Non invasive tests in CAD evaluation of patients with diabetes

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I declare no conflict of interst for this lecture

The scope of the problem

Cardiac risk assessment in asymptomatic diabetes: Combing different imaging modalities and surrogate markers?

Arthur J. H. A. Scholte, MD, PhD

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This article has been corrected. See J Nucl Cardiol. 2011 May 12; 18(4): 801.

The growing number of patients who develop diabetes mellitus (DM) is a great concern for public health care. Type 2 DM comprises 90% of all diabetic patients worldwide, and is largely the result of excess body weight and physical inactivity. Long term complications of DM include microvascular damage and macrovascular injuries. These complications reduce life expectancy and quality of life, and significantly increase morbidity. Due to the often masked symptoms of DM, the disease may be diagnosed several years after onset when complications have already occurred. Often, the prognosis of patients with DM depends on the presence of cardiovascular disease. Coronary artery disease (CAD) is the leading cause of morbidity and mortality in individuals with type 2 DM.[1] The 10-year mortality rate in patients with known CAD and diabetes exceeds 70%.[2]

The scope of the problem

Some studies suggest that the risk for future cardiac death in patients with diabetes without known CAD is similar to that in non-diabetic patients with overt clinical CAD.[2] In addition, early and late outcomes of diabetic patients with acute coronary syndromes are worse than those of their non-diabetic counterparts. To compound the problem, myocardial ischemia is often asymptomatic in patients with DM, and CAD is frequently in an advanced state, when becoming clinically manifest.[3,4] The previously described adverse clinical outcomes in patients with diabetes underscores the need to develop practical approaches to detect CAD in an early stage before clinical symptoms occur. Thus, early detection of CAD and myocardial ischemia appears to be important to reduce morbidity and mortality from cardiovascular disease in asymptomatic patients with type 2 DM. Identification of these asymptomatic diabetic patients might be important to intervene early and to increase long term survival. From a management perspective, patients with high risk characteristics on testing for myocardial ischemia may benefit from coronary revascularization. With regard to pharmacological therapy, the knowledge that a patient with diabetes has CAD may indicate the need to initiate or intensify pharmacological therapy with aspirins, statins, and angiotensin converting enzyme (ACE) inhibitors. Results from the BARI 2D trial showed no significantly differences in survival rates as well as in freedom from major cardiovascular events between optimal medical therapy and revascularization.[5] So, it seems that testing for ischemia should be reserved for selected individuals with a strong suspicion of high risk CAD.

1 Cardiovascular risk assessment in people with dysglycaemia:

2 Markers that may add predictive value to conventional CV risk factors

Recommendations	Class	Level
Risk stratification should be considered as part of the evaluation of patients with DM and IGT.	IIa	C
Cardiovascular risk assessment is recommended in people with DM and IGT as a basis for multifactorial management.	I	B

- **LOW**
- **MODERATE**
- **HIGH**

(*DM*)

- **VERY HIGH**

(*DM+≥1CVD risk factor or target organ damage*)

The 2012 Joint European Society guidelines on CVD prevention

- **Incremental value to the clinical risk assessment**

- **ABI (ancle brachial index)**

<0.9 indicates presence of PAD

>1.3 indicates calcified, noncompressible arteries

- **IMT (carotid intima-media thickness) and carotid plaques**

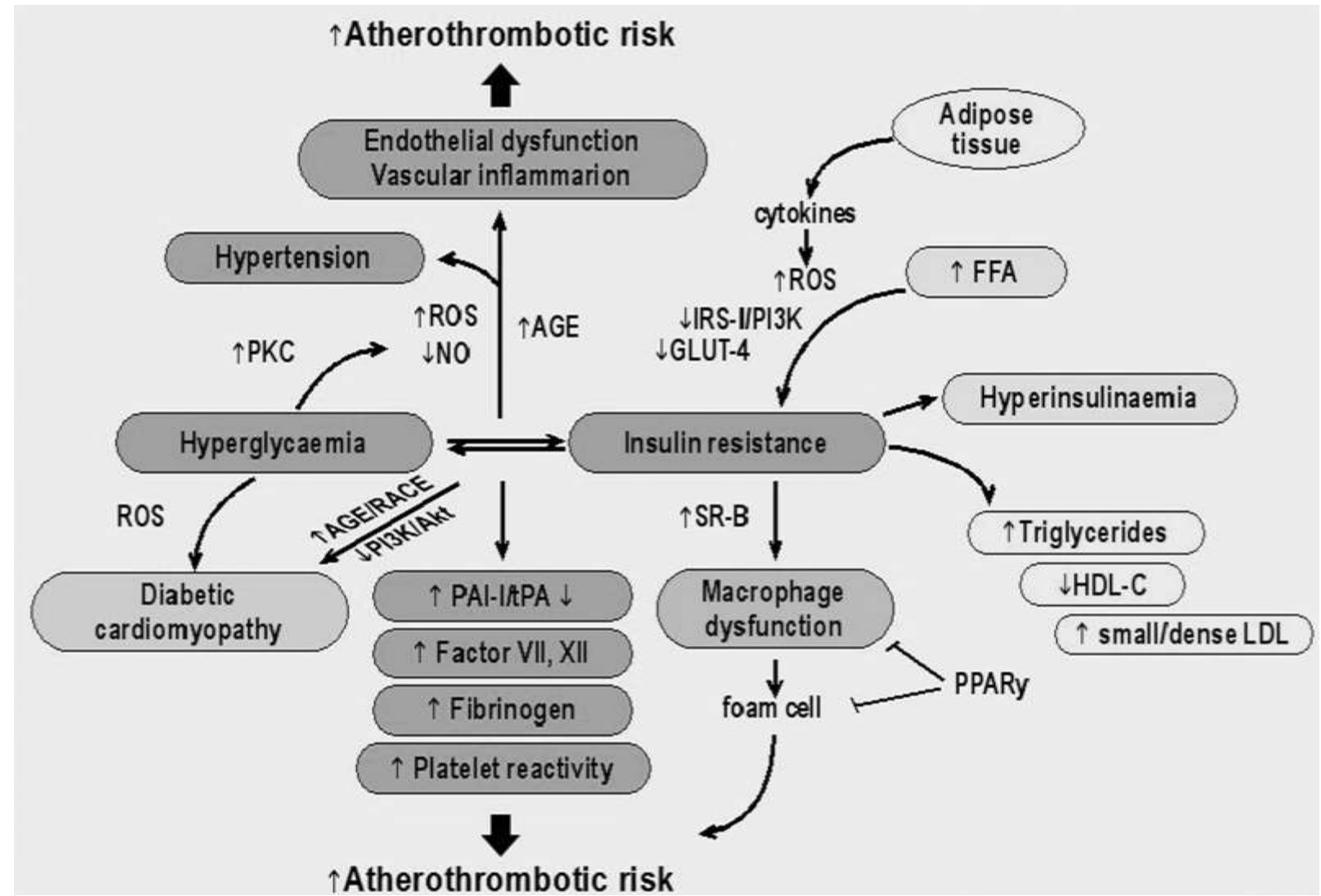- *Increase in carotid IMT values >1mm, leads to a 2-fold greater risk of acute MI over 3 years*

❸ Cardiovascular risk assessment in people with dysglycaemia:

MULTIFACTORIAL MANAGEMENT

- Risk factors (lifestyle habits incl. smoking, hypertension, and dyslipidaemia).

- Micro- and macrovascular disease and autonomic dysfunction.

- Co-morbidities (e.g. heart failure and arrhythmias).

- Inducible ischaemia (exercise testing, stress echo-cardiography, myocardial scintigraphy).

- Myocardial viability & LV function (echo-Doppler and/or MRI).

Molecular basis of cardiovascular disease in diabetes mellitus

The cardiovascular continuum in diabetes mellitus

↑Atherothrombotic risk

Endothelial dysfunction
Vascular inflammarion

Adipose tissue

cytokines

Hypertension

↑ROS
↓NO

↑PKC

↑ROS

↑AGE

↓IRS-I/PI3K
↓GLUT-4

↑ FFA

Hyperinsulinaemia

Hyperglycaemia

Insulin resistance

ROS

↑AGE/RACE
↓PI3K/Akt

↑SR-B

↑Triglycerides

↓HDL-C

Diabetic cardiomyopathy

↑ PAI-I/tPA ↓

Macrophage dysfunction

↑ small/dense LDL

↑ Factor VII, XII

↑ Fibrinogen

foam cell

PPARγ

↑ Platelet reactivity

↑Atherothrombotic risk

Atheroma from people with DM has more lipid, inflammatory changes and thrombus than those free from DM.

MECHANISMS /CLINICAL PRESENTATION OF MYOCARDIAL ISCHEMIA

ARE THERE DIFFERENCESS in diabetic patients?

Pathogenesis
Stable anatomical atherosclerotic and/or functional alterations of epicardial vessels and/or microcirculation
Natural history
Stable symptomatic or asymptomatic phases which may be interrupted by ACS
Mechanisms of myocardial ischaemia
Fixed or dynamic stenoses of epicardial coronary arteries
Microvascular dysfunction
Focal or diffuse epicardial coronary spasm
The above mechanisms may overlap in the same patient and change over time
Clinical presentations

Ω CAD is more often **silent** in patients with diabetes, and is silent in up to 75% of asymptomatic subjects aged 65 years or older, **endothelial dyssfunction** is more often in diabetic patients, seems even more important than **atherosclerosis**.

Ω Therefore, the evaluation for CAD in asymptomatic diabetic patients is gaining increasing clinical importance.

Silent ischaemia

- Up to 60% of myocardial infarctions may be asymptomatic, diagnosed only by systematic ECG screening.

- Silent myocardial ischaemia affects 20–35% of DM patients who have additional risk factors, and 35–70% of patients with SMI have significant coronary stenoses whereas, in the others, SMI may result from from endothelial dysfunction and/or alteration of coronary microcirculation.

- Silent myocardial ischaemia may be detected by ECG stress test, myocardial scintigraphy or stress echocardiography.

- Routine screening for CAD in asymptomatic patients is controversial. It is not recommended by the ADA, since it does not improve outcomes as long as CV risk factors are treated. This position is, however, under debate and the characteristics of the patients who should be screened for CAD need to be better defined.

- Further evidence is needed to support screening for SMI in all high-risk patients with DM. Screening may be performed in patients at a particularly high risk, such as those with evidence of PAD or high CAC score or with proteinuria, and in people who wish to start a vigorous exercise programme.

9.2 Patients with diabetes (see web addenda)

Mortality due to CVD is increased three-fold in diabetic men and two- to five-fold in diabetic women, compared with age- and sex-matched non-diabetic persons. A target HbA1c <7% (<53 mmol/mol) and target blood pressure <140/85 mmHg are recommended in recent European Guidelines on CVD prevention. The high prevalence of significant CAD and prohibitively high cardiovascular mortality may suggest the usefulness of routine screening extended to asymptomatic patients. In the absence of outcome trials confirming a clinical benefit, this strategy is not recommended. Coronary artery revascularization of diabetics remains a challenge. The decision to use either PCI or CABG as preferred mode of revascularization should be based on anatomical factors, together with clinical factors and other logistical or local factors (see chapter 8 and *Figure* 6). As a rule, PCI is recommended in diabetic patient with single-vessel disease. Conversely, given the results of the FREEDOM trial, CABG is recommended in diabetic patients with multivessel disease after discussion in a Heart Team meeting.

Recommendations	Class	Level
In asymptomatic adults with hypertension or diabetes a resting ECG should be considered for CV risk assessment.	IIa	C
In asymptomatic adults at intermediate risk (see SCORE for definition of intermediate risk - www.heartscore.org) measurement of carotid intima-media thickness with screening for atherosclerotic plaques by carotid ultrasound, measurement of ankle-brachial index or measurement of coronary calcium using CT should be considered for CV risk assessment.	IIa	B
In asymptomatic adults with diabetes, 40 years of age and older, measurement of coronary calcium using CT may be considered for CV risk assessment.	IIb	B
In asymptomatic adults without hypertension or diabetes a resting ECG may be considered.	IIb	C
In intermediate-risk asymptomatic adults (see SCORE for definition of intermediate risk - www.heartscore.org), (including sedentary adults considering starting a vigorous exercise programme), an exercise ECG may be considered for CV risk assessment particularly when attention is paid to non-ECG markers such as exercise capacity.	IIb	B
In asymptomatic adults with diabetes or asymptomatic adults with a strong family history of CAD or when previous risk assessment testing suggests high risk of CAD, such as a coronary artery calcium score of 400 or greater stress imaging tests (MPI, stress echocardiography, perfusion CMR) may be considered for advanced CV risk assessment.	IIb	C
In low- or intermediate-risk (based on SCORE) asymptomatic adults stress imaging tests are not indicated for further CV risk assessment.	III	C

Diagnostic accuracy of imaging test in asymptomatic diabetic patients

Table 1—

Diagnostic accuracy imaging tests

	General population		Diabetic patients	
	Sensitivity	Specificity	Sensitivity	Specificity
Functional imaging (ref.)				
Nuclear imaging (11–14)	86	74	80–97	56–88
Stress echocardiography (15–18)	71–84	82–93	81–82	54–88
Contrast echocardiography (21, 22)	89	63	89	52
First-pass perfusion MRI (21)	84	85	NA	NA
Stress cine MRI (21)	89	84	NA	NA
Anatomical imaging (ref.)				
CAC score	NA	NA	NA	NA
MRI angiography (27)	72	86	NA	NA
MSCT angiography (28, 29)	91	96	95	95
EBCT angiography (30)	87	91	NA	NA

• Data are percentages. CAC, coronary artery calcium. NA, not available.

Clinical Risk and Guidelines Appropriate Use Criteria

- Guidelines for the Clinical Use of Cardiac Radionuclide Imaging in **2003** (ACC, AHA and ASNC), stated that "it is not clear that detecting asymptomatic preclinical CAD with therapeutic intervention will reduce risk beyond that indicated by risk factor profiling."

- However these guidelines do suggest that **"in some asymptomatic patients, testing may be appropriate when there is a high-risk clinical situation."**

- The **2010** ACC/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic adults suggests a severe restriction of the use of stress imaging, potentially **limiting its application to DIABETICS.**

- But, an ideal asymptomatic population to discuss the role of MPI are **patients with CHD risk equivalents** (diabetes mellitus, other atherosclerotic disease (peripheral arterial disease, abdominal aortic aneurysm, carotid artery disease), a 20% 10-year risk of CHD by Framingham projections, and since resentlu erectile dysfunction).

Patients at high cardiovascular heart disease risk based on standard Adult Treatment Panel (ATP) III criteria are sutable for CHD detection **by noninvasive imaging modalities.**
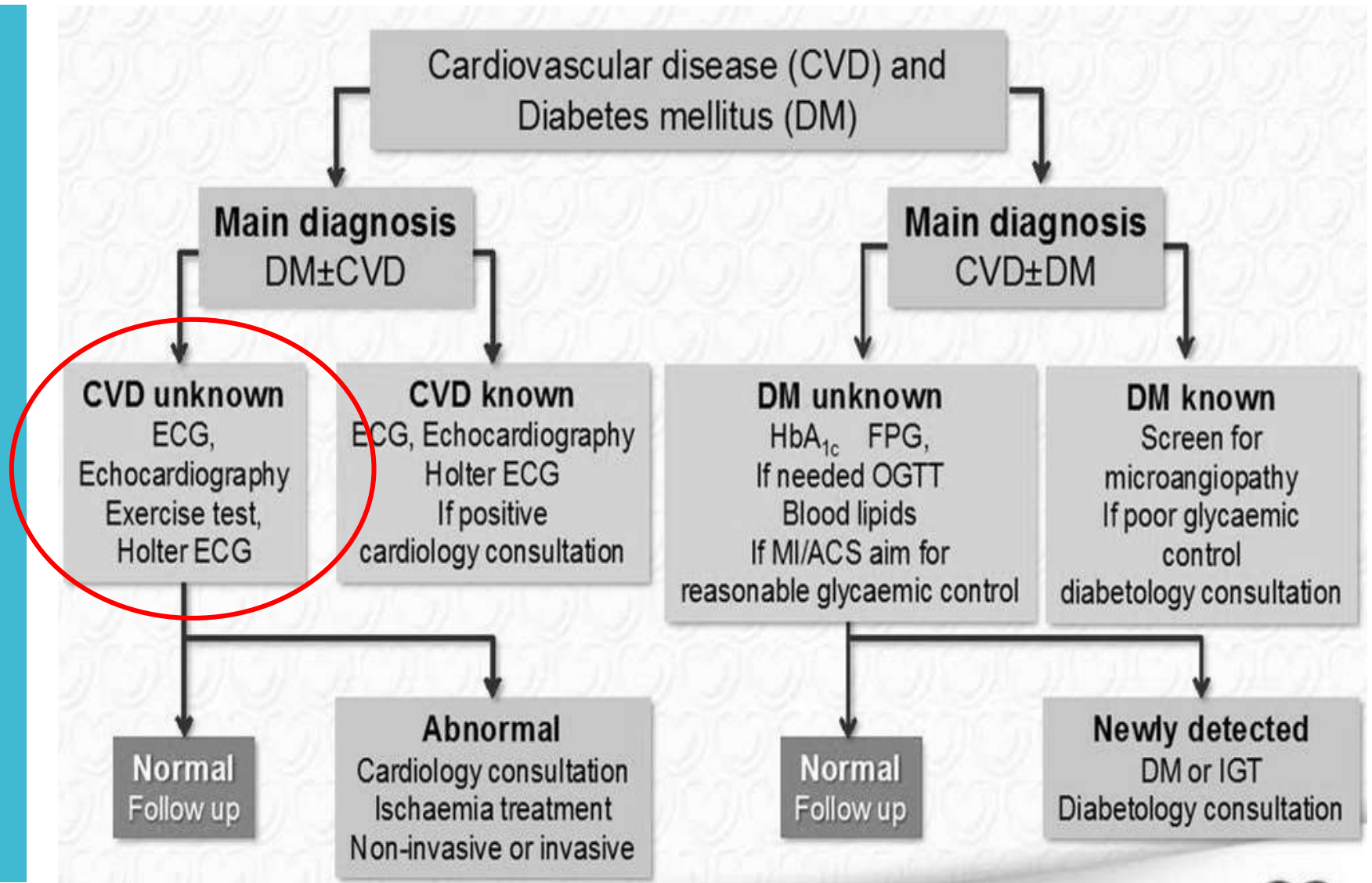
Clinical Risk and Guidelines Appropriate Use Criteria

STEPWISE APPROACH

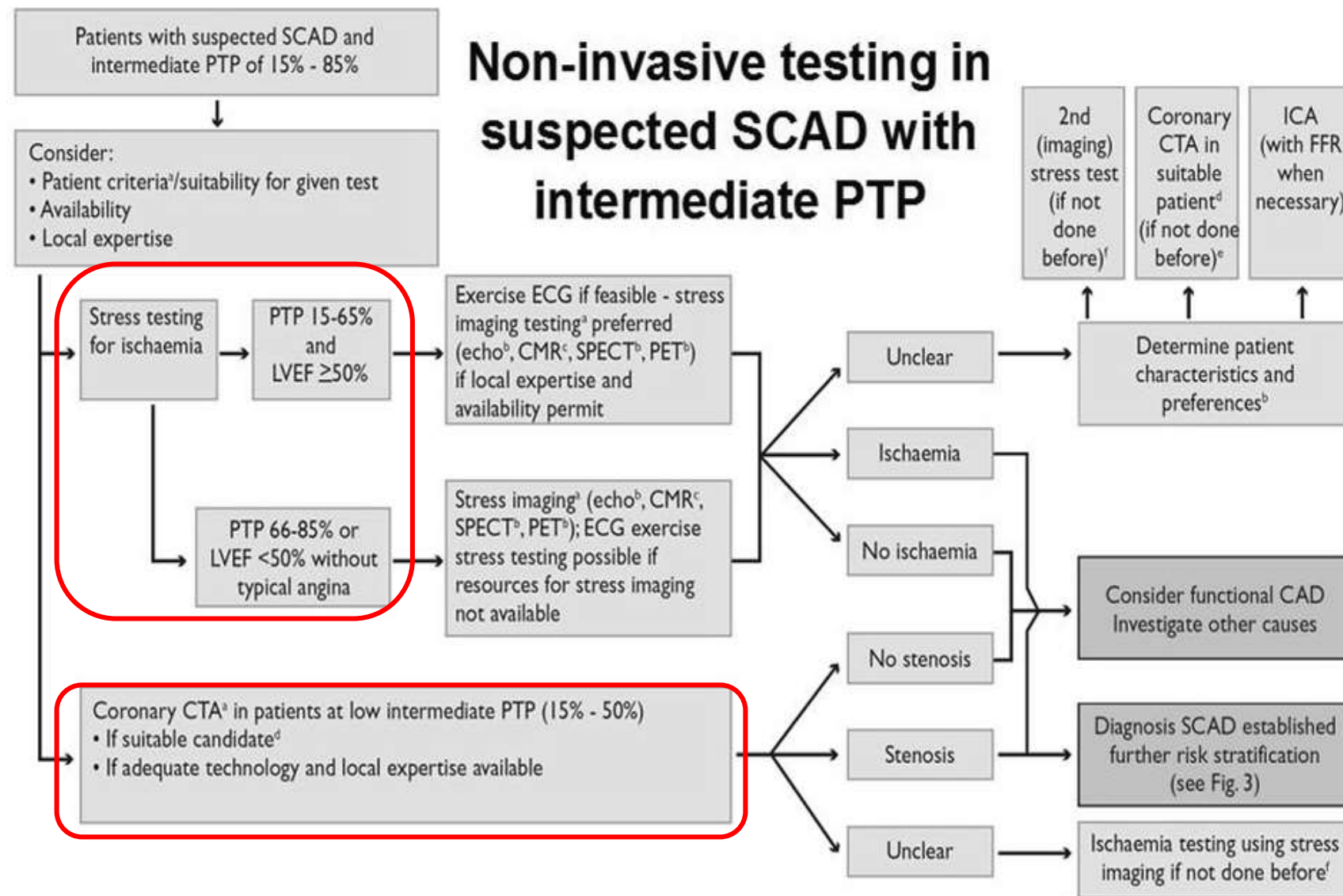1. Patints at high cardiovascular heart disease risk with a moderately abnormal (100-400) CACS; and

2. Patients with a severely abnormal CACS (>400), in whom silent myocardial ischemia is known to be prevalent,

are sutable for CHD detection **by noninvasive imaging modalities.**

- 25% of asymptomatic patients have either a moderate (15%) or a severe (10%) CACS.

- 25% of asymptomatic patients who have at least a moderate CACS, and 40% of asymptomatic patient who have at least severe CACS will have abnormal MPI.

Principles for diagnosis of CVD in diabetic patient

Cardiovascular disease (CVD) and Diabetes mellitus (DM)

Main diagnosis
DM±CVD

Main diagnosis
CVD±DM

CVD unknown
ECG, Echocardiography
Exercise test, Holter ECG

CVD known
ECG, Echocardiography
Holter ECG
If positive
cardiology consultation

DM unknown
HbA$_{1c}$ FPG,
If needed OGTT
Blood lipids
If MI/ACS aim for
reasonable glycaemic control

DM known
Screen for
microangiopathy
If poor glycaemic
control
diabetology consultation

Normal
Follow up

Abnormal
Cardiology consultation
Ischaemia treatment
Non-invasive or invasive

Normal
Follow up

Newly detected
DM or IGT
Diabetology consultation

Principles for non-invasive diagnosis of SCAD

Non-invasive testing in suspected SCAD with intermediate PTP

Patients with suspected SCAD and intermediate PTP of 15% - 85%

Consider:
• Patient criteria[a]/suitability for given test
• Availability
• Local expertise

Stress testing for ischaemia

PTP 15-65% and LVEF ≥50%

Exercise ECG if feasible - stress imaging testing[a] preferred (echo[b], CMR[c], SPECT[b], PET[b]) if local expertise and availability permit

PTP 66-85% or LVEF <50% without typical angina

Stress imaging[a] (echo[b], CMR[c], SPECT[b], PET[b]); ECG exercise stress testing possible if resources for stress imaging not available

Coronary CTA[a] in patients at low intermediate PTP (15% - 50%)
• If suitable candidate[d]
• If adequate technology and local expertise available

Unclear

Ischaemia

No ischaemia

No stenosis

Stenosis

Unclear

Determine patient characteristics and preferences[b]

Consider functional CAD Investigate other causes

Diagnosis SCAD established further risk stratification (see Fig. 3)

Ischaemia testing using stress imaging if not done before[f]

2nd (imaging) stress test (if not done before)[f]

Coronary CTA in suitable patient[d] (if not done before)[e]

ICA (with FFR when necessary)

Recommendations for CVD risk assessment in asymptomatic patients with Diabetes

Class IIa

In asymptomatic adults with diabetes, 40 years of age and older, **measurement of CAC** is reasonable for cardiovascular risk assessment. (*Level of Evidence: B*)

Class IIb

Measurement of HbA1C may be considered for cardiovascular risk assessment in asymptomatic adults with diabetes. (*Level of Evidence: B*)

Stress MPI may be considered for advanced cardiovascular risk assessment in asymptomatic adults with diabetes or when previous risk assessment testing suggests a high risk of CHD, such as a CAC score of 400 or greater. (*Level of Evidence: C*)

① Role of CAC in diabetic subjects

② Comparison with imaging modalities

③ Usefulness in Motivating Patients

√ The prevalence of CAD on multislice CT in asymptomatic patients with type 2 diabetes ranges from 60 - 80%.

√ **The CAC score is predictive beyond conventional risk factors, and is an independent prognosticator in diabetic patients.**

√ Absent coronary calcium is associated with a low **incidence of ischaemia** on SPECT/PET.

√ Increasing CAC is associated with an increased **risk of an adverse cardiac event**, and for every increase in CAC the risk is higher in diabetics than non-diabetic patients, both in patients with normal, and in those with perfusion scan abnormalities.

√ The rationale for CACS as an initial test is that it is most sensitive for detecting early atherosclerosis, with relatively low radiation exposure (1-2 mSv).

CCS (Agaston)	Risk	Description
0	Non-identified	Negative test. Findings are consistent with a low risk of having a cardiovascular event in the next 5 years.
1-10	Minimal	Minimal atherosclerosis is present. Findings are consistent with a low risk of having a cardiovascular event in the next 5 years.
11-100	Mild	Mild coronary atherosclerosis is present. There is likely mild or minimal coronary stenosis. A mild risk of having CAD exists.
101-400	Moderate	Moderate calcium is detected in the coronary arteries and confirms the presence of atherosclerotic plaque. A moderate risk of having a cardiovascular event exists.
>400	High	A high calcium score may be consistent with significant risk of having a cardiovascular event within the next 5 years
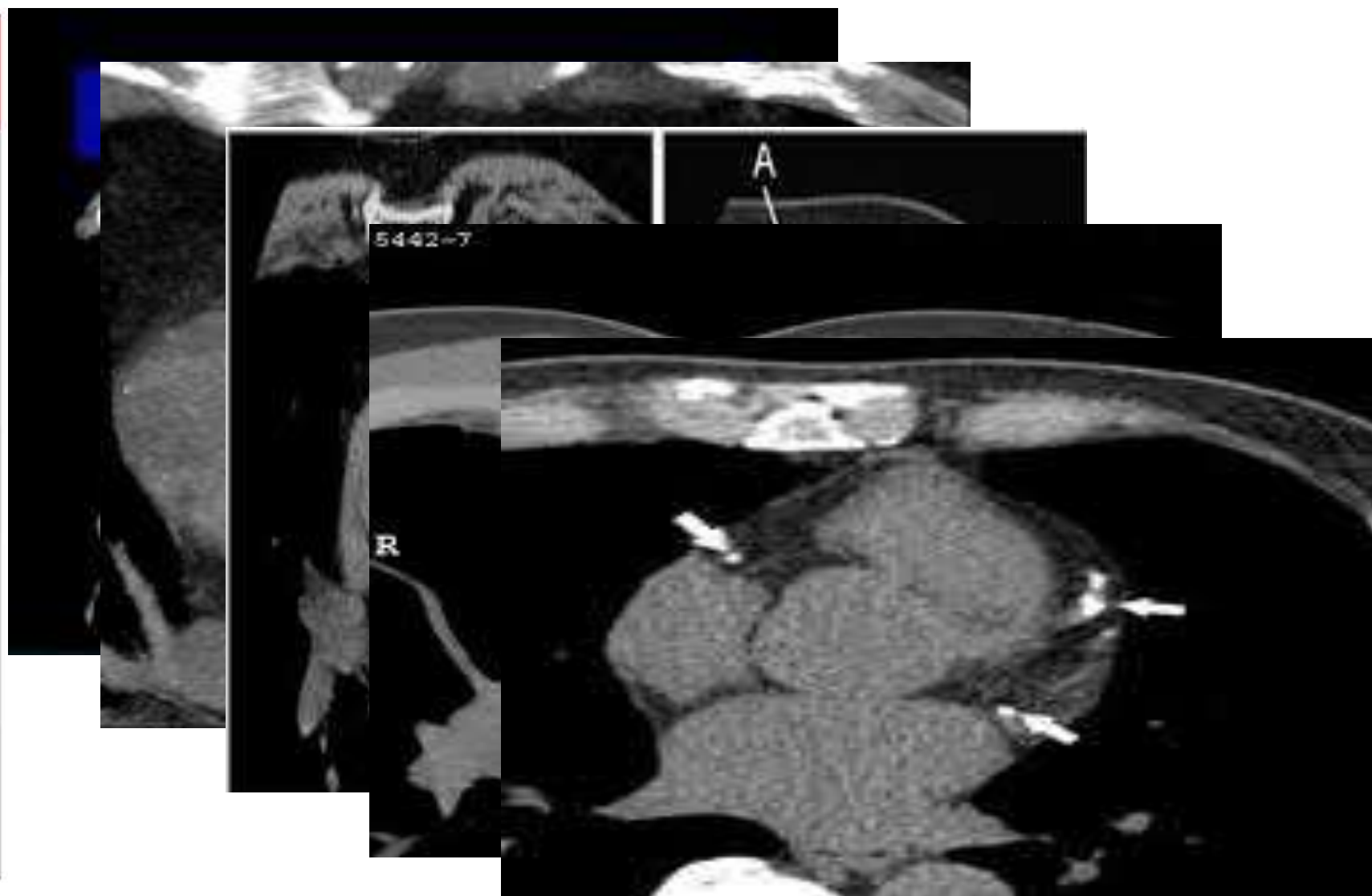
PREDICT
(Patients with Renal Impairment and Diabetes Undergoing Computed Tomography) study (589pts)

At a median of 4 years' follow-up, in a predictive model that included CAC score and traditional risk factors, the CAC score was a highly significant independent predictor of CHD events or stroke. The model found that a doubling in calcium score was associated with a 32% increase in risk of events.
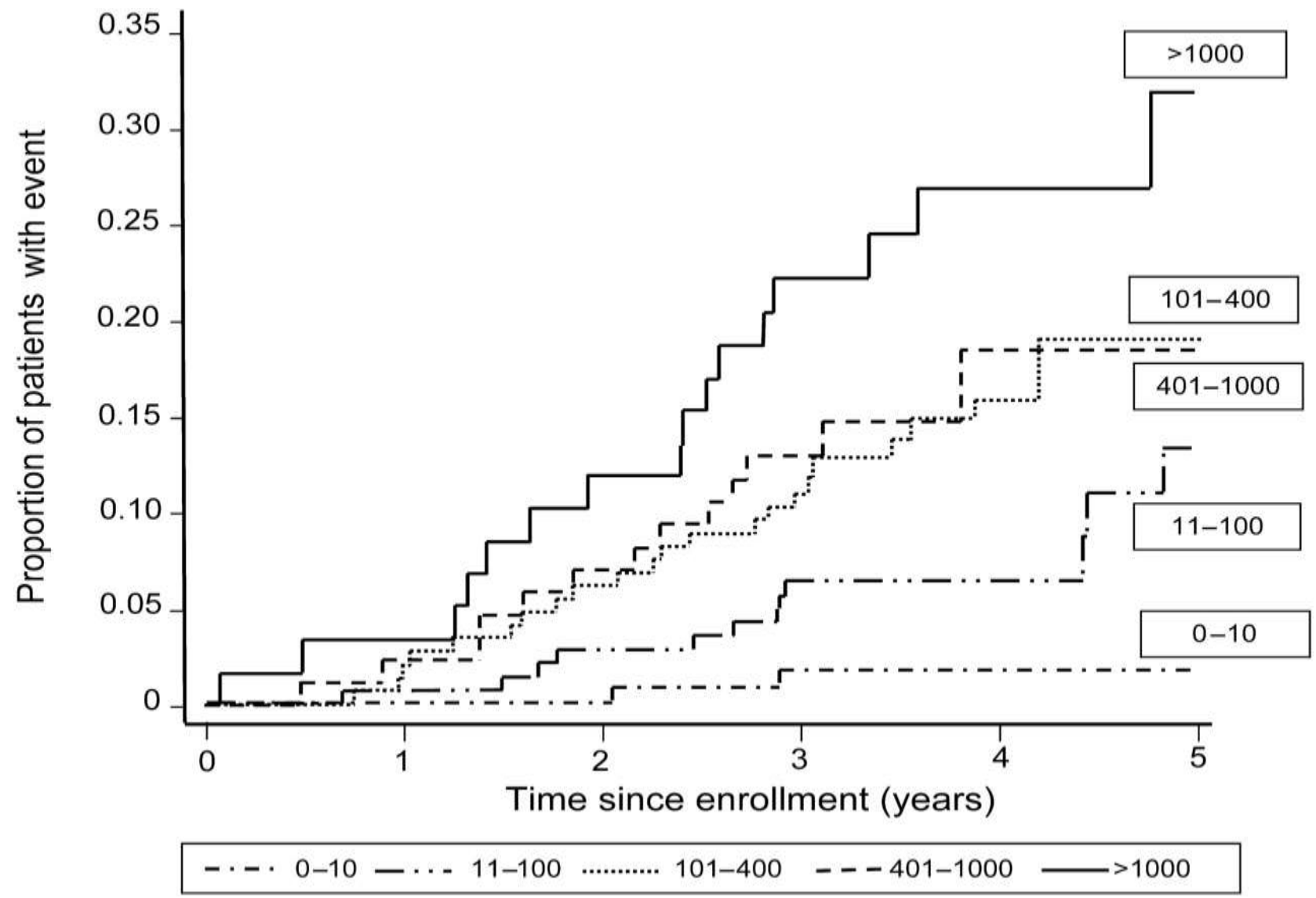
Comparative analyse of:
Framingham risk scor, UKPDS risk scor, and CAC score
for predicting cardiovascular events

OR = 10.1 for AU score 100 - 400, and
OR = 58.1 for AU scores >1000

Prognostic role of coronary calcium in asymptomatic patients

Ω **Subclinical atherosclerosis**, measured by coronary artery calcium (CAC) imaging, has been found superior to established risk factors for **predicting silent myocardial ischaemia and short-term outcome.**

Ω CAC and myocardial perfusion scintigraphy findings were synergistic for the prediction of short-term cardiovascular events.

incidence of an abnormal myocardial perfusion scintigraphy scan [72].

Commonly used tests to diagnose the presence of CAD

	Diagnosis of CAD	
	Sensitivity (%)	Specificity (%)
Exercise ECG[a]	45-50	85-90
Exercise stress echocardiography	80-85	80-88
Exercise stress SPECT	73-92	63-87
Dobutamine stress echocardiography	79-83	82-86
Dobutamine stress MRI[b]	79-88	81-91
Vasodilator stress echocardiography	72-79	92-95
Vasodilator stress SPECT	90-91	75-84
Vasodilator stress MRI[b]	67-94	61-85
Coronary CTA[c]	95-99	64-83
Vasodilator stress PET	81-97	74-91

Exercise ECG recommendations for asymptomaticdiabetic patients

CLASS IIb

- 1. An exercise ECG may be considered for cardiovascular risk assessment in intermediate-risk asymptomatic adults (including sedentary adults considering starting a vigorous exercise program), particularly when attention is paid to non-ECG markers such as exercise capacity.

(Level of Evidence: B)

Exercise ECG for Silent Myocardial Ischemia

- The value of exercise ECG testing to detect silent ischemia and assess prognosis has been evaluated in a few small studies of asymptomatic patients with diabetes.

- ECG stress testing has an approximate 50% sensitivity and 80% specificity. The positive predictive value for detecting CAD using coronary angiography as the gold standard ranges between 60% and 94% and was higher in men than women.

- Recommendations for exercise stress testing for risk assessment do not appear to be different in patients with diabetes and patients without diabetes.

- The standard exercise test has similar diagnostic characteristics in diabetic as in nondiabetic patients.

ROC curves in patients with (top) and without (bottom) diabetes. The AUC is similar between the two groups, suggesting comparable predictive accuracy of the exercise test.

(Chest. 2001;119(5):1576-1581)
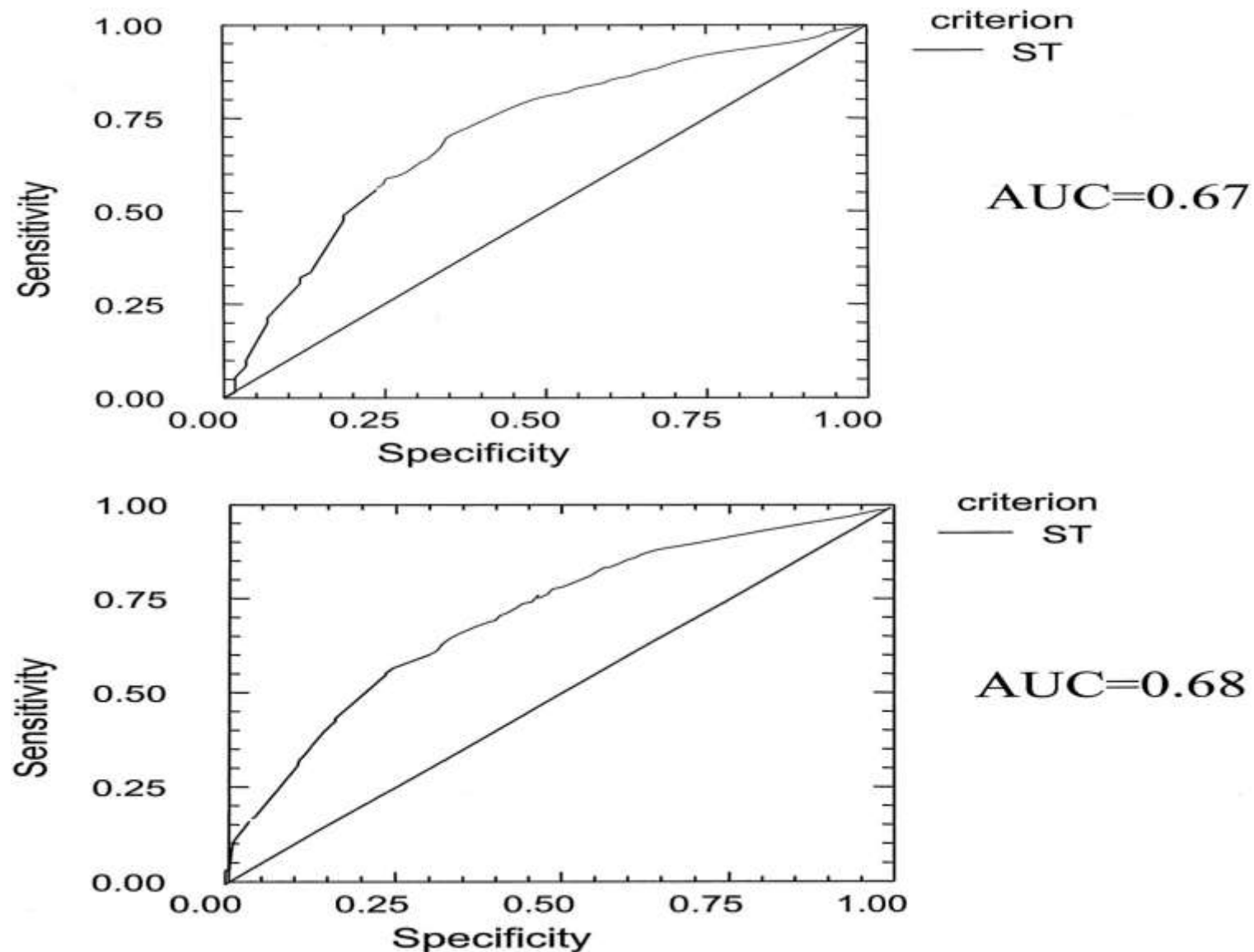
NON INVASIVE IMAGING MODALITIES TO DETECT ICHAEMIA

SPECT MPI

Appropriate indications

In asymptomatic patients without prior CAD

❑ **At high CVD risk based on Adult Treatment Panel (ATP) III criteria**;

❑ **At high CVD risk with:**
- **Moderately abnormal (100-400) CACS; or**
- **Severely abnormal CACS ([400)**

- Only 25% of asymptomatic patients will have a moderate (15%) or a severe (10%) CACS.

- The limited role of MPI in the asymptomatic patient with risk factors for CAD is not due to its inaccuracy in risk stratifying but by the very low prevalence of an abnormal study demonstrating ischemia (5%).

- Routine testing with MPI would result in unnecessary radiation exposure in the vast majority of patients. However, the likelihood of an abnormal MPI significantly increases to 25% in asymptomatic patients who have at least a moderate CACS and to 40% when the CACS is severe.

- The rationale for CACS as an initial test is that it is most sensitive for detecting early atherosclerosis and with relatively low radiation exposure (1-2 mSv). Based on CACS results, MPI can be selectively targeted to the small percentage of asymptomatic patients most likely to have ischemia.

MPI SPECT

stresors and protocols

□ **SPECT MPI stressors**
- **exercise stress** (preferred in patients who [...] normal ECG)
- **pharmacologic stress** (vasodilators) testing in patients unable to exercise, and/or have abnormal basal ECG

□ **RADIOPHARMACEUTICALS**
- **technetium (Tc)-99m tracers** limit radiation exposure and improve overall image quality
- **thallium (Tl)-201** in certain specific patients groups.

□ **SPECT MPI stress protocols**
- One-Day Tc-99m Rest/Stress Protocol
- One-Day Tc-99m Stress/Rest Protocol
- Two-Day Stress/Rest Tc99m Protocol
- Two-Day Rest/Stress Tc-99m Protocol
- Stress-Only Tc-99m Protocol
- One-Day Rest Tl-201/Stress Tc-99m Dual Isotope Protocol
- One-Day Tl-201 Stress/Redistribution Protocol

Perypheral artery disease and diabetic neuropathy

Patient-centered imaging, 2012

Ω Reversible ischaemia on myocardial scintigraphy scan in the anterior wall.
Ω An occluded diagonal artery on invasive coronary angiogram.
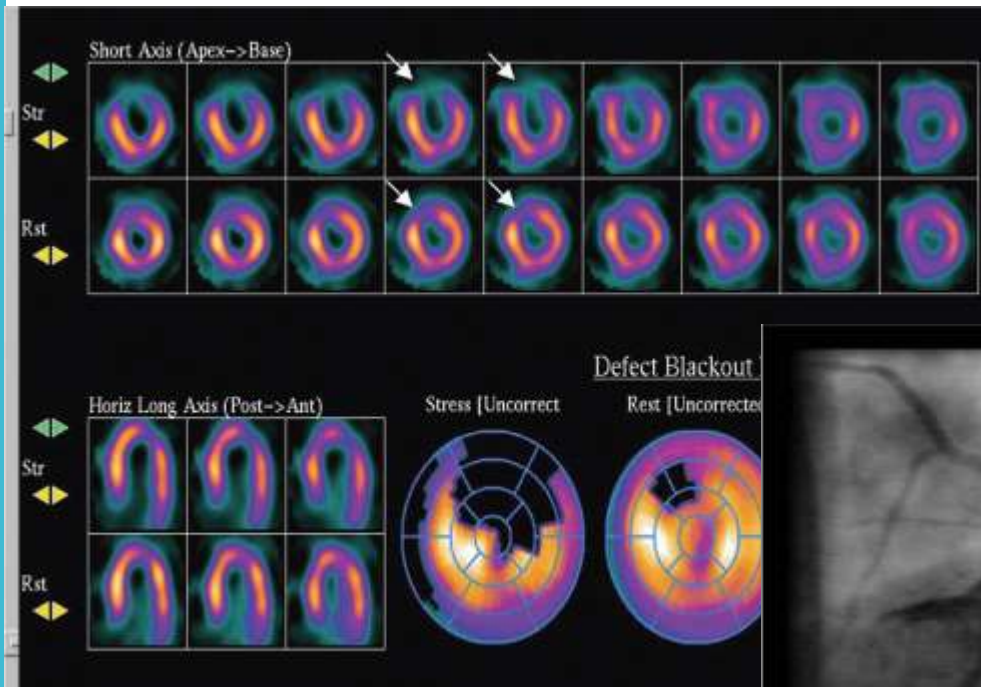
## Evidence of Value for Risk Assessment for Coronary Atherosclerosis or Ischemia to **Guide Treatment** or **Change Patient Outcomes**

- Abnormal MPI has been found in 21% to 59% of asymptomatic diabetic patients. Traditional and emerging cardiac risk factors were not associated with abnormal MPI.

- In the **DIAD study**, 561 low-risk asymptomatic patients were randomized to screening with adenosine SPECT perfusion imaging and 562 patients were randomized to no testing. All patients had a normal resting ECG and no prior history of CAD. Over a mean follow-up of 4.8 years, the cumulative event rate was 2.9% (0.6% per year).
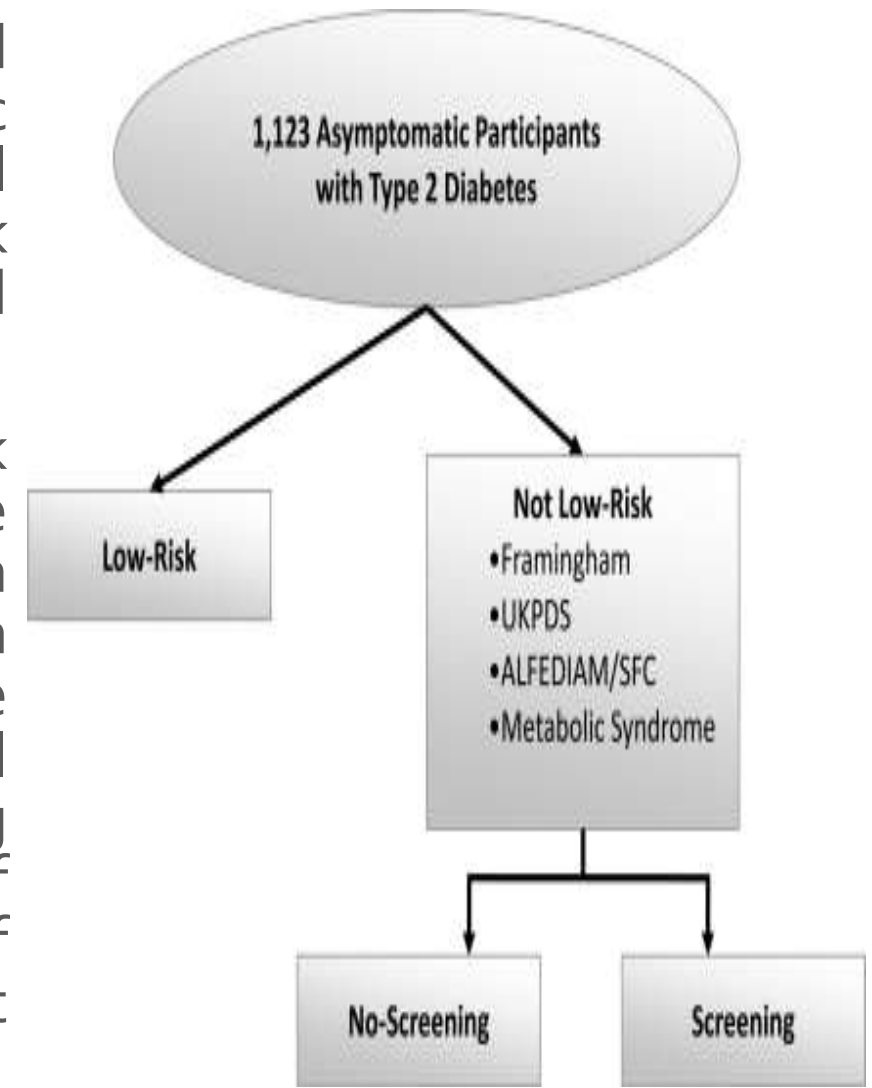
A, **Cumulative incidence of CE** in 561 participants randomized to systematic baseline screening with stress myocardial perfusion imaging (MPI) and 562 participants randomized to receive no screening.

B, **Cumulative incidence of CE according to results of stress MPI**: normal, small defect, moderate or large defect, and nonperfusion abnormality. No cardiac events occurred in participants who were randomized to, but did not complete screening MPI
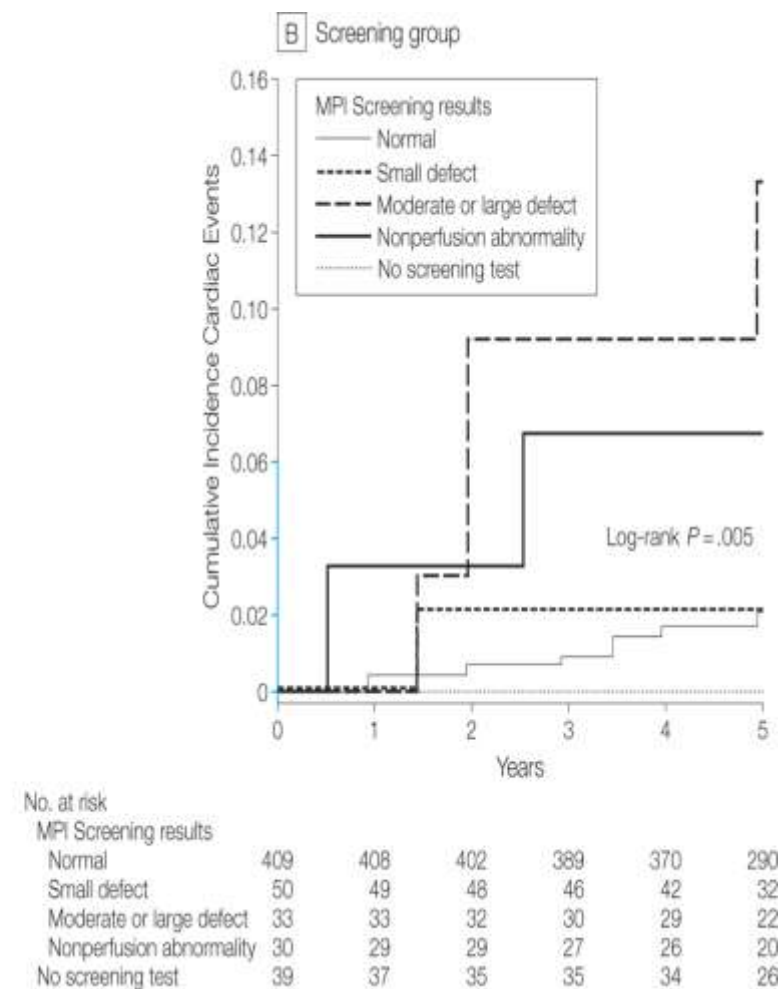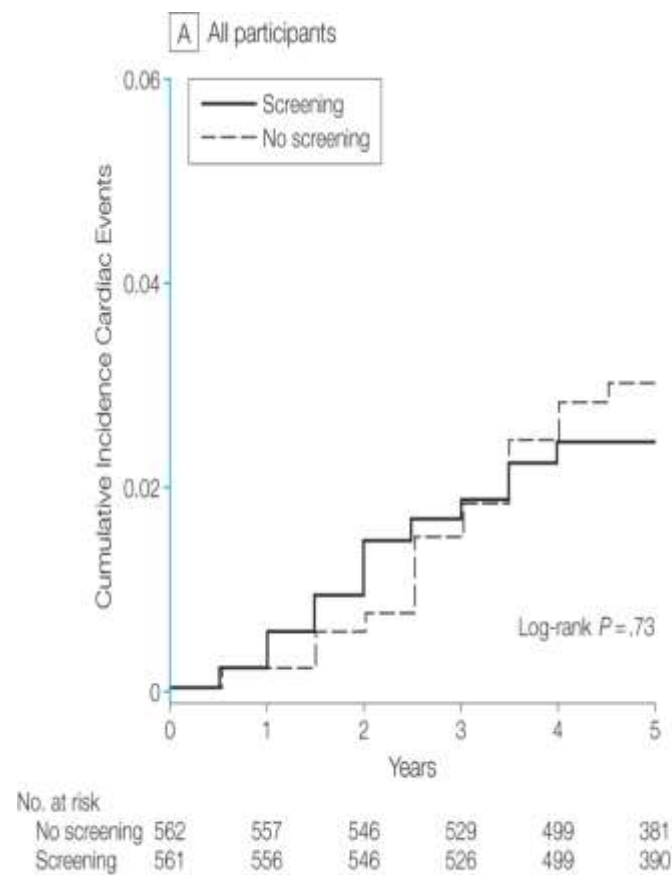
RESULTS:
❑There was no difference in event rates between the 2 groups.
❑In the tested group, those with moderate or large defects had a higher cardiac event rate than those with a normal scan or small defects.

Table 1. Appropriate use criteria for asymptomatic patients[1]

Indication	Appropriate use score (1-9)
Detection of CAD/risk assessment	
High CHD risk (ATP III risk criteria)	A (7)
Intermediate CHD risk (ATP III risk criteria)	U (5)
ECG uninterpretable	
Intermediate CHD risk (ATP III risk criteria)	I (3)
ECG interpretable	
Low CHD risk (ATP III risk criteria)	I (1)
Risk assessment with prior coronary calcium Agatston Score	
Agatston score less than 100	I (2)
Agatston score between 100 and 400	U (5)
Low to intermediate CHD risk	
Agatston score between 100 and 400	A (7)
High CHD risk	
Agatston score greater than 400	A (7)

Diagnostic accuracy of CAC and MPI SPECT in diabetic patients

Table 4—

Evidence for (silent) ischemia or atherosclerosis in studies with asymptomatic diabetic patients (Only studies with >500 patients are included.)

Author (ref.)	Patients (n)	Patient characteristics	Technique	Abnormal study	Details
Anand et al. (56)	510	Type 2 diabetes	EBCT calcium scoring	46.3%	19.6% mild calcium (score 11–100 AU); 5.5% extensive calcium (score >1,000 AU)
Sconamiglio et al. (58)	1,899	Type 2 diabetes	MCE; dipyridamole	60%	59.4% of 1,121 patients with more than two risk factors; 60% of 778 patients with at least one risk factor
Wackers et al. (57)	522	Type 2 diabetes	Nuclear imaging, SPECT; adenosine, low-level exercise	21%	16% of perfusion abnormalities involved >5% of the left ventricle
Miller et al. (69)	1,738	Diabetic patients	Nuclear imaging, SPECT; exercise, pharmacologic	59%	20% considered to represent high risk
Zellweger et al. (59)	1,737	Diabetic patients	Nuclear imaging, SPECT; exercise, pharmacologic	39–51%	39% of 826 asymptomatic patients; 51% of 151 patients short of breath; 44% of 760 patients with angina
Rajagopalan et al. (60)	1,427	Diabetic patients	Nuclear imaging, SPECT; exercise, pharmacologic	58%	20% considered to represent high risk

• MCE, myocardial contrast echocardiography.

SPECT MPI in asymptomatic diabetic patients, 2013

Circulation. Cardiovascular imaging

Prevalence and Predictors of Ischemia and Outcomes in Outpatient Diabetic Patients Referred for SPECT Myocardial Perfusion Imaging

Jamieson M. Bourque, MD, MHS, Chetan A. Patel, MD, [...], and George A. Beller, MD

Additional article information

Abstract

Background

The prevalence of ischemia and its prediction of events are unclear in outpatient diabetic patients in the modern era of intensive medical management. We sought to identify the prevalence of ischemia, subsequent cardiac events, and impact of gender, stress type, and symptom status on these findings in a cohort of outpatient, stable diabetic patients referred for SPECT myocardial perfusion imaging (MPI).
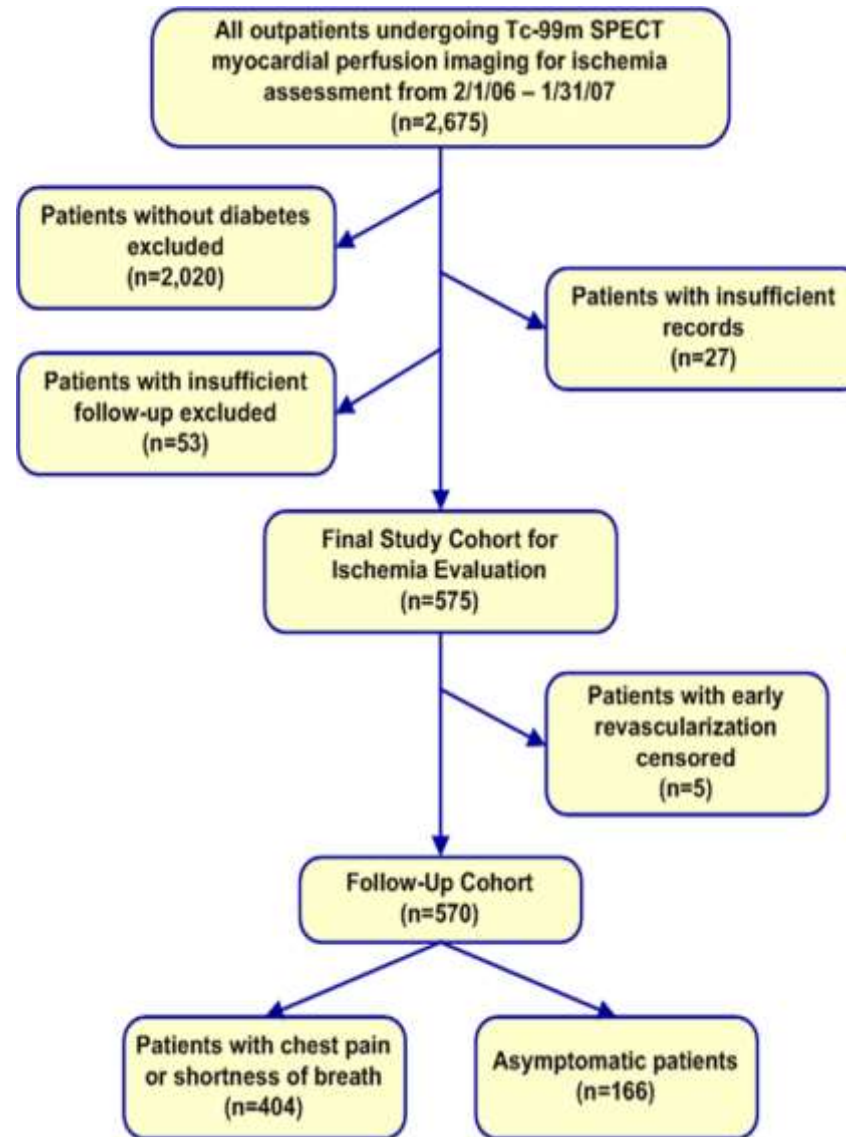
Methods and Results

Study design
Study results

All outpatients undergoing Tc-99m SPECT myocardial perfusion imaging for ischemia assessment from 2/1/06 – 1/31/07 (n=2,675)

Patients without diabetes excluded (n=2,020)

Patients with insufficient records (n=27)

Patients with insufficient follow-up excluded (n=53)

Final Study Cohort for Ischemia Evaluation (n=575)

Patients with early revascularization censored (n=5)

Follow-Up Cohort (n=570)

Patients with chest pain or shortness of breath (n=404)

Asymptomatic patients (n=166)

Table 2

Findings on exercise and pharmacologic stress and myocardial perfusion imaging presence or absence of chest pain or shortness of breath

| Characteristic | Exercise Stress (n=200) | | | Pharma |
	Symptomatic (n (%))	Asymptomatic (n(%))	P-value	Symptom (n(%))
Total patients	163	37		246
METS achieved (median (25th 75th percentiles)*	8.0 (6.6, 10.0)	8.6 (7.0, 10.1)	0.61	
≥10 METS achieved*	37 (23.1)	7 (58.3)	0.007	
Peak exercise heart rate	144 (133, 157)	140 (132, 151)	0.31	
Maximum systolic BP*	199 (180, 222)	204 (178, 223)	0.64	
Maximum diastolic BP*	85 (75, 97)	89 (73, 100)	0.49	
Chest pain during stress	23 (14.1)	1 (2.7)	0.054	
>1mm stress ST depression	10 (11.7)	7 (18.0)	0.28	9 (3.2)

Study results

Over median 4.4 years follow-up, the rate of cardiac death/nonfatal myocardial infarction (MI) was moderate at 2.6%/year (cardiac death 0.8%/year) in the total cohort but was 5.7%/year in those with ischemia (p<0.001). Pharmacologic stress predicted a higher cardiac event rate (p<0.001) but symptoms did not (p=0.55).
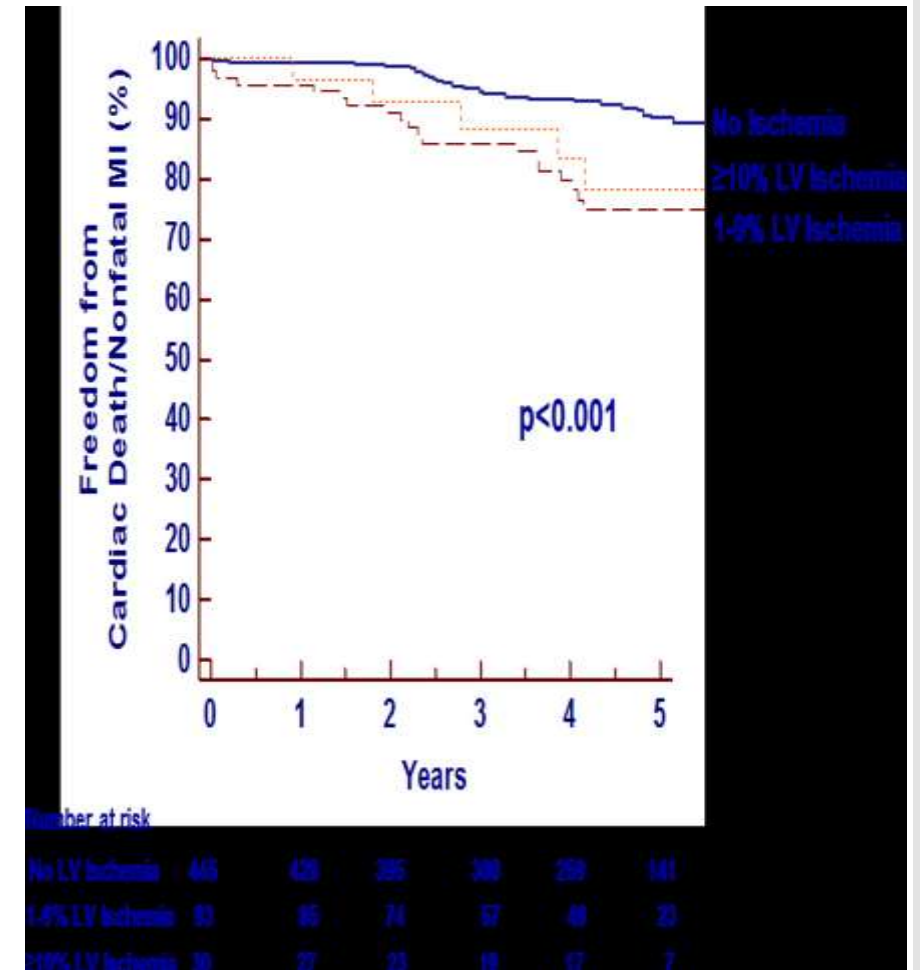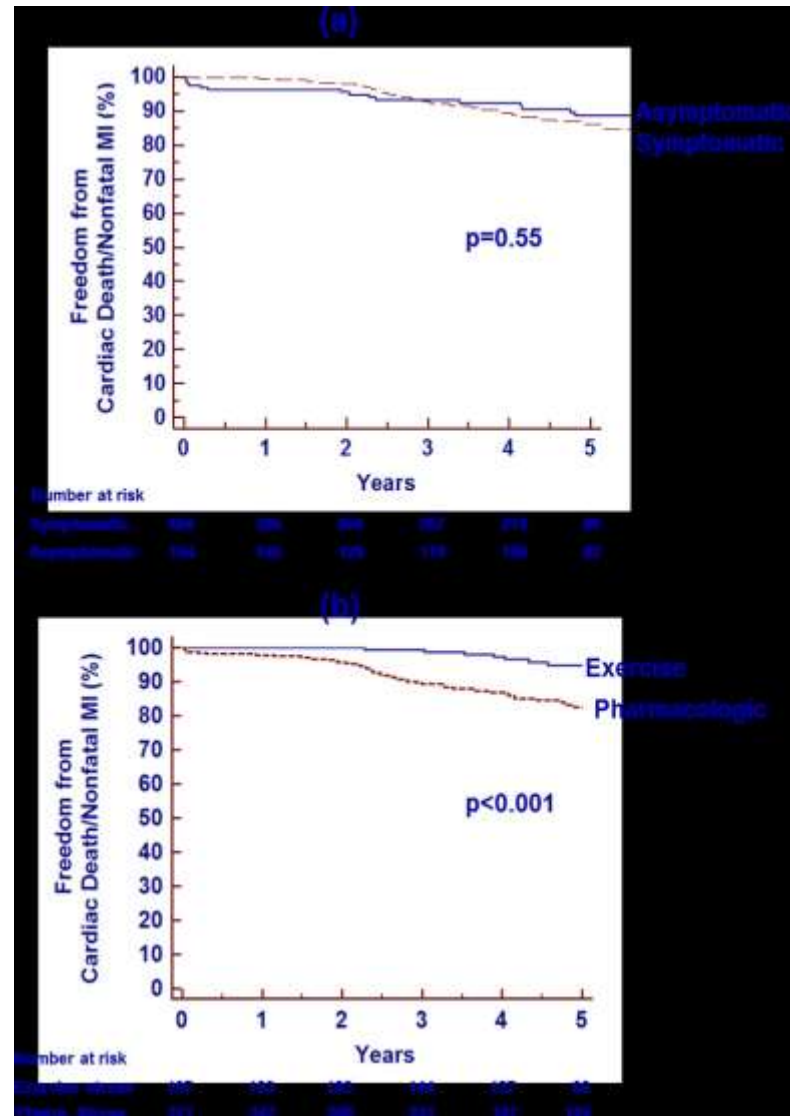
RECOMMENDATION

- **Clinical risk assessment is key with regards to applying MPI** for the evaluation of asymptomatic individuals, although the exact method of risk determination remains unclear. (*conventional risk models not applicable?*)

- In many settings, **a tiered approach to clinical evaluation is warranted**, with risk determination and **possibly other testing such as calcium scoring preceding the performance of MPI**.

- Certain subgroups of asymptomatic patients warrant special attention and consideration for MPI: those with a family history of premature CHD, CAD risk equivalents (peripheral vascular disease, ED) and impaired functional capacity, high-risk patients (20% CHD risk for MI or death within 10 years) constitute a cohort where MPI would be appropriate.

- The data for the use of **MPI in diabetics appears to be reasonable for high-risk diabetics,** including older individuals and those with an abnormal ECG or an elevated calcium score.

Stressechocardiography (SE)

CLASS III: NO BENEFIT

1. Stress echocardiography is not indicated for cardiovascular risk assessment in low- or intermediate-risk asymptomatic adults. (Exercise or pharmacologic stress echocardiography is primarily used for its role in advanced cardiac evaluation of symptoms suspected of representing CHD and/or estimation of prognosis in patients with known coronary artery disease or the assessment of patients with known or suspected valvular heart disease.)

(Level of Evidence: C)

Stressechocardiography (SE)

- Stress echocardiography is the combination of 2D echocardiography with a physical, pharmacological stress. The diagnostic endpoint for the detection of myocardial ischemia is the induction of a transient worsening in regional function during stress.

- Among different stressors of comparable diagnostic and prognostic accuracy:

- Exercise provides a more physiological environment and additional physiological data, such as exercise time and workload, changes in heart rate, blood pressure and ECG. Thus, exercise is the test of choice when feasible.

- Pharmacological test is preferred when there is already a significant resting wall motion abnormality:

- Dobutamine for viability assessment, and/or if the patient is unable to exercise adequately. Until recently, SE relied on inducible wall thickening abnormalities as a marker of ischaemia, but introduction of contrast media increased visuability.

- Dipyridamole is the safest and simplest pharmacological stressor and the most suitable for combined wall motion and coronary flow reserve assessment.

Non_invasive_tests_in_CAD_evaluation_of_patients[1].pptx

ASSOCIATION WITH INCREASED RISK

USEFULNESS IN MOTIVATING PATIENTS OR GUIDING THERAPY

- There is very little information in the literature on the use of stress echocardiography **in asymptomatic individuals for the purposes of cardiovascular risk assessment.** Accordingly, the Class III (LOE: C) recommendation for stress echocardiography reflects a lack of population evidence of this test for risk assessment purposes.

- There are little clinical studies in patients with type 2 diabetes. One small series compared screening with combined exercise ECG and dobutamine SE to a no-screening strategy in 141 patients with type 2 diabetes. The series found that the screening strategy was associated with reduced cardiac events when those with inducible wall motion abnormalities (21%) underwent revascularization.

- There have been no randomized trials on exercise echocardiography to suggest that it can be used **to motivate lifestyle behavior changes in asymptomatic adults**. One small pilot trial in patients with type 2 diabetes, found no clear indication that an exercise echocardiogram can be used to motivate asymptomatic adults or guide their therapy.

STRES MRI
Diagnostic accuracy

- Stress is achieved by the same mechanisms as for other techniques, exercise or pharmacological. The myocardium is imaged during the first pass of a bolus of gadolinium during stress. The normally perfused myocardium enhances with contrast.

- Reversible ischaemia is visually assessed as a reversible low-signal defect in the absence of delayed enhancement. An infarct shows up as an enhancing area as opposed to normal myocardium, which is black or "nulled" on the delayed enhancement sequences with gadolinium.

- A recent meta-analysis confirmed a high sensitivity of 89% and a moderate specificity of 80% for the diagnosis of significant CAD in a population with a high prevalence of CAD of 57%. The value of stress CMR in low-prevalence populations is not clear. False positive tests can be attributed to the presence of artefacts, poor gating and motion artefacts.

Stres MRI

A hypoperfusion defect in the inferior wall on stress MRI.
(b) No hyperfusion defect in the inferior wall on rest images.
(c) Occlusion in the mid-right coronary artery on coronary angiogram.
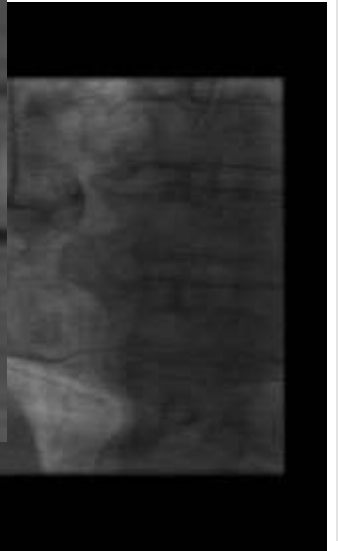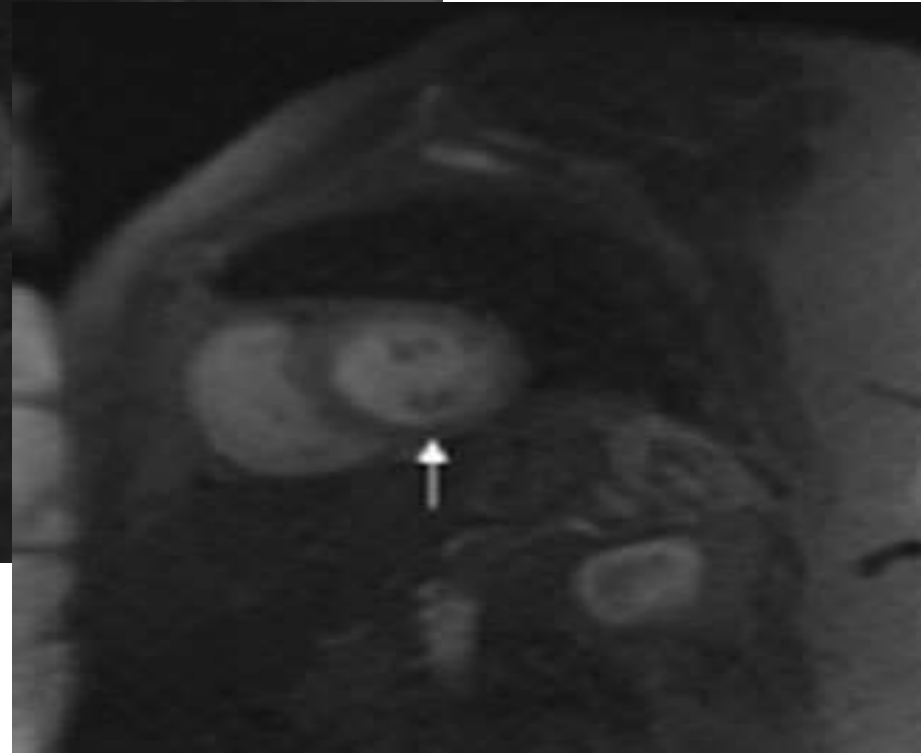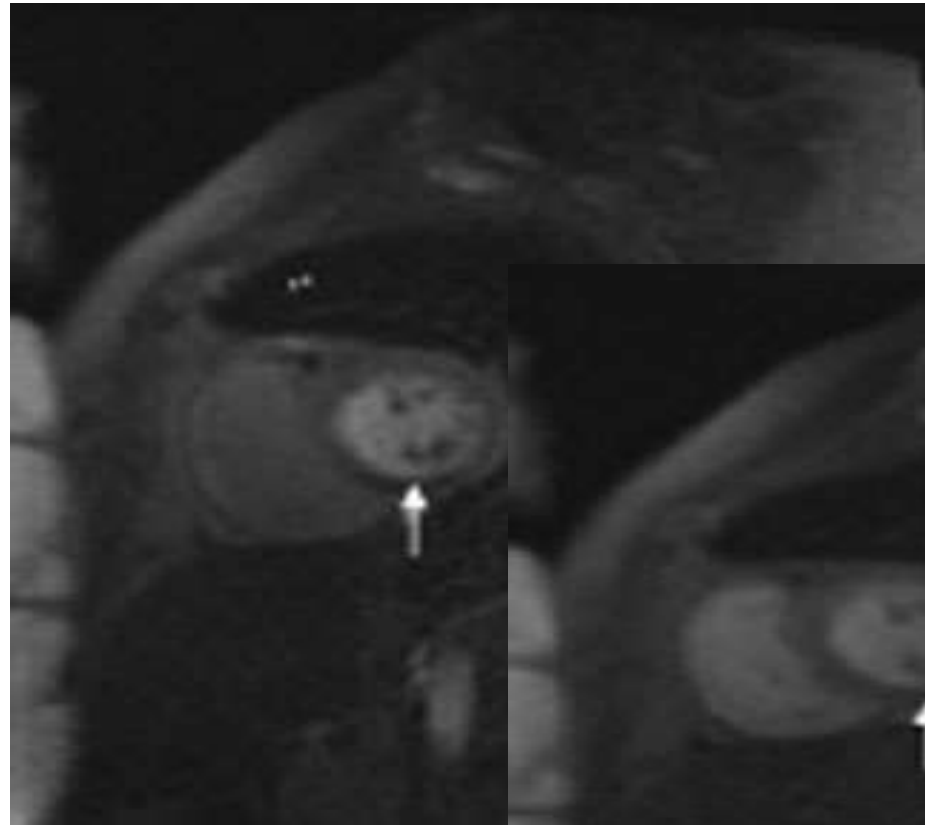
Assessment of cardiac function

- This is considered to be the **gold standard for global and regional left ventricular functional analysis**. It is superior to echocardiography for the following reasons:

  (1) the newer sequence, allows good demarcation of the endocardial border and blood pool contrast; and

  (2) unlike echo, there is no geometric assumption and the LVEF can be calculated with reasonable accuracy even in distorted ventricles

COMPARISON with other imaging modalities

- ## Comparison with SPECT

- A comparison of stress CMR and SPECT in 234 patients in 18 centres worldwide was the basis of the **MR-IMPACT (magnetic resonance imaging for myocardial perfusion assessment in coronary artery disease) trial**. It showed that stress CMR using 0.1 mmol kg –1 gadolinium performed better than SPECT (area under the curve of 0.86 vs 0.67) and that stress MR performed better than SPECT in the diagnosis of multivessel disease. CMR also consistently detects more subendocardial defects than SPECT or PET imaging. Nearly half of the segments with subendocardial infarcts are missed on SPECT and PET.

- ## Comparison with stress echocardiography

- Delayed enhancement CMR has a better negative predictive value than SE, particularly in segments with severe dysfunction. Dobutamine echocardiography has a low sensitivity of 26% in severe left ventricular dysfunction, the very segments whose viability assessment needs to be accurate. This is because contractility depends on the delivery of adequate amount of oxygen to an intact contractile apparatus. In severely dysfunctional segments, ionotropic reserve is hampered owing to an exhausted coronary flow reserve.

Stres MRI

Enhancement in an infarct involving the anterior and anteroseptal walls of the left ventricle on delayed enhancement images on MRI.

- Viability imaging on CMR relies on the demonstration of scar tissue 10–20 min after the administration of gadolinium on the delayed enhancement.

- In a study involving 50 consecutive patients who were imaged before and after revascularisation, Kim et al showed that the extent of the infarct on delayed enhancement sequences predicted functional recovery after revascularisation. **The extent of the infarct was expressed as a percentage of the myocardium that enhanced with contrast.**

- Absence of enhancement and enhancement of more than 75% of myocardium were the best predictors of functional recovery 79+/-36 days after revascularisation.

PET is not using for CAD screening in asymptomatic patient

PET
Positron
emission
tomography

- **PET can be used to assess myocardial perfusion and/or viability.** PET allows acquisition of gated "stress" data during peak hyperemic blood flow with calculation of a peak stress LVEF.

- **RADIOPHARMACEUTICALS:**

- rubidium-82 (Rb-82), nitrogen-13 ammonia (N-13 ammonia) for perfusion,

- F-18 FDG in cardiac PET viability studies.

- **STRESSORS:**

- **Pharmacologic stressors** (adenosine, dipyridamole, and dobutamine have been developed for Rb-82 and N-13 ammonia)

- **Exercise stress** (is possible, but is challenging due to the short half-lives of the radiotracers)

PET

Perfusion + viability + measuring of the absolute myocardial blood flow
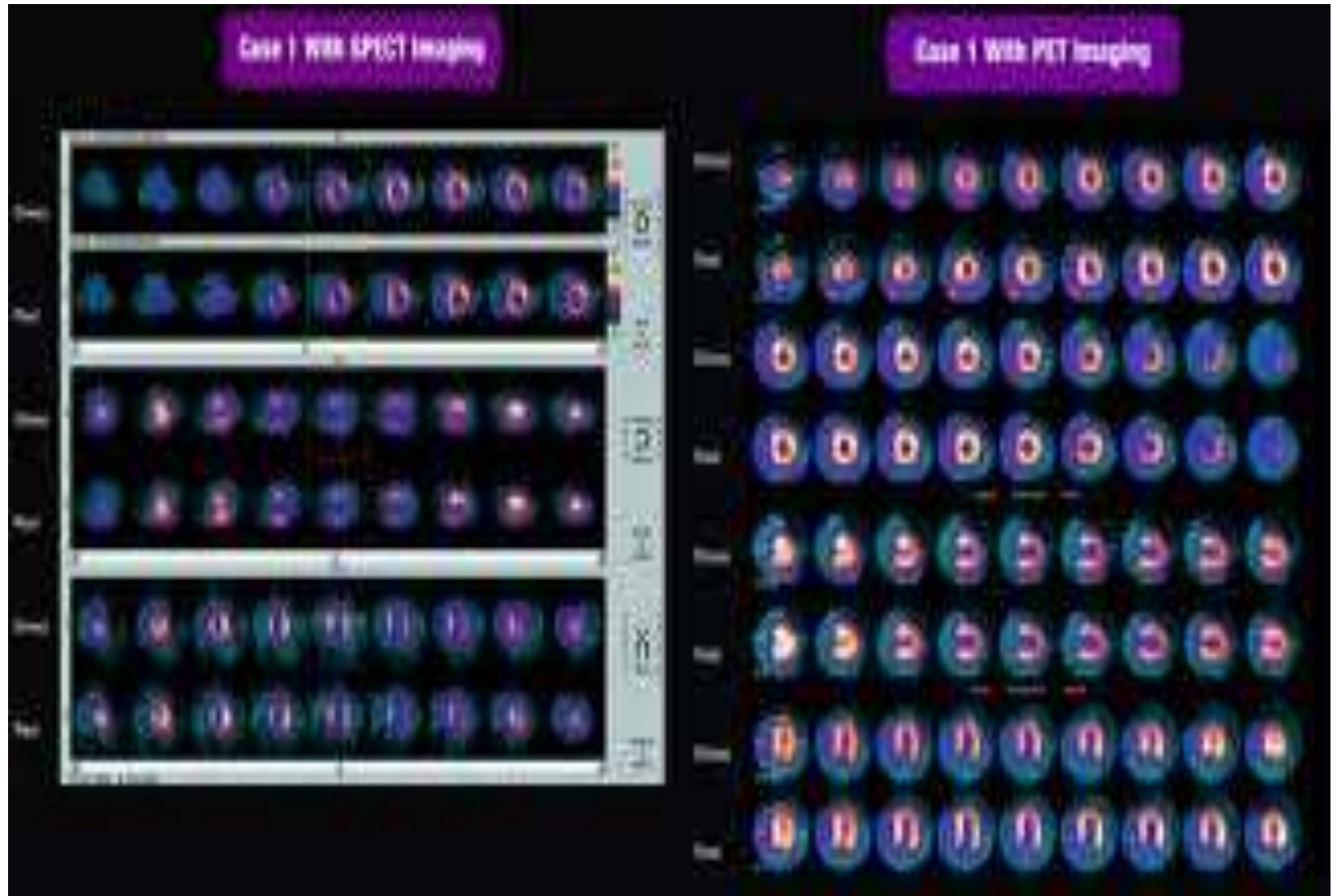
HYBRID TECHNIQUES

MULTIMODALITY IMAGING

- **Hybrid imaging is a novel technique combining functional and anatomical aspects, which holds much promise for future clinical application. The limited evidence available today indicates a higher diagnostic accuracy, as compared with single techniques.**

- CAC scanning may be emerging as the initial test of choice for most asymptomatic patients. The advent of hybrid SPECT-CT and PET-CT scanners may signify an important new opportunity for the combined use of these modalities in the higher-risk asymptomatic patient population.

- With PET/CT systems, customizable CT imaging options include coronary artery calcium scoring (CACS) and/or CT coronary angiography.

- Hybrid SPECT/CT, PET/CT, customizable CT imaging options include coronary artery calcium scoring (CACS) and/or CT coronary angiography.

- As performed with SPECT/PET, fusion of CT angiography (CTA) with perfusion images can create **multi-modality images** integrating anatomy and physiology IN THE SAME STUDY.

- Initial reports also point to the prognostic value of hybrid imaging.

Risk stratification using ischaemia testing

Table 19 Risk stratification using ischaemia testing

Recommendations	Class[a]	Level[b]
Risk stratification is recommended based on clinical assessment and the result of the stress test initially employed for making a diagnosis of SCAD.	I	B
Stress imaging for risk stratification is recommended in patients with a non-conclusive exercise ECG[d]	I	B
Risk stratification using stress ECG (unless they cannot exercise or display ECG changes which make the ECG non evaluable) or preferably stress imaging if local expertise and availability permit is recommended in patients with stable coronary disease after a significant change in symptom level.	I	B
Stress imaging is recommended for risk stratification in patients with known SCAD and a deterioration in symptoms if the site and extent of ischaemia would influence clinical decision making.	I	B
Pharmacological stress with echocardiography or SPECT should be considered in patients with LBBB.	IIa	B
Stress echocardiography or SPECT should be considered in patients with paced rhythm.	IIa	B

Prognostic accuracy of SE in diabetic patients

Table 3—

Stress echocardiographic studies on prognosis in symptomatic patients with diabetes

Year	Author (ref.)	Patients (*n*)	Stressor	Abnormal stress echocardiography (%)	Mean follow-up (months)	Hard event in abnormal stress echocardiography (%/year)	Hard event in normal stress echocardiography (%/year)
2001	Elhendy et al. (48)	563	Exercise	60	36	4.7	1.5
2001	Bigi et al. (70)	259	Dobutamine, dipyridamole	42	24 ± 22	7.9	3
2001	Marwick et al. (46)	937	Exercise, dobutamine	40	3.9 ± 2.3 years	10	4
2001	Sozzi et al. (71)	396	Dobutamine	82	36	6.2	4.8
2003	D'Andrea et al. (72)	325	Dobutamine, dipyridamole	46	34	13.8	4.8

- Data are means ± SD unless otherwise indicated. Hard events include cardiac death or nonfatal myocardial infarction.

Risk ASSESSMENT AND PROGNOSIS WITH IMAGING MODALITIES IN ASYMPTOMATIC DIABETIC PATIENT

Table 2—

Nuclear imaging studies on prognosis in symptomatic patients with diabetes (based on ref. 39)

Year	Author (ref.)	Patients (n)	Tracer	Stressor	Abnormal MPI (%)	Mean follow-up (months)	Hard events in abnormal MPI (%/year)	Hard events in normal MPI (%/year)
1987	Felsher et al. (66)	123	^{201}TL	Exercise	56	36	4.8	1.3
1999	Kang et al. (14)	1,271	^{201}TL, MIBI	Exercise, adenosine	41	24 ± 8	3.9–7.9	1.2
2002	Schinkel et al. (67)	207	MIBI	Dobutamine	64	49 ± 29	6.6*	0.7*
2002	Giri et al. (40)	929	^{201}TL, MIBI	Exercise, adenosine	48	36 ± 18	5.0–6.4	3.6–3.9
2003	Berman et al. (68)	5,333	^{201}TL, MIBI	Adenosine	37–62	27 ± 9	4.7–9.0*	1.8–2.5
2004	Zellweger et al. (59)	911	^{201}TL, MIBI	Exercise, adenosine	44–51	24	5.6–13.2	2.0–3.3
2004	Miller et al. (69)	2,998	^{201}TL, MIBI	Exercise, adenosine, dipyridamole, dobutamine	60	70 ± 42	3.6–5.9	NA

- Data are means ± SD unless otherwise indicated. Hard events include cardiac death or nonfatal myocardial infarction. ^{201}TL, thallium-201 chloride; MIBI, technetium-99m sestamibi; MPI, myocardial perfusion imaging; NA, not available.

CONCLUSION

- Different cardiac imaging modalities provide complementary information about various aspects of CAD.

Although recent ACCF/AHA guidelines suggest that peripheral arterial flow-mediated dilation is not recommended in asymptomatic patients, stress MPI may be considered in asymptomatic patients with diabetes.[24] Conversely, a recent post hoc analysis of the DIAD study showed that patients with intermediate/high risk baseline risk had a low annual cardiac event rate, which was not altered by routine screening for inducible ischemia.[25] The current prospective multicenter study is still in progress and by increasing the number of patients it may give answer to the question if we still need to *combine* different imaging modalities and surrogate markers to identify the high risk asymptomatic patient with type 2 DM.

- An integrated approach combining anatomical and functional imaging is important in guiding treatment options and in risk stratification.

Questions to be solved:

Timing and Frequency of follow-up for Risk Assessment

- There is little information available in the research literature to suggest the <u>optimal timing to initiate risk assessment in adults.</u>

- There is also limited information to inform decisions about <u>frequency of risk assessment</u> in persons who are at low or intermediate risk on initial risk assessment.

- High-risk persons are likely to initiate treatment strategies, and repeat risk assessment is likely to be a standard component of patient follow-up.

- More research on the optimal timing to begin and repeat risk assessment in the asymptomatic patient is warranted.

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