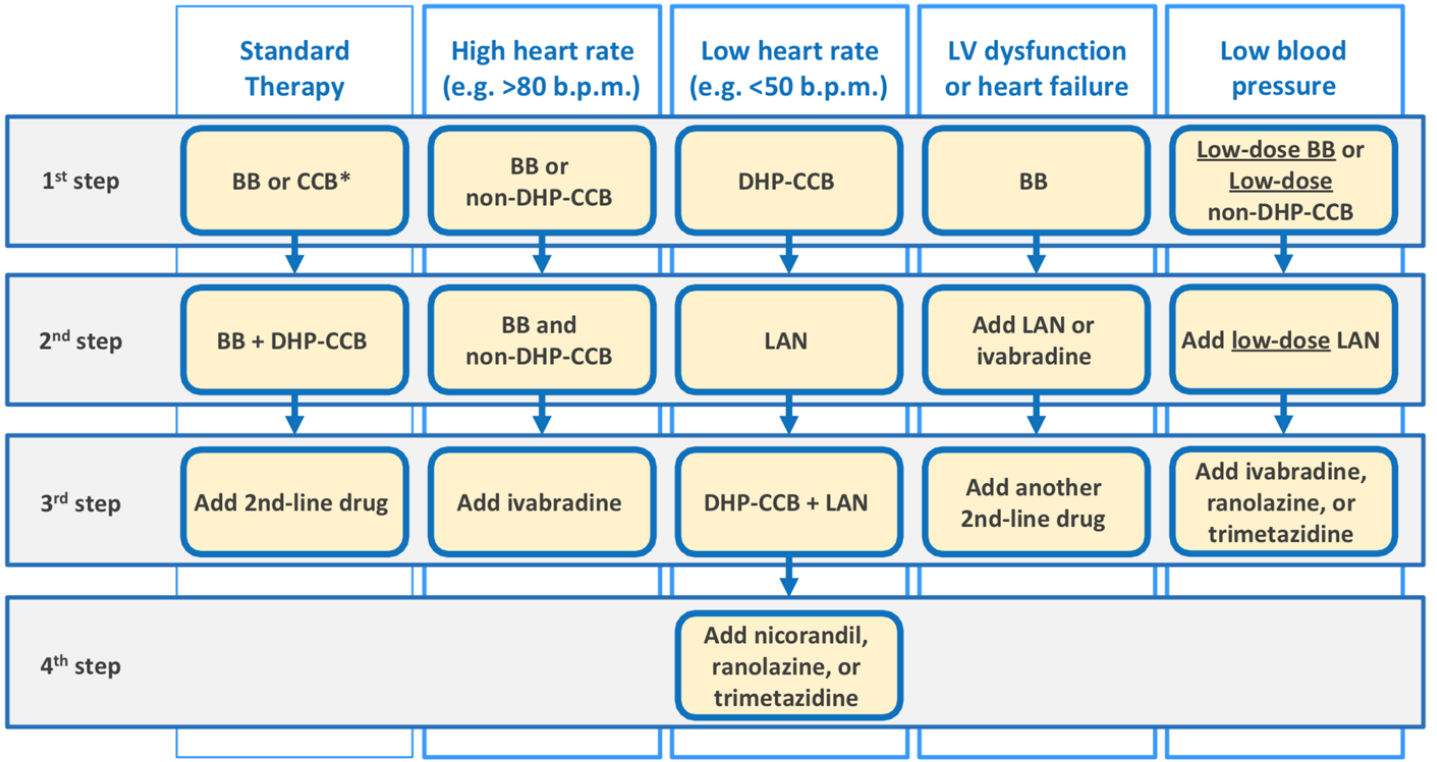


Figure 8 Suggest stepwise strategy for long term anti-ischaemic drug therapy in patients with chronic coronary syndromes and specific baseline characteristics. The proposed stepwise approach must be adapted to each patient's characteristics and preferences. Given the limited evidence on various combinations of drugs in different clinical conditions, the proposed options are only indicative of potential combinations and do not represent formal recommendations. BB = beta-blocker; bpm = beats per minute; CCB = [any class of] calcium channel blocker; DHP-CCB = dihydropyridine calcium channel blocker; HF = heart failure; LAN = long-acting nitrate; LV = left ventricular; non-DHP-CCB = non-dihydropyridine calcium channel blocker.

Limitations of conventional anti-anginal drugs

Contraindications/ Side effects	Nitrates	β-Blockers	Ca Antagonists
Decompensated HF			
Asthma			
Closed angle glaucoma			
AV bock 3rd degree			
Hypotension			
Fatigue			
Bradycardia			
Reflex tachycardia			
Erectile dysfunction			
Peripheral edema			
Bronchospasm			
Mood disorders, nightmares			
Flushing			
Headaches			
Dyslipidemia			
Worsening of glucose intolerance			
Tolerance			
Phosphodiasterase inhibito			

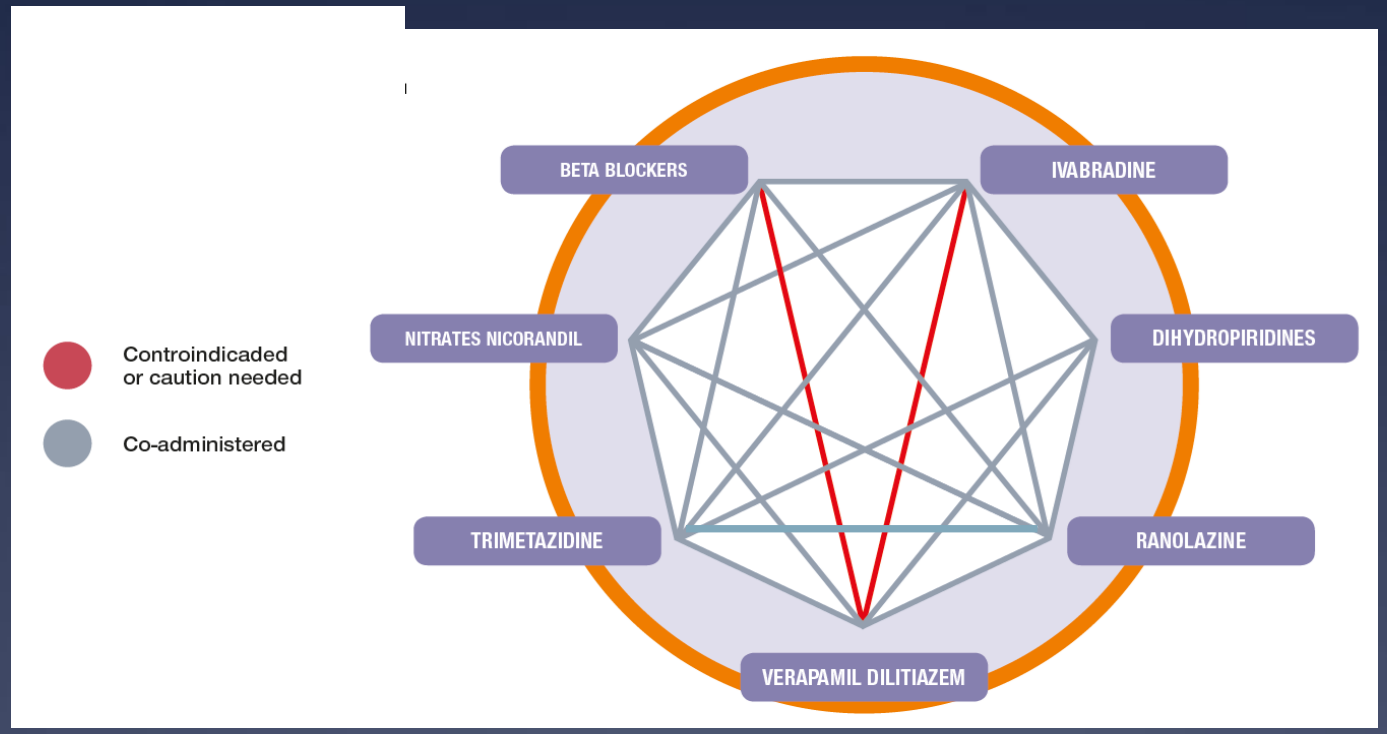
The average dosage of β-blockers in CLARIFY is at 50 % of the recommended range

Table 1
The use of beta-blockers in the CLARIFY population (32,914 patients). [a]Percentages of patients receiving any beta-blocker (patients could be taking more than one beta-blocker at the baseline visit). According to recommendations in stable angina[b] [21,22] and/or chronic heart failure[c] [23]. [d]75% of the total CLARIFY population.

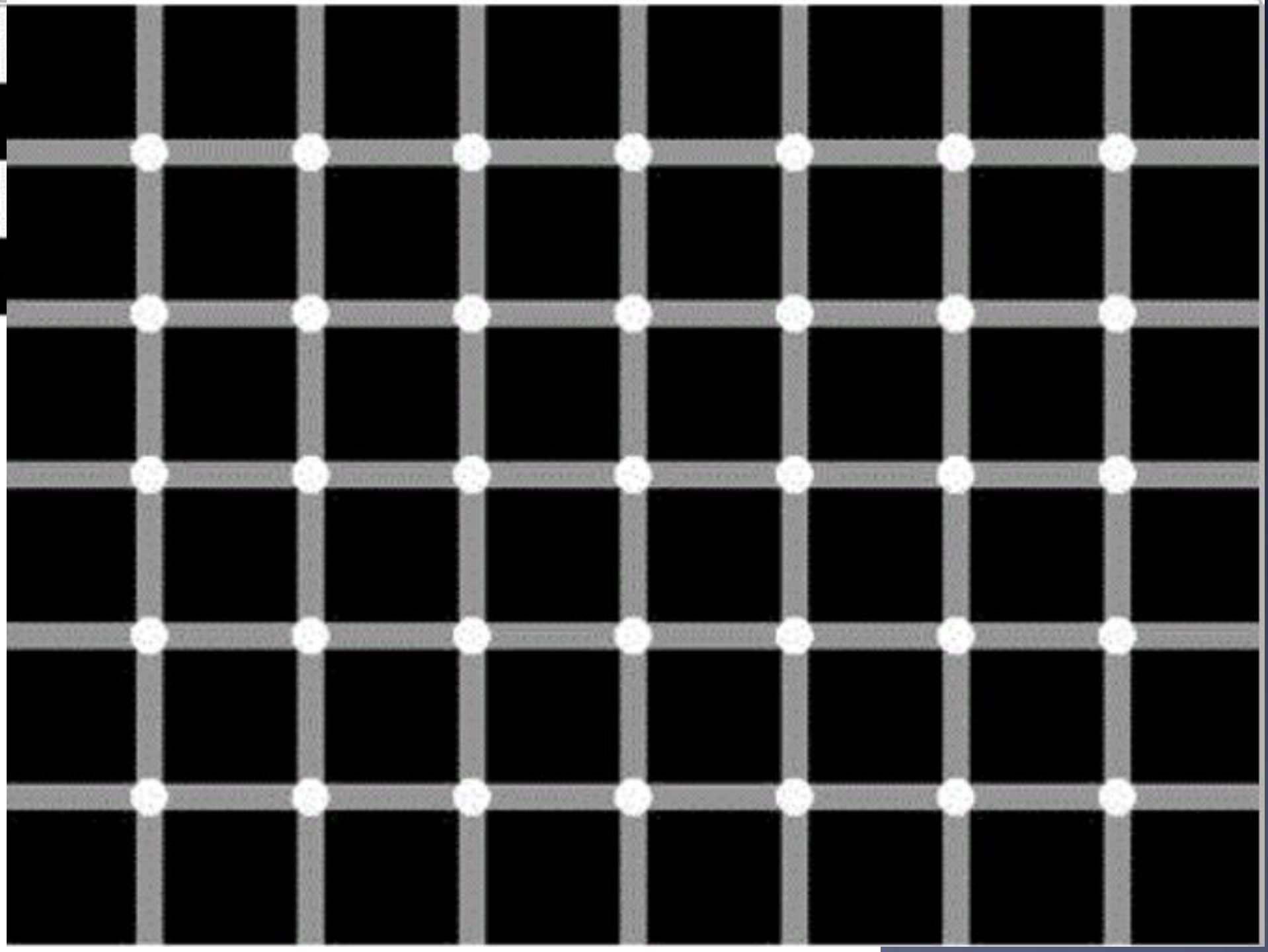
	Patients, n (%)[a]	Dosage (mg/day), mean ± SD	Recommended range[b] (mg/day)
Any beta-blocker	24,754[d]		
Atenolol	3685 (15%)	52.88 ± 27.11	25–100[b]
Bisoprolol	8446 (34%)	4.92 ± 2.96	2.5–10[b]/10[c]
Carvedilol	2872 (12%)	22.71 ± 15.92	50[c]
Metoprolol tartrate	3838 (16%)	75.67 ± 51.94	50–100[b]
Metoprolol succinate	3125 (13%)	70.85 ± 44.56	200[c]
Nebivolol	1404 (6%)	4.68 ± 1.83	2.5–5[b]/10[c]
At least one other beta-blocker	1373 (5%)		

Tendera ,CLARIFY, IJC 178,2014,119-124

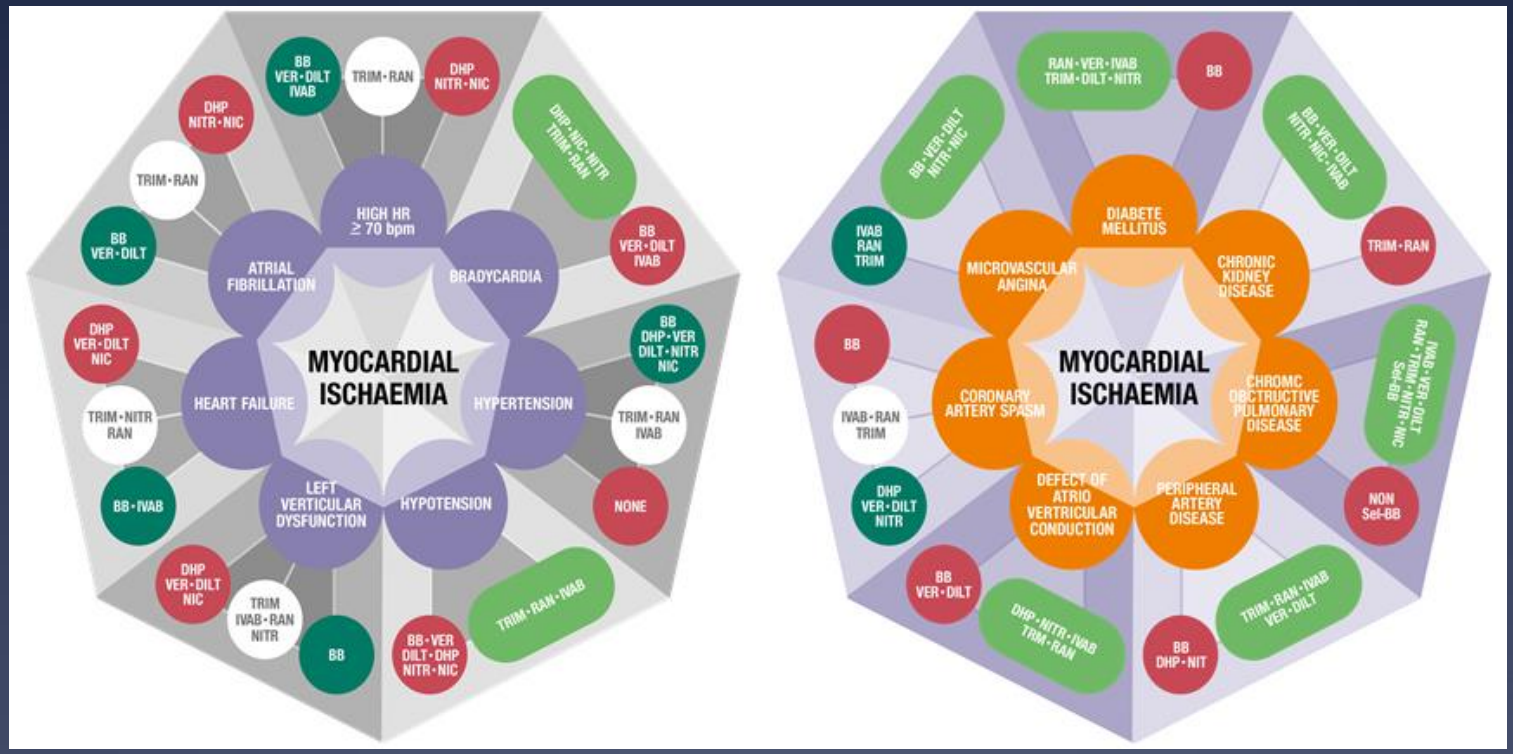
Pharmacological management of angina



Ferrari R, et al. *Nature Reviews Cardiology* **volume 15**, pages 120–132 (2018)

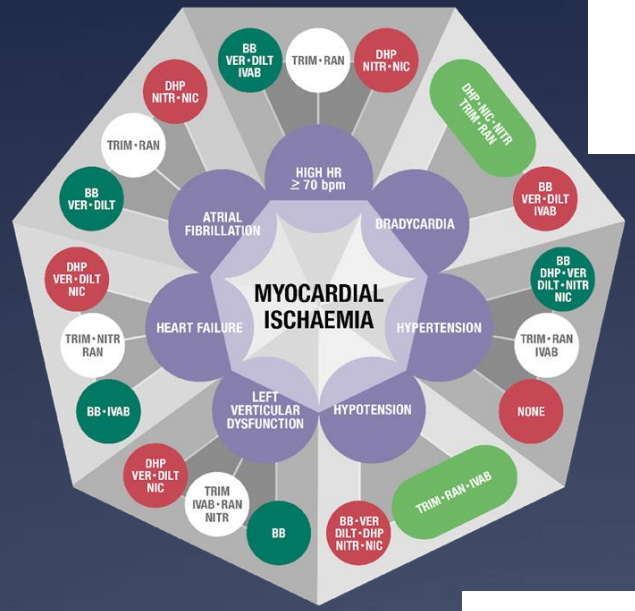


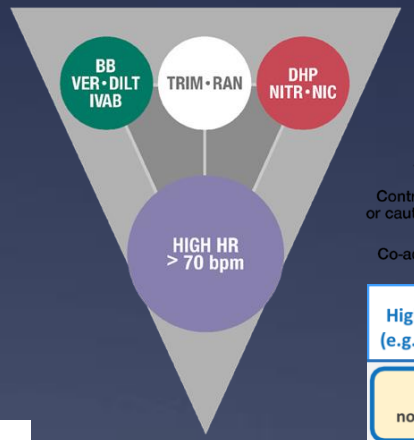
Therapeutic approach according to clinical features and comorbidities

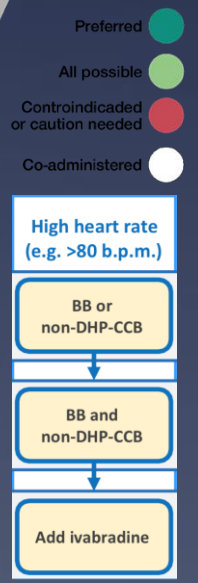


Ferrari R et al. *Nat Rev Cardiol*. 2018;15:120-32

Flexibility of the DIAMOND approach according to patient features and comorbidities

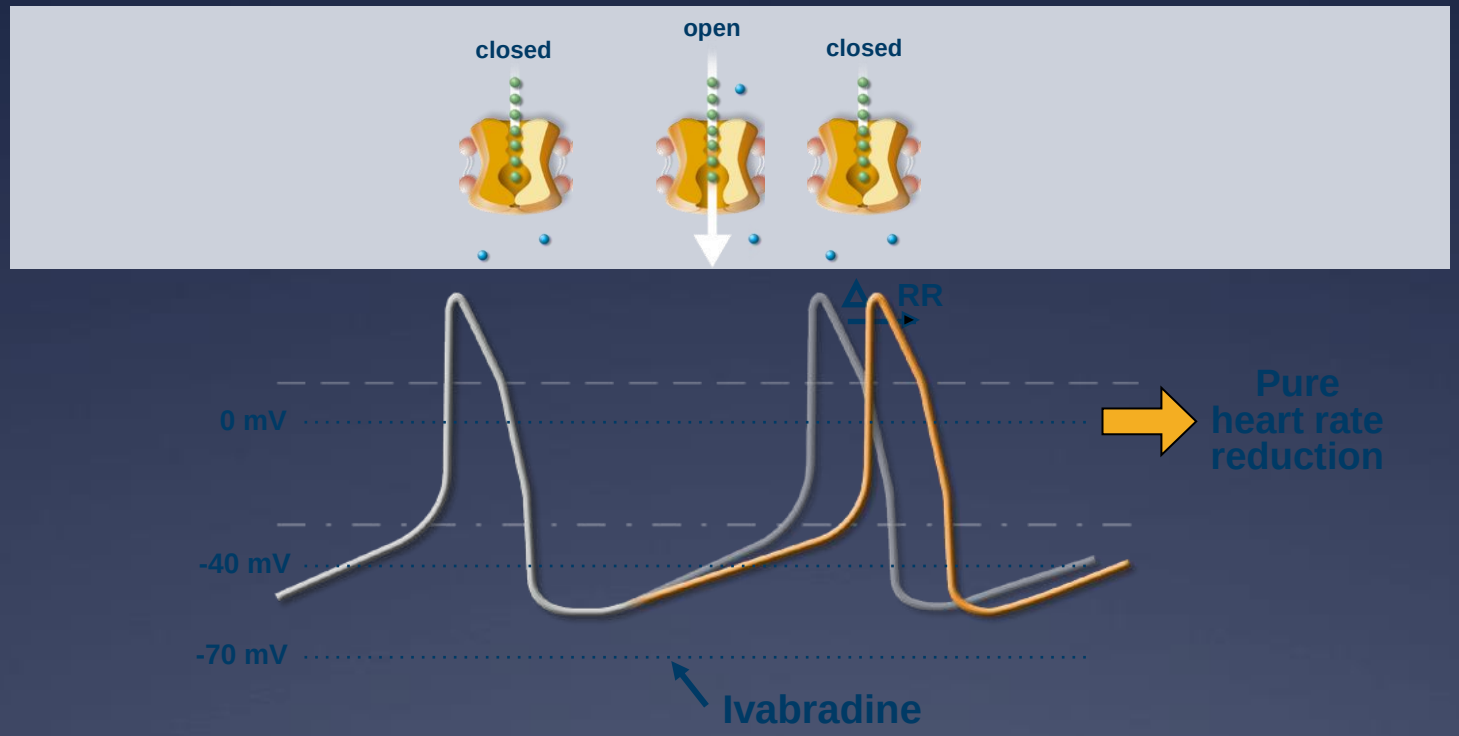






Ferrari R et al. *Nat Rev Cardiol*. 2018;15:120-32

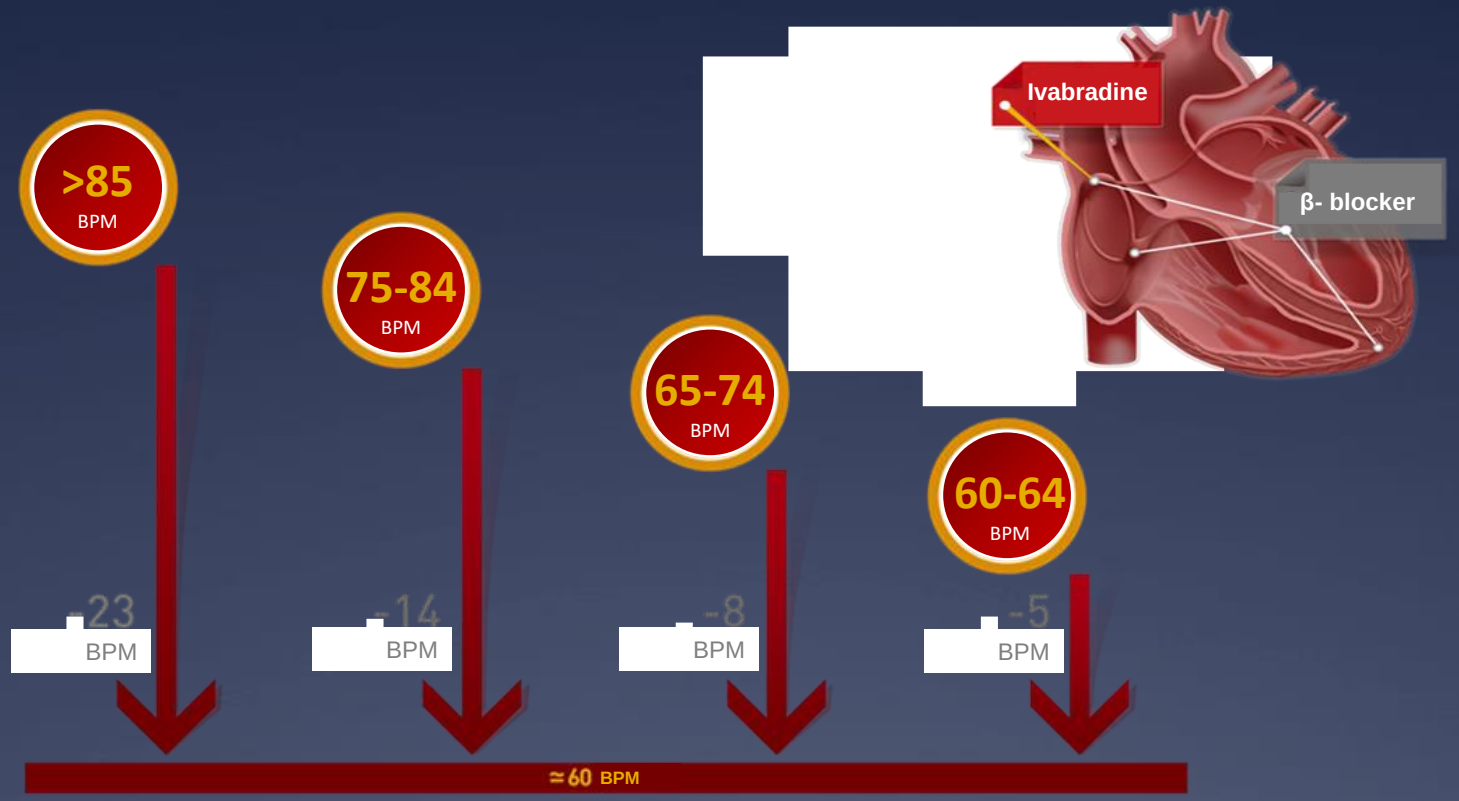
Ivabradine: pure heart rate reduction



I_f inhibition reduces the diastolic depolarization slope, and thereby lowers heart rate

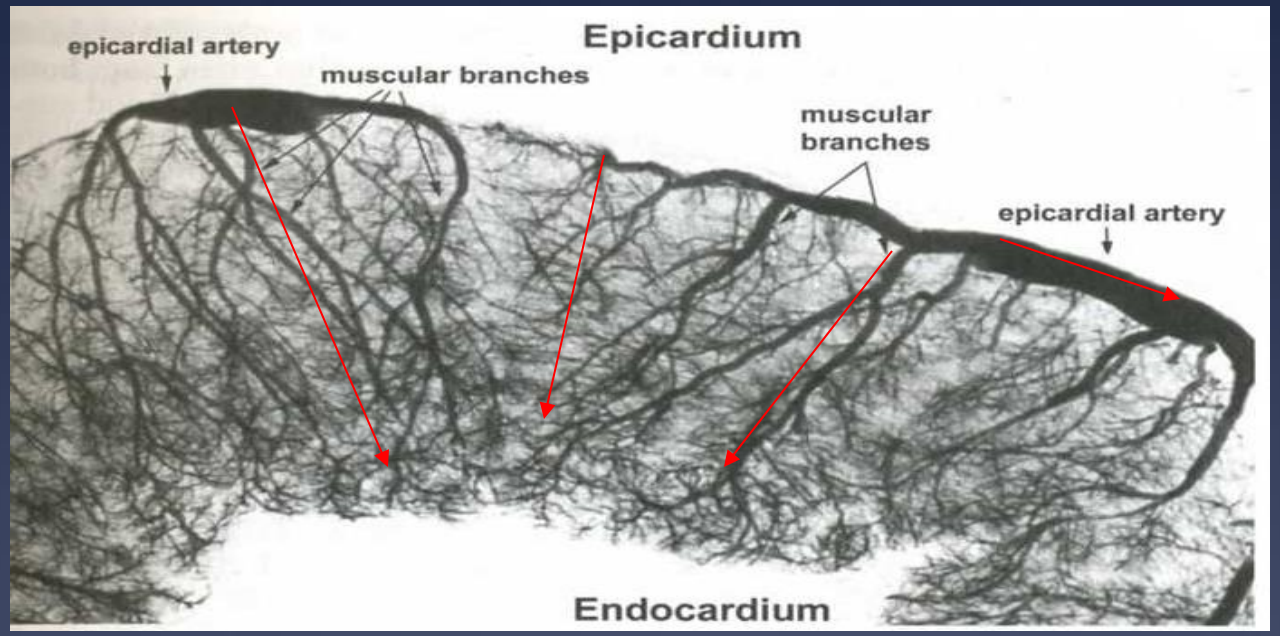
Thollon C, et al. *Brit J Pharmacol*. 1994;112:37-42.

differently:
dependent on the initial level of HR thus avoiding bradycardia,



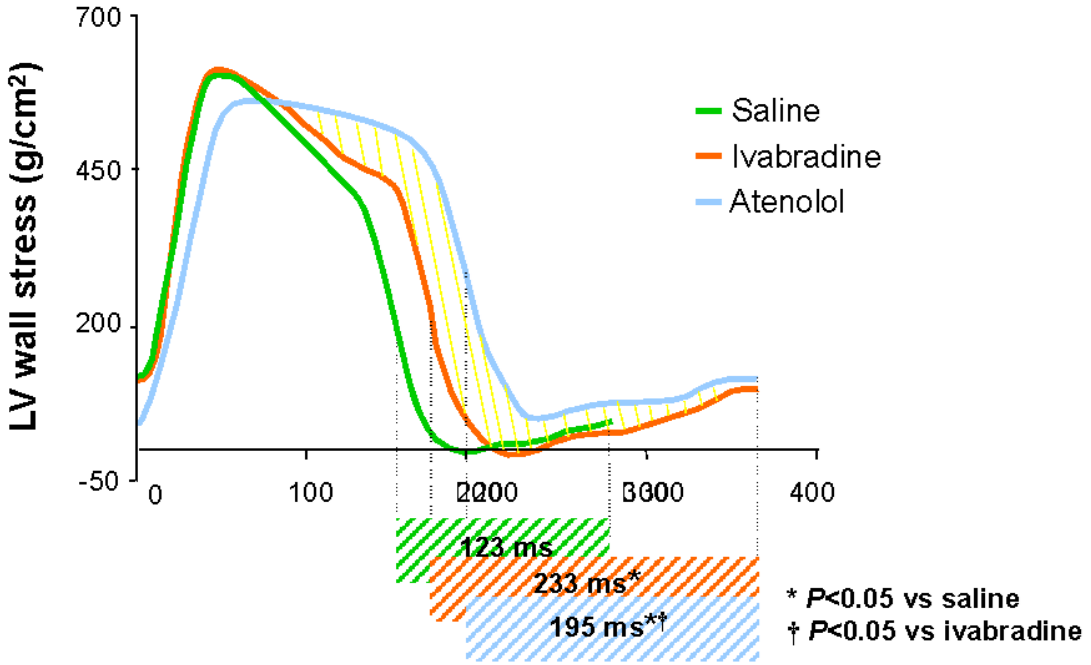
Borer JS, Heuzey JY. Characterization of the heart rate-lowering action of Corlentor. *Am J Ther.* 2008;15:461-473.

Circulation of blood in coronary arteries



Coronary flow occurs only in diastole « An increase of 1% of diastolic time, increases blood flow by 2,6 to 6% in the subendocardium » - The difference between coronary artery pressure and LVEDP drives subendocardial perfusion

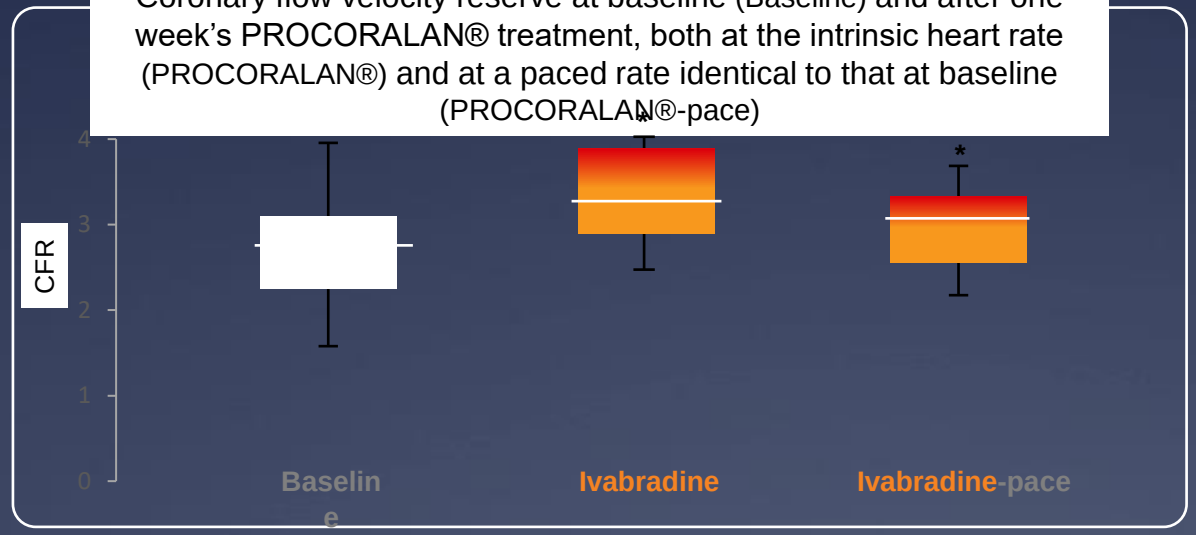
Ivabradine increases diastolic time by 6min/hour



Colin P, et al. *Am J Physiol Heart Circ Physiol.* 2003;284:H676-H682.

Ivabradine increases coronary flow reserve 1 week after treatment initiation

Coronary flow velocity reserve at baseline (Baseline) and after one week's PROCORALAN® treatment, both at the intrinsic heart rate (PROCORALAN®) and at a paced rate identical to that at baseline (PROCORALAN®-pace)

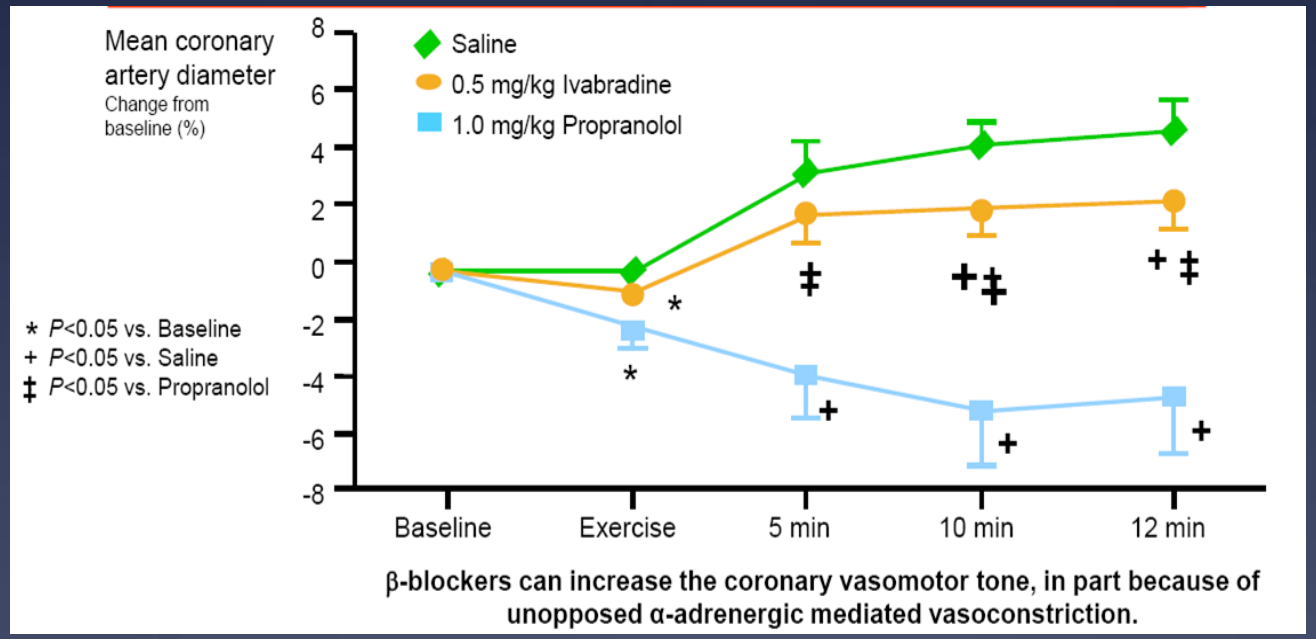


Diagnostic coronary angiography to measure coronary flow velocity (APV cm/s) in a non-culprit vessel and in a culprit vessel after treatment with Procoralan.

n=21
Duration 1 week
*p<0.001 vs baseline

Skalidis EI et al., *Atherosclerosis* 2011;215:160-165

Ivabradine preserves coronary vasodilation during effort



β-blockers can increase the coronary vasomotor tone, in part because of unopposed α-adrenergic mediated vasoconstriction.

Simon L, et al. *J Pharmacol Exp Ther.* 1995;275:659-666.

Ivabradine provides better coronary flow reserve than Bisoprolol for the same HR reduction

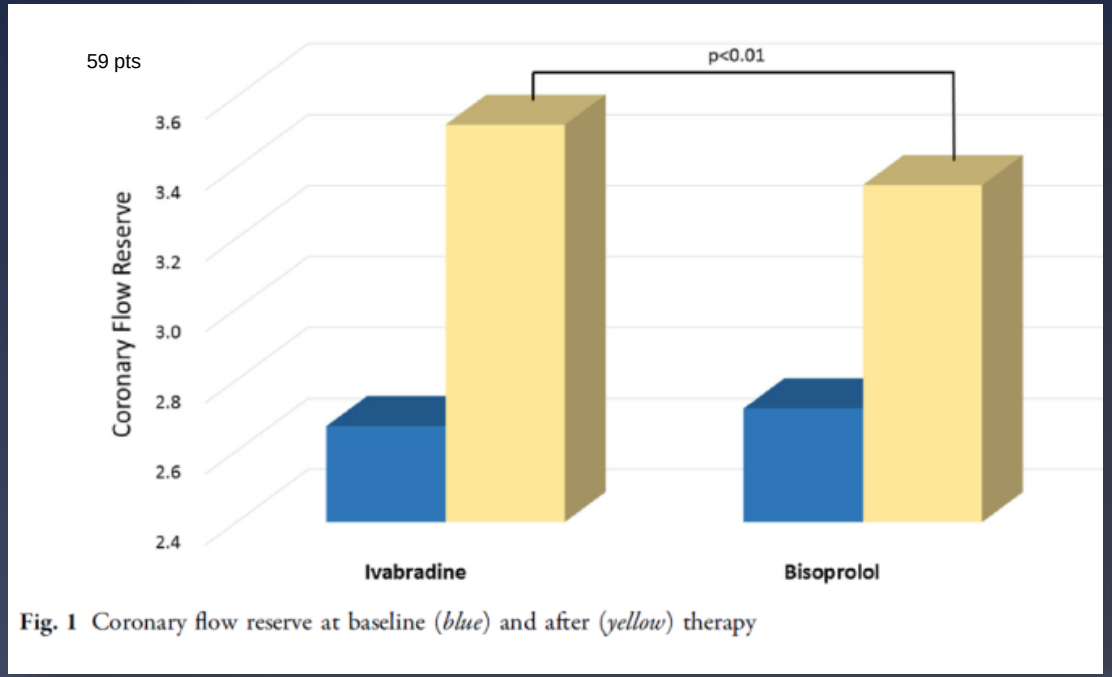
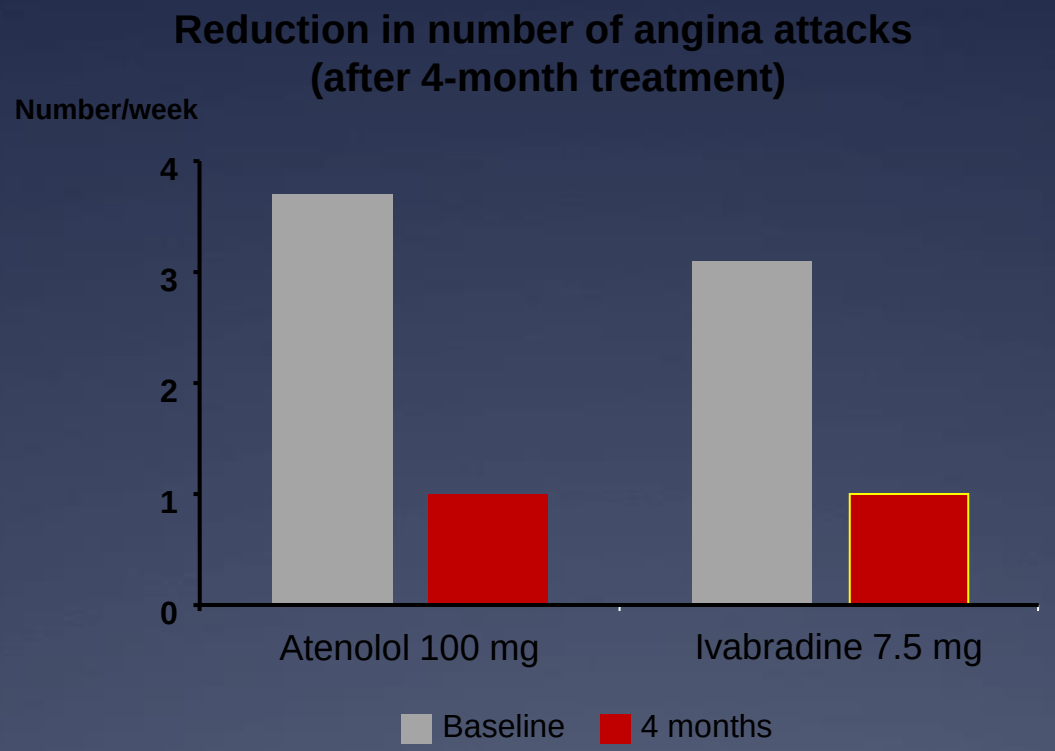


Fig. 1 Coronary flow reserve at baseline (*blue*) and after (*yellow*) therapy

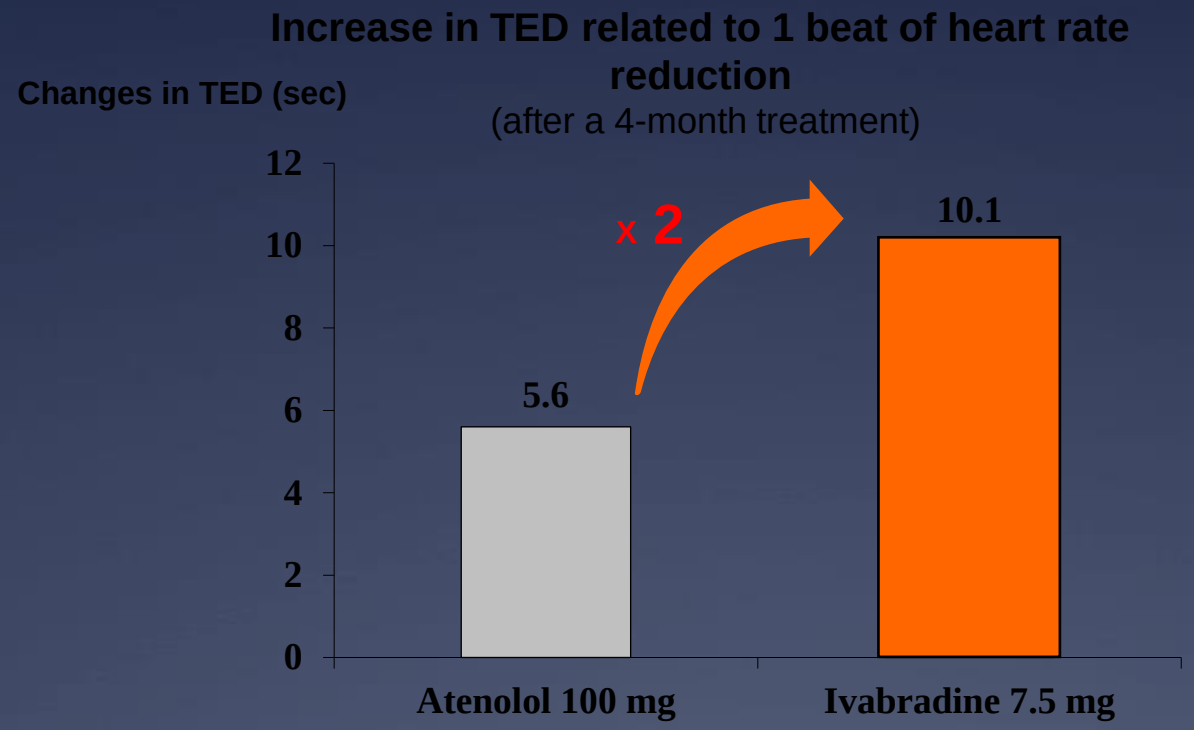
Tagliamonte et al,Adv in Therapy 2015 32:757-767

Antianginal effect of ivabradine



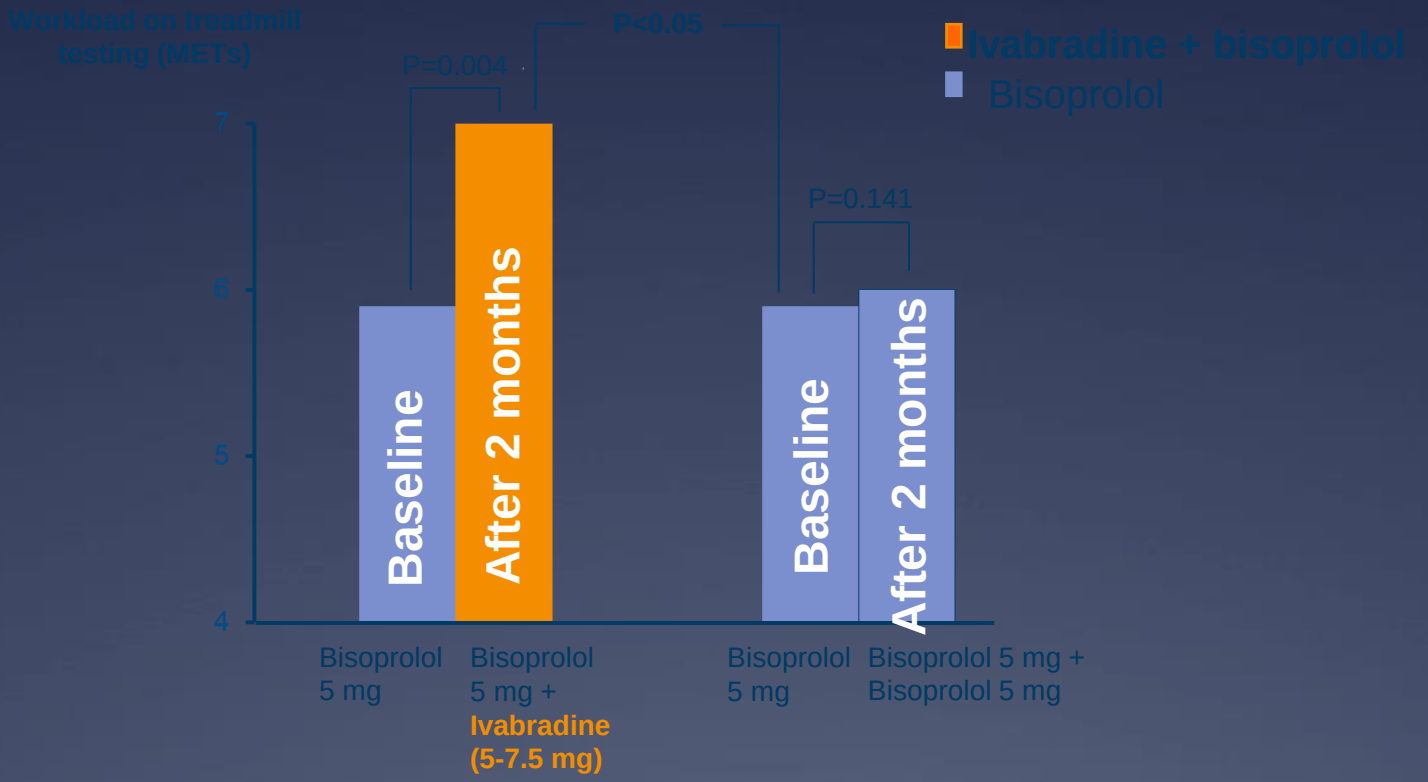
Tardif JC, et al. *Eur Heart J*. 2005;26:2529-2536.

Comparative anti-ischaemic effect of ivabradine and beta-blocker



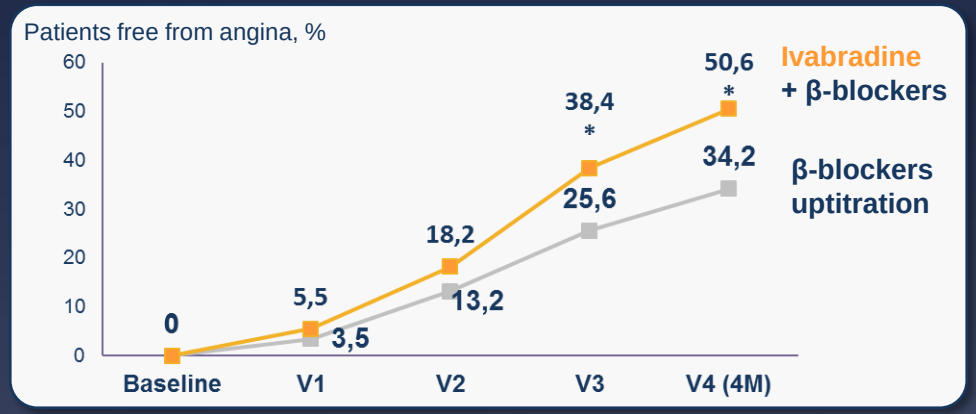
Tardif JC. *Drugs of Today*. 2008;44:171-181.

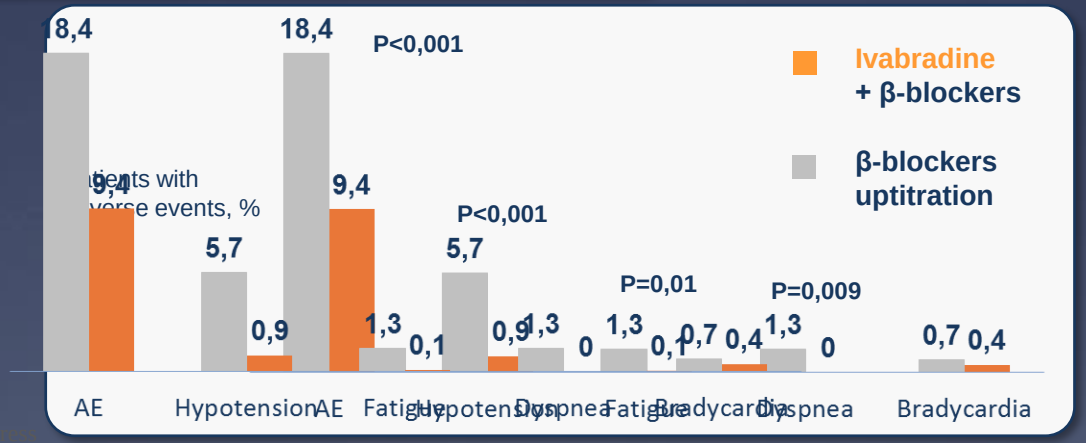
Combining ivabradine with beta-blocker provides additional anti-ischemic efficacy



Amosova E. et al. *Cardiovasc Drugs Ther.* 2011.

Efficacy of ivabradine/BBs compared to uptitration of BBs in patients with stable angina (CONTROL-2 study)

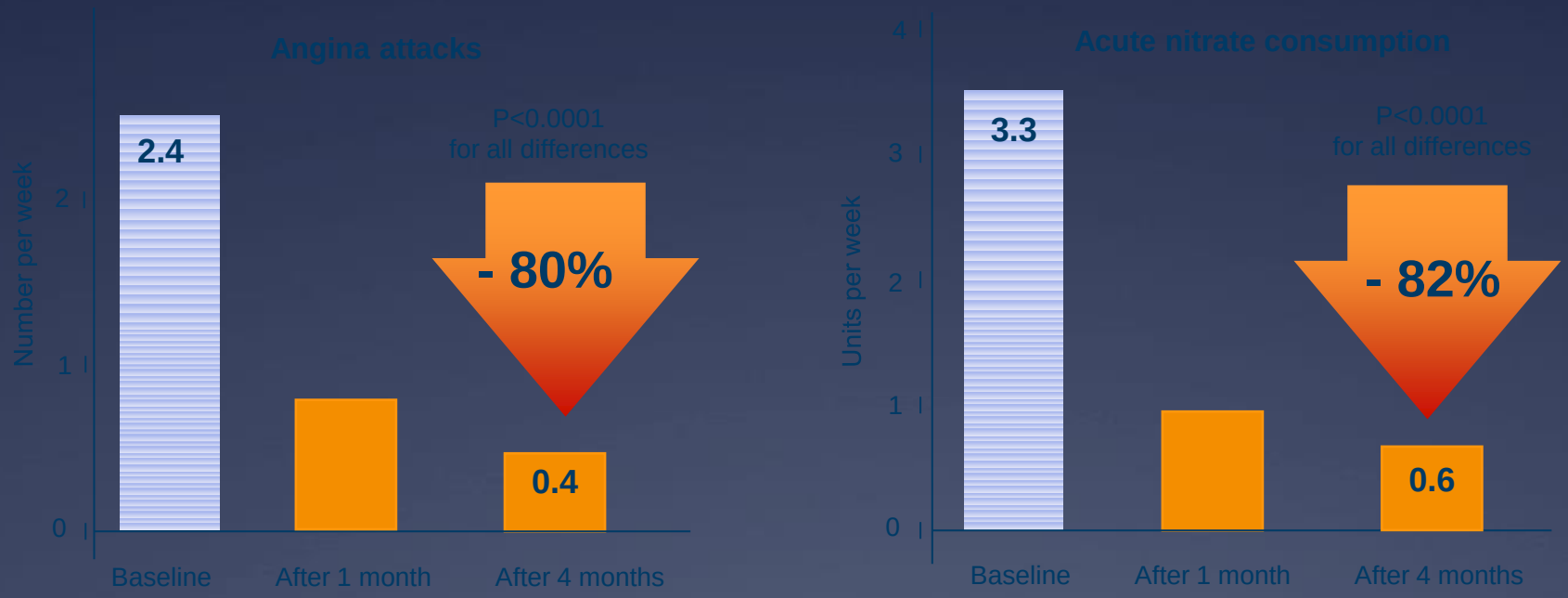




Glezer M et al. Adv in Ther In Press

REDUCTION: antianginal efficacy of ivabradine in clinical practice

Multicenter, prospective, open label study (Germany): 4 954 angina patients, 4 months follow-up



Efficacy graded by physicians as being "excellent/very good" in 97% of the patients

Köster R, Kaehler J, Meinertz T, for the REDUCTION Study Group. *Am Heart J.* 2009;158:e51-e57.

Effect of Ivabradine in 14,256 patients with coronary artery disease

	Baseline	Follow up
Heart Rate	83	69
Angina/week	3.3	0.67
GTN Use	1.7	0.3
Cardiac deaths		8
Discontinuation		136
Severe adverse reactions		9
Confirmed SARs		0

Italian Drug Agency – Ivabradine Registry

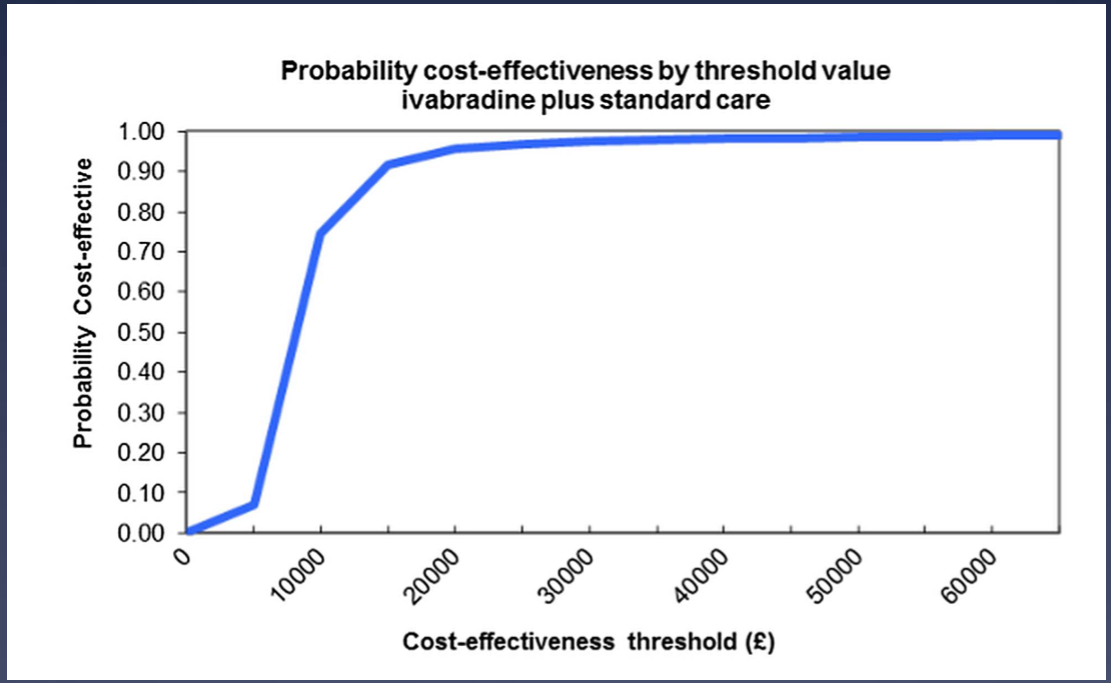
Consistent antianginal efficacy of ivabradine across all subpopulations of angina patients

Data pooled from 5 randomized trials in patients with stable angina pectoris receiving ivabradine for 3 or 4 months (n=2425)

*CABG: coronary artery bypass graft; COPD: chronic obstructive pulmonary disease; MI: myocardial infarction; PTCA: percutaneous transluminal coronary angioplasty; PVD: peripheral vascular disease

Tendera M, et al. *Cardiology*. 2009;114:116-125.

Cost-effectiveness of ivabradine



Ivabradine is expected to have a 95% chance of being cost-effective in the EU licensed population using the current National Institute of Health and Care Excellence (NICE)

Griffiths A, et al. Heart 2014;100:1031–1036. doi:10.1136/heartjnl-2013-304598

COST-EFFECTIVENESS ANALYSIS OF IVABRADINE IN CHRONIC STABLE ANGINA PATIENTS IN A FINNISH SETTING

Félix J[1], Almeida J[1], Joutseno J[2], Alegre P[3]
[1]Exigo Consultores, Alhos Vedros, Lisbon, Portugal, [2]Servier Finland OY, Vantaa, Finland,

RESULTS: For each 100 patients using ivabradine in comparison with amlodipine we estimate a 36 LYs (95%CI: [18;57]) or 30 QALYs (95%CI: [17;47]) gain.
Incremental cost-effectiveness ratios for ivabradine utilization were a12,886/LY and a 15,060/QALY.

CONCLUSIONS: Ivabradine is a cost- effective alternative for the treatment of SA when compared to generic amlodipine in a Finnish setting of patients with contraindication or intolerance to beta-blockers and resting HR 70 bpm.

DOI: https://doi.org/10.1017/S0266462318003598

Insights for clinical practice

- Angina with or without ischemia carries an adverse prognosis
- Medical therapy for the treatment of angina should be implemented using the Diamond approach that goes beyond the indications of the guidelines and should be implemented in daily practice
- Ivabradine is effective in reducing angina and ischaemia in patients with CCS and, in association with BB, confers greater anti-ischemic effect than BB alone, increases tolerability, exercise capacity and QOL in patients with angina
- Ivabradine is cost-effective and should be implemented in the majority patients with IHD and co-morbidities

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 SEPTEMBER 18, 2014 VOL. 371 NO. 12

Ivabradine in Stable Coronary Artery Disease without Clinical Heart Failure

Kim Fox, M.D., Ian Ford, Ph.D., Philippe Gabriel Steg, M.D., Jean-Claude Tardif, M.D., Michal Tendera, M.D.

Concluding that…… Among patients who had stable coronary artery disease without clinical heart failure, the addition of ivabradine to standard background therapy to reduce the heart rate did not improve outcomes

* A randomized, double-blind, placebo-controlled trial of ivabradine, added to standard background therapy, in 19,102 patients who had both stable CAD without clinical heart failure and a heart rate of 70 beats per minute or more.

* After a median follow-up of 27.8 months, there was no significant difference between the ivabradine group and the placebo group in the incidence of the primary end point (6.8% and 6.4%, respectively; hazard ratio, 1.08; 95% confidence interval, 0.96 to 1.20; P=0.20), nor were there significant differences in the incidences of death from cardiovascular causes and nonfatal myocardial infarction.

Signify Study

* randomized, double-blind, placebo-controlled trial of ivabradine, added to standard background therapy, in 19,102 patients who had both stable coronary artery disease without clinical heart failure and a heart rate of 70 beats per minute or more

* No significant differences in the incidences of death from cardiovascular causes and nonfatal myocardial infarction.

* Ivabradine was associated with an increase in the incidence of the primary end point among patients with activity-limiting angina but not among those without activity-limiting angina (P=0.02 for interaction). The incidence of bradycardia was higher with ivabradine than with placebo (18.0% vs. 2.3%, P<0.001).

N Engl J Med 2014; 371:1091-1099

Why Signify study fails

* SIGNIFY had a high prevalence of risk factors owing to the inclusion criteria, the annual incidence of the primary end point was relatively low (approximately 2.8%), probably owing to the background therapy the patients were receiving, which was administered according to current guidelines.

* It is possible that ivabradine decreased the heart rate too much or that there may be a J-shaped.

* It is also possible that heart-rate–reducing antianginal agents have no effect on outcomes in patients with stable coronary artery disease. Although there is historical evidence of a benefit of beta-blockers after myocardial infarction, there is little current evidence of their benefit with respect to hard clinical outcomes in patients who have stable coronary artery disease without left ventricular dysfunction.

* The benefit observed with lowering the heart rate in patients with heart failure but not in those with stable coronary artery disease may reflect the fact that an elevated heart rate is due to different pathophysiological mechanisms in these two conditions. In patients with heart failure, there is neurohormonal activation, which in itself leads to ventricular remodeling, further left ventricular dysfunction, and a vicious cycle of decline. In contrast, there is no neurohormonal activation in stable coronary artery disease without left ventricular dysfunction.

Beautiful Study

* Enrolled 10 917 eligible patients who had coronary artery disease and a left-ventricular ejection fraction of less than 40% in a randomised, double-blind, placebo-controlled, parallel-group trial.

* 5479 patients received 5 mg ivabradine, with the intention of increasing to the target dose of 7·5 mg twice a day, and 5438 received matched placebo in addition to appropriate cardiovascular medication.

* no affect the primary composite outcome (hazard ratio 0·91, 95% CI 0·81–1·04, p=0·17), cardiovascular death, or admission to hospital for new-onset or worsening heart failure.

* There was a reduce secondary endpoints: admission to hospital for fatal and non-fatal myocardial infarction (0·64, 95% CI 0·49–0·84, p=0·001) and coronary revascularisation (0·70, 95% CI 0·52–0·93, p=0·016).

•. 2009 Oct;30(19):2337-45

Subanalysis of Beautiful study

- Of the BEAUTIFUL population, 13.8% had limiting angina at baseline (734 ivabradine, 773 placebo); of these, 712 patients had heart rate > or =70 b.p.m. *Median duration of follow-up was 18 months. Ivabradine was associated with a 24% reduction in the primary endpoint (cardiovascular mortality or hospitalization for fatal and non-fatal myocardial infarction [MI] or heart failure) (HR, 0.76; 95% CI, 0.58-1.00) and a 42% reduction in hospitalization for MI (HR, 0.58, 95% CI, 0.37-0.92).*

- *In patients with heart rate > or =70 b.p.m., there was a 73% reduction in hospitalization for MI (HR, 0.27, 95% CI, 0.11-0.66) and a 59% reduction in coronary revascularization (HR, 0.41, 95% CI, 0.17-0.99). Ivabradine was safe and well tolerated.*

Eur Heart J. 2009 Oct;30(19):2337-45

SHIFT study

- 6558 patients with stable symptomatic chronic HF of New York Heart Association (NYHA) class II–IV, with severe left ventricular systolic dysfunction (EF ⩽ 35%) of both ischaemic and nonischaemic aetiology. Follow up 23 month.

- ivabradine use was associated with a reduction in the primary endpoint of the composite of cardiovascular death or hospitalization for worsening HF symptoms (HR 0.82, 95% CI 0.75–0.90, $p < 0.0001$). These findings were principally driven by hospital admissions for worsening HF (21% in the placebo group versus 16% in the ivabradine group; HR 0.74, 95% CI 0.66–0.83, $p < 0.0001$).

- For the secondary end points, there was no difference in the all-cause or CV mortality (HR 0.90, $p = 0.092$ and HR 0.91, $p = 0.128$ respectively). Ivabradine was associated with a reduction in all-cause hospitalization (HR 0.89, $p = 0.003$).

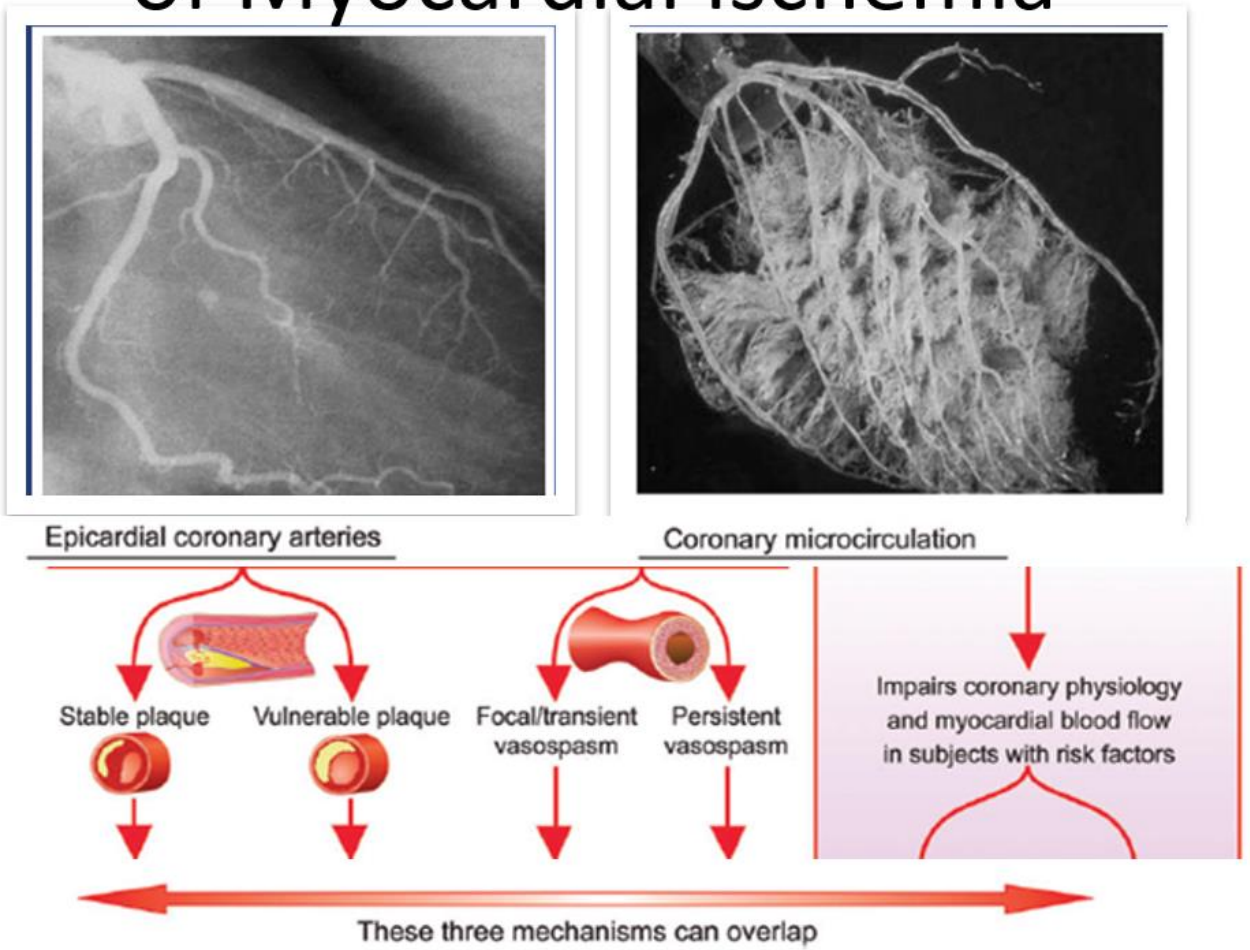
Incidence of angina in different populations

Table 8. Age-standardized incidence rate of stable angina pectoris per 1,000 persons, age ≥30 years, 2010

Region	Women	Men	Total
Asia Pacific, High Income	2.26	2.87	2.56
Asia, Central	4.56	6.39	5.37
Asia, East	2.53	3.15	2.84
Asia, South	2.74	3.57	3.16
Asia, Southeast	2.26	2.85	2.54
Australasia	2.42	3.11	2.76
Caribbean	2.50	3.14	2.80
Europe, Central	2.99	4.01	3.46
Europe, Eastern	3.84	5.54	4.54
Europe, Western	2.28	3.06	2.65
Latin America, Andean	2.22	2.58	2.39
Latin America, Central	2.41	2.96	2.67
Latin America, Southern	2.11	3.02	2.53
Latin America, Tropical	3.12	4.08	3.57
North Africa/Middle East	3.40	4.27	3.83
North America, High Income	2.45	3.35	2.88
Oceania	2.48	3.88	3.15
Sub-Saharan Africa, Central	2.22	3.10	2.63
Sub-Saharan Africa, East	2.66	3.21	2.92
Sub-Saharan Africa, Southern	2.33	2.95	2.61
Sub-Saharan Africa, West	2.80	3.18	2.98

Forouzanfar MH et al. *Glob Heart*. 2012;7:331-42

Macrovascular and Microvascular Causes of Myocardial Ischemia



These **functional** and **structural** phenomena can act **simultaneously** in the same patient

Crea F, Camici PG, Bairey Merz CN. Eur Heart J. 2014;35(17):1101-11

Case study

* 68 yr old Malay lady. Active lady
* Known hypertension and hyperlipidemia 10 year.
* Current medications:

Cardiprin	100 mg daily
Felodipine	5 mg daily
Simvastatin	20 mg on

Case study

* Angina on exertion 1 month. On and off. Height 155 cm, Weight 69 kg (BMI 28.7).
* The BP is 140/80 mmHg and the is pulse 84 bpm. Clinical examination normal
* Blood: Total cholesterol 4.7 mmol/L , LDL 2.6 mmol/L , HDL 1.0 mmol/L, TG 2.0 mmol/L FBS 8.0 mmol/L, HbA1c 8.0%. Renal profile and urine normal.
* ECG normal. Echocardiography was done and it showed a normal cardiac anatomy with no regional LV wall abnormalities seen at rest.
* Positive stress Echo for ischeamia at High work load mainly at the inferior and posterior territory.

Case study : How would You managed her

* Risk factor modification and go on medical treatment.
* Do other test like MSCT angiogram.
* Counselled patient for Invasive coronary angiogram.

That the Diabetic need to be address with Metformin in combination with SGLT2 inhibitor and the Felodipine was replace with ACEI and for the angina I started with Bisoprolol and Trimetazidine

What is Optimal Medical treatment

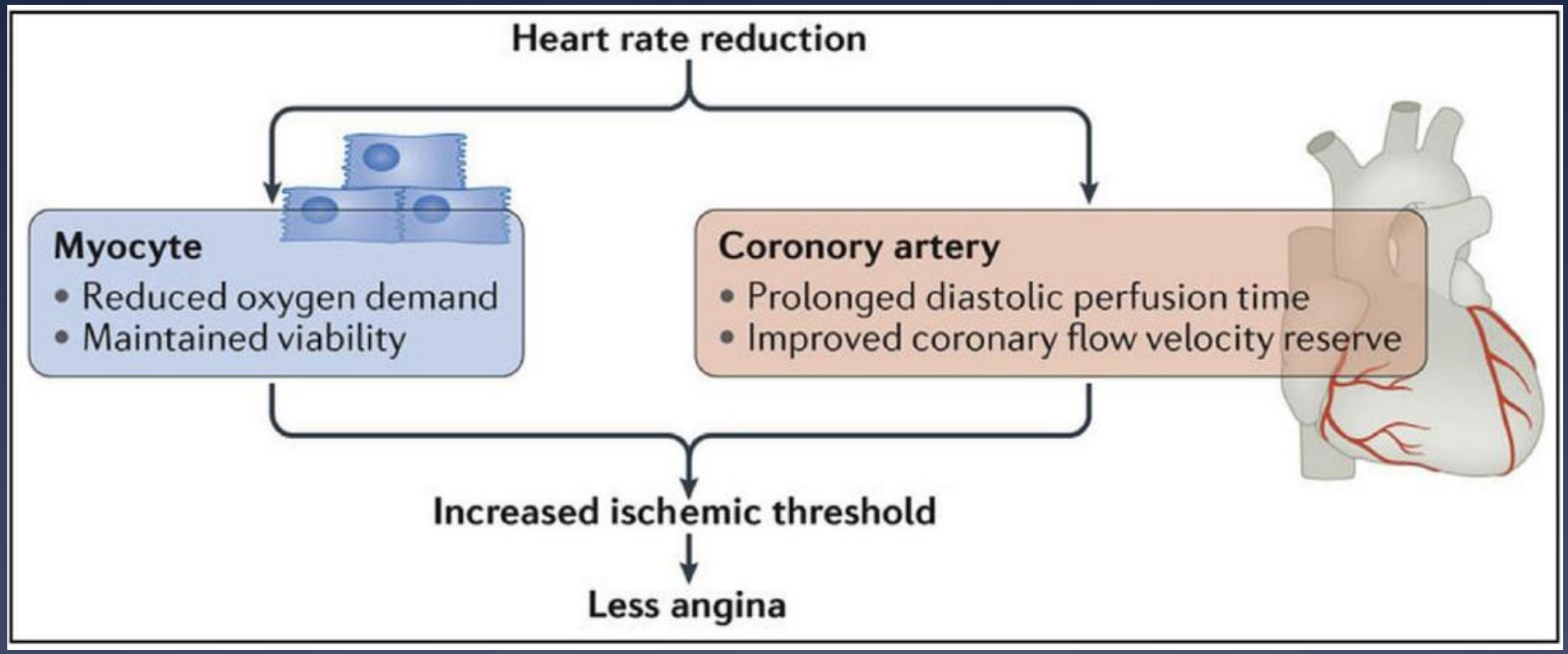
* The combination of intensive, evidence-based pharmacologic intervention with life-saving interventions comprises optimal medical therapy (OMT).

* OMT is recommended by guidelines for all stable IHD patients, regardless of whether revascularization is performed.

* Optimal medical therapy consisted of antiplatelet therapy, anti-ischemic therapy, and aggressive lipid and blood pressure control.

* Based on the strength of the evidence, recommending more-aggressive medical therapy for patients with moderate-to-severe angina, and PCI or CABG for many patients in whom symptoms persist

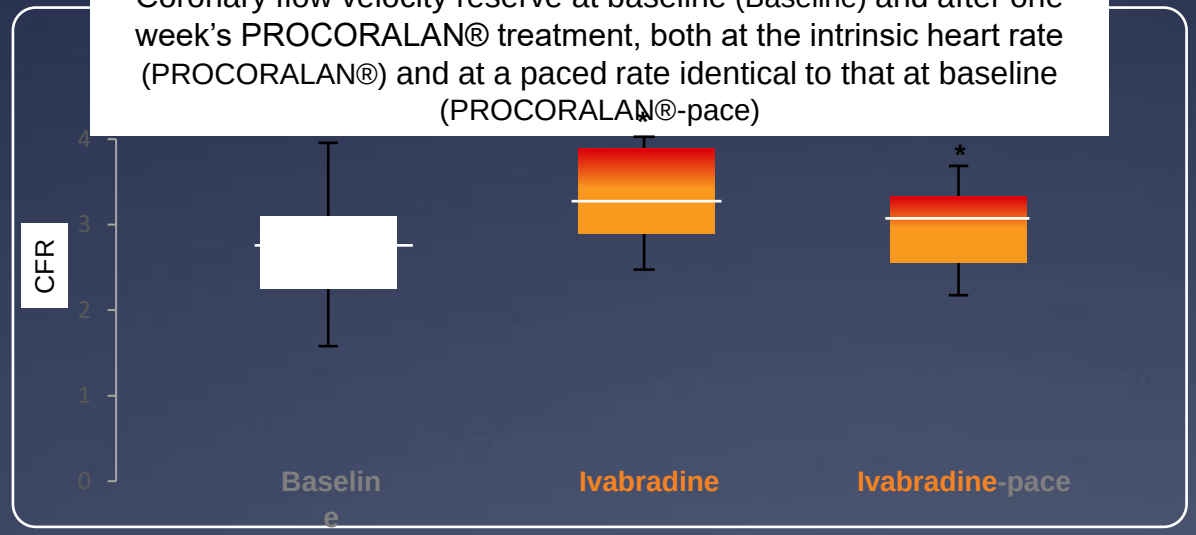
Beneficial effects of heart rate reduction in angina



DiFrancesco D, Borer JS. The funny current. Drugs. 2007;67:15e24.

Ivabradine increases coronary flow reserve 1 week after treatment initiation

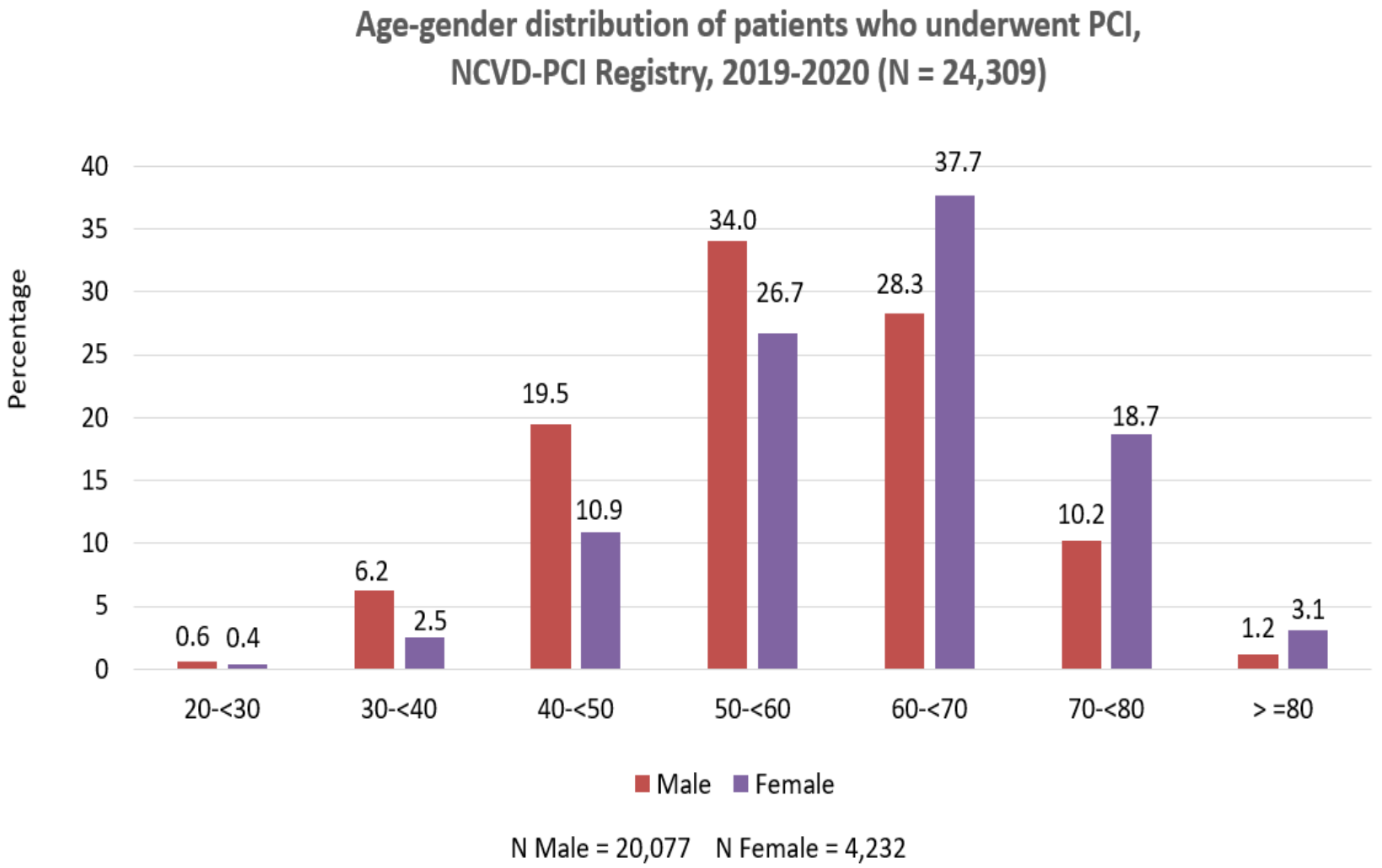
Coronary flow velocity reserve at baseline (Baseline) and after one week's PROCORALAN® treatment, both at the intrinsic heart rate (PROCORALAN®) and at a paced rate identical to that at baseline (PROCORALAN®-pace)



Diagnostic coronary angiography to measure coronary flow velocity (APV cm/s) in a non-culprit vessel and in a culprit vessel after treatment with Procoralan.

n=21
Duration 1 week
*p<0.001 vs baseline

Skalidis EI et al., *Atherosclerosis* 2011;215:160-165



W.A. Wan Azman (Ed). Annual Report of the NCVD-PCI Registry, Year 2019-2020. Kuala Lumpur, Malaysia: National Cardiovascular Disease Database, 2023.

Clinical Background and CV risk factors

Medical history (%)	2007-2009 (n=10,709)	2010-2012 (n=13,750)	2013-2014 (n=14,136)	2015-2016 (n=19,494)	2017-2018 (n=21,618)	2019-2020 (n=24,309)
Dyslipidaemia	73.2	70.8	59.4	54.8	48.8	54.8
Hypertension	73.4	72.8	66.8	68.1	63.7	66.3
Diabetes	46.1	45.3	43.3	45.2	43.1	44.0
Diabetes Treatment						

Medical history (%)	2007-2009 (n=10,709)	2010-2012 (n=13,750)	2013-2014 (n=14,136)	2015-2016 (n=19,494)	2017-2018 (n=21,618)	2019-2020 (n=24,309)
Smoking status						
Former (quit > 30 days)	28.2	27.8	21.8	22.5	21.8	22.1
Current (any tobacco use within last 30 days)	18.8	23.0	27.8	26.8	25.4	25.9

W.A. Wan Azman (Ed). Annual Report of the NCVD-PCI Registry, Year 2019-2020. Kuala Lumpur, Malaysia: National Cardiovascular Disease Database, 2023.

Circulation

Circulation. March 26th 2019;139:1603–1611.

ORIGINAL RESEARCH ARTICLE

Quantifying Importance of Major Risk Factors for Coronary Heart Disease

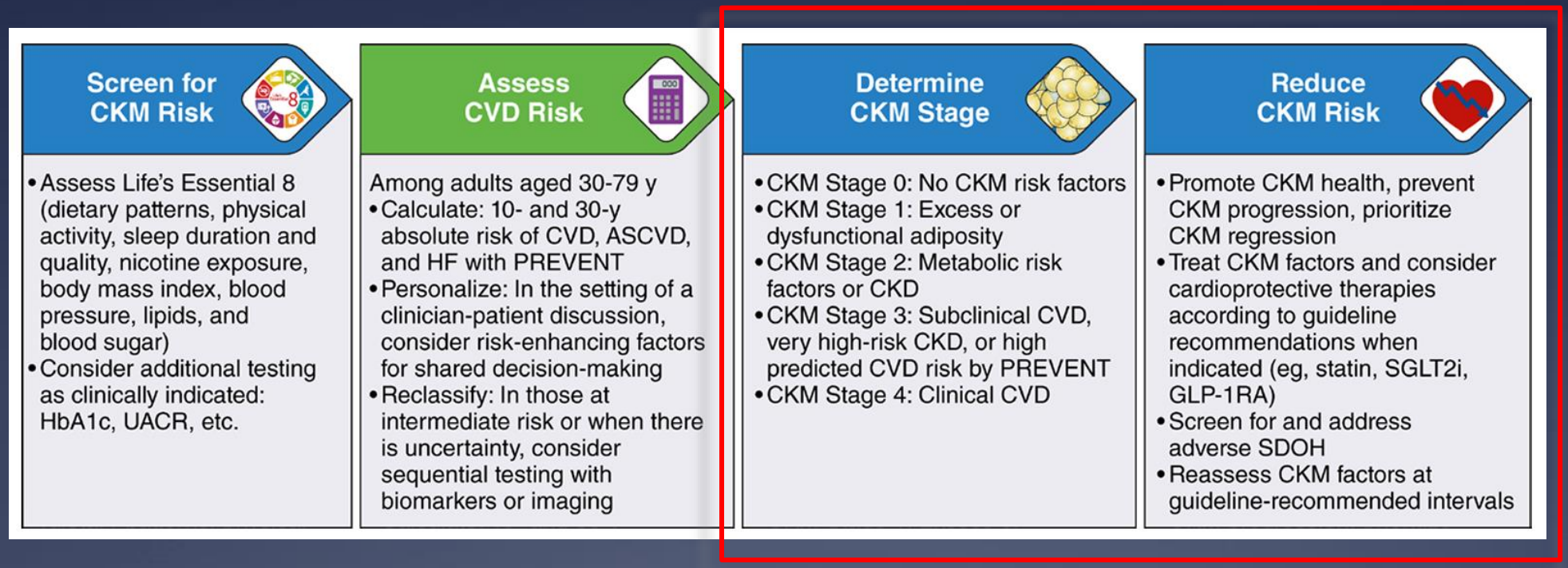
BACKGROUND: To optimize preventive strategies for coronary heart disease (CHD), it is essential to understand and appropriately quantify the contribution of its key risk factors. Our objective was to compare the associations of key modifiable CHD risk factors—specifically lipids, systolic

attributable fractions for SBP, non–high-density lipoprotein cholesterol (non–HDL-C), diabetes mellitus, and smoking. Expected absolute risk reductions for antihypertensive and lipid-lowering treatment were assessed.

Michael J. Pencina, PhD
Ann Marie Navar, MD, PhD
Daniel Wojdyla, MS
Robert J. Sanchez, PhD

Concluding.....that Our models indicate by eliminating or controlling these individual factors would lead to substantial reductions in total population CHD events.

Conceptual framework for risk-based prevention of cardiovascular disease integrating risk assessment with PREVENT and cardiovascular-kidney-metabolic health staging



R. Khan et al. Risk of Cardiovascular Disease Incorporating CKM Health. Circulation. December 12, 2023;148:1982–2004