Strategie per la definizione diagnostica delle complicanze cardiovascolari in fase preclinica

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Disclosures

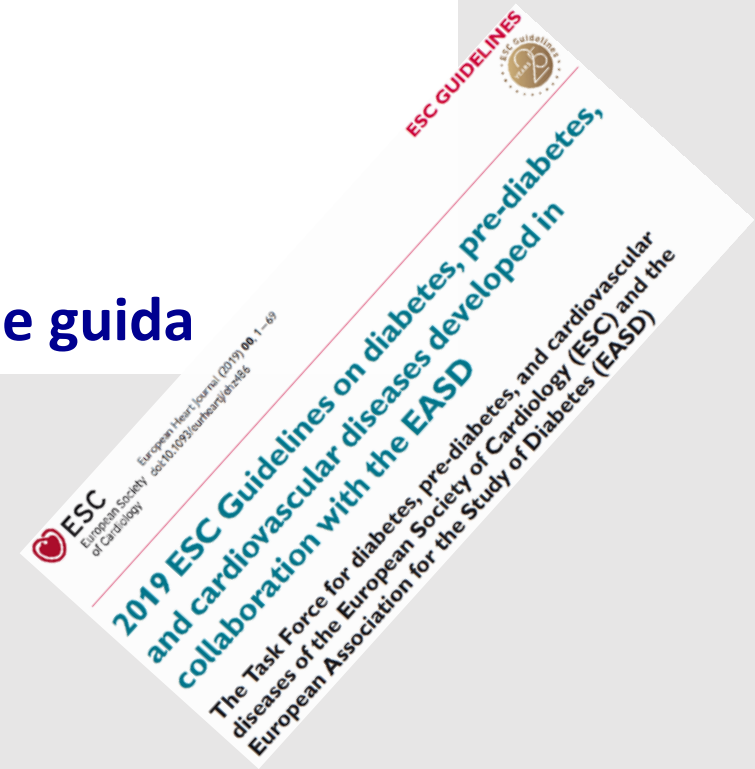
Il dr. Andrea Natali dichiara di aver ricevuto negli ultimi due anni compensi o finanziamenti dalle seguenti Aziende Farmaceutiche e/o Diagnostiche:

- Boehringer Ingelheim
- Lilly

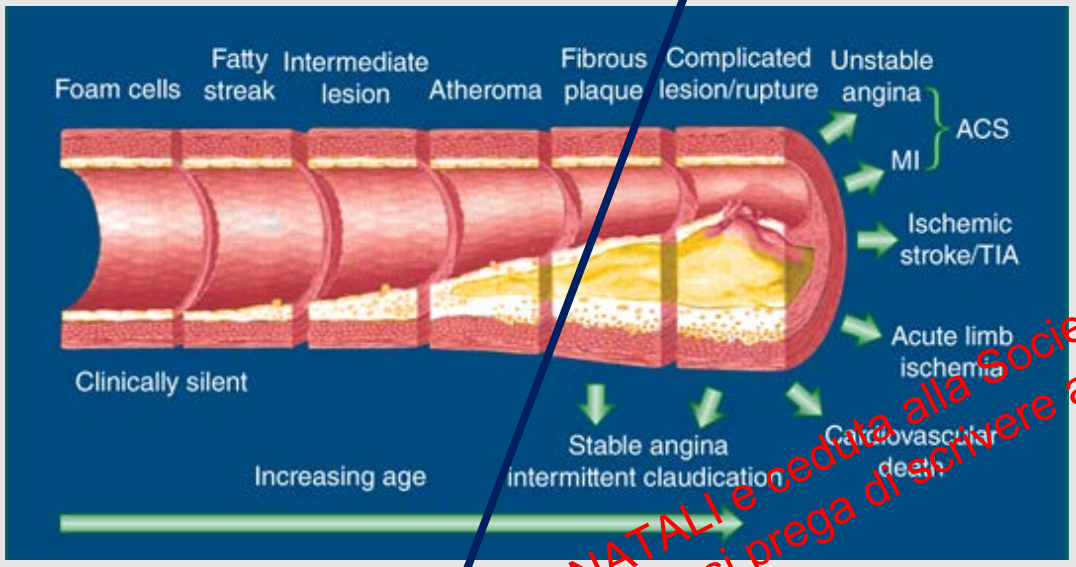
Dichiara altresì il proprio impegno ad astenersi, nell'ambito dell'evento, dal nominare, in qualsivoglia modo o forma, aziende farmaceutiche e/o denominazione commerciale e di non fare pubblicità di qualsiasi tipo relativamente a specifici prodotti di interesse sanitario (farmaci, strumenti, dispositivi medico-chirurgici, ecc.).

Outline

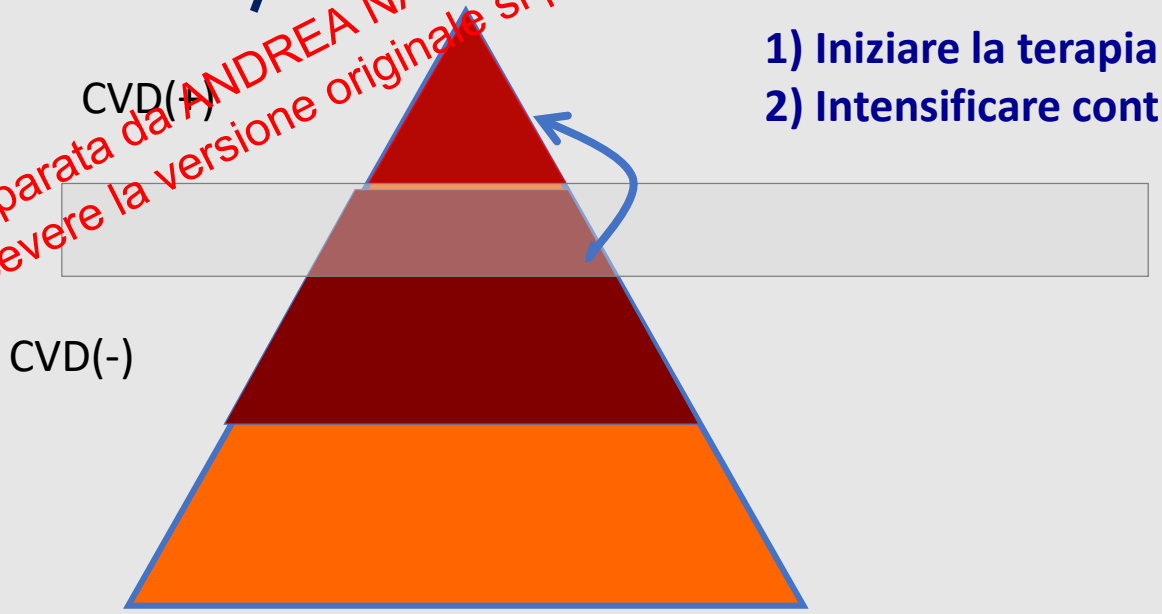
1. Perché cercare le complicanze in fase pre clinica
2. Intercettare lo scompenso cardiaco e la FA
3. Arteriopatia periferica
4. Malattia cerebro vascolare
5. Reverse screening
6. Coronaropatia: cosa dicono le linee guida



1) Perché fare screening ?



1) Iniziare la terapia specifica
2) Intensificare controllo CVRFs



1) Per intensificare la terapia (LDL; ASA&BP?)

Table 7 Cardiovascular risk categories in patients with diabetes[a]

		LDL target	ASA (75-100)
Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)	**<50 mg/dl and ∂≥50%**	**May be if no controind.**
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor	**<70 mg/dl and ∂≥50%**	**May be if no controind.**
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors	**<100 mg/dl**	**Not recommended**

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]
[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.

Recommendations for the use of antiplatelet therapy in primary prevention in patients with diabetes

Recommendations	Class[a]	Level[b]
In patients with DM at high/very high risk,[c] aspirin (75 - 100 mg/day) may be considered in primary prevention in the absence of clear	IIb	A

2013	2019
BP targets	
BP target <140/85 mmHg is recommended for all < 140/85	Individualized BP targets are recommended SBP to 130 mmHg and, if well tolerated, <130 mmHg, but not <120 mmHg In older people (>65 years) target SBP to a range of 130-139 mmHg DBP to <80 mmHg but not <70 mmHg 120 - **130 - 140** **80 - 70**
	On-treatment SBP to <130 mmHg should be considered for patients at high risk of cerebrovascular events or diabetic kidney disease **< 130**

2) Per trattamento euglicemizzante appropriato ?

Table 7 Cardiovascular risk categories in patients with diabetes[a]

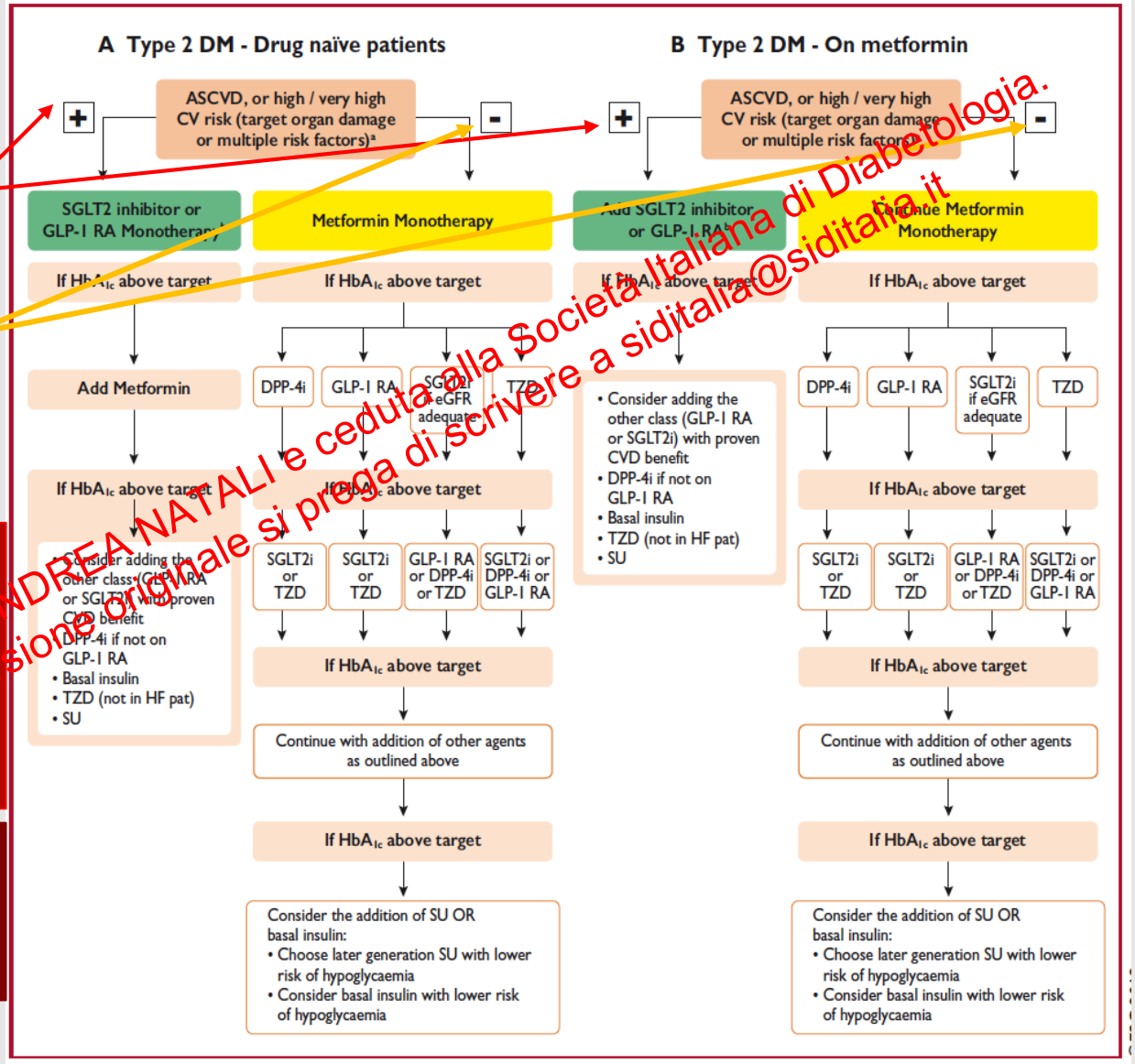
Very high risk	Patients with DM **and** established CVD **or** other target organ damage[b] **or** three or more major risk factors[c] **or** early onset T1DM of long duration (>20 years)
High risk	Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor
Moderate risk	Young patients (T1DM aged <35 years or T2DM aged <50 years) with DM duration <10 years, without other risk factors

© ESC 2019

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; T1DM = type 1 diabetes mellitus; T2DM = type 2 diabetes mellitus.
[a]Modified from the 2016 European Guidelines on cardiovascular disease prevention in clinical practice.[27]
[b]Proteinuria, renal impairment defined as eGFR <30 mL/min/1.73 m^2, left ventricular hypertrophy, or retinopathy.
[c]Age, hypertension, dyslipidemia, smoking, obesity.

CVD or
Proteinuria
eGFR < 30
LVH
Retinopathy
≥3 RFs
T1D >20 yrs dis dur

Dis dur ≥10yrs and
≥1 RF
(HT, Dyslip, Smok, Obesity)

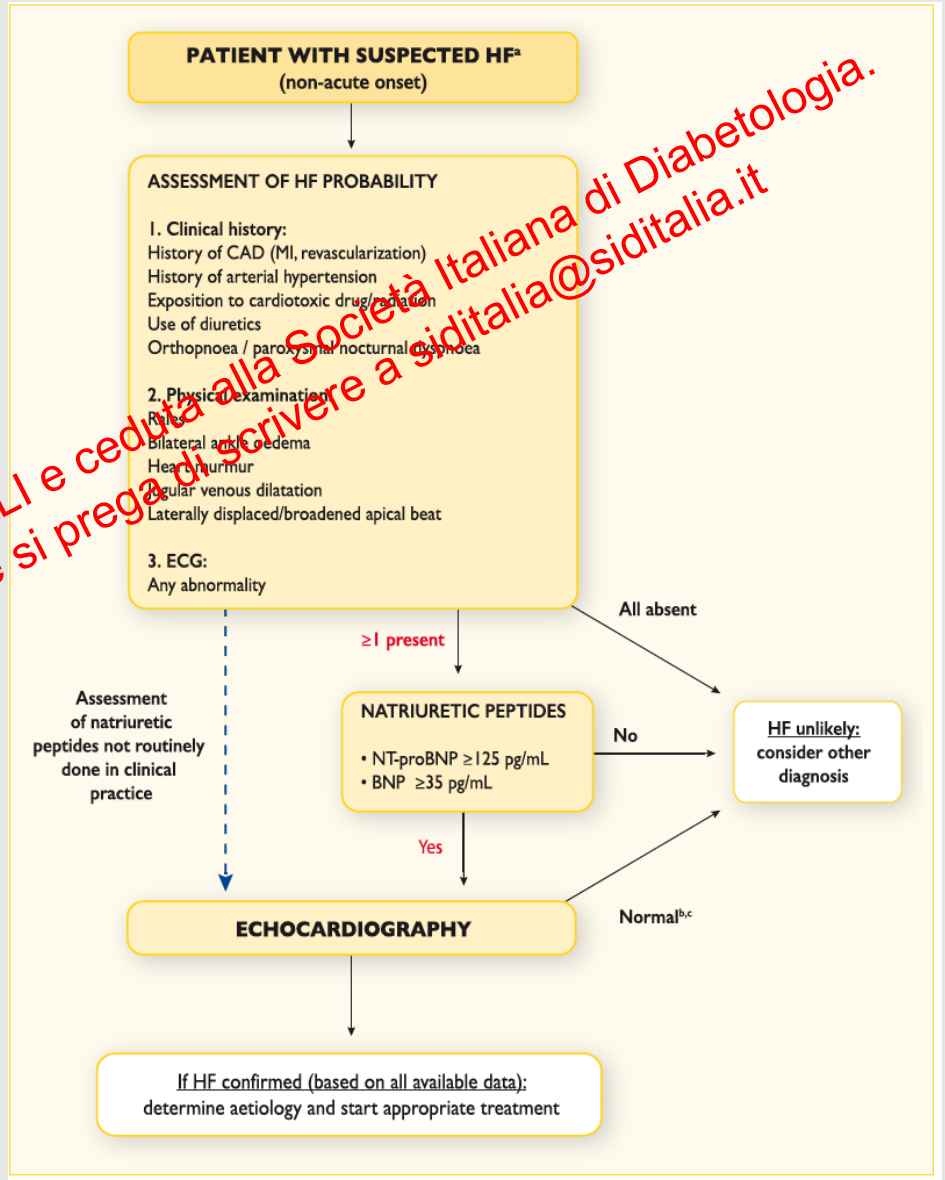


Heart failure screening

Table 4.1 Symptoms and signs typical of heart failure

Symptoms	Signs
Typical	**More specific**
Breathlessness Orthopnoea Paroxysmal nocturnal dyspnoea Reduced exercise tolerance Fatigue, tiredness, increased time to recover after exercise Ankle swelling	Elevated jugular venous pressure Hepatojugular reflux Third heart sound (gallop rhythm) Laterally displaced apical impulse
Less typical	**Less specific**
Nocturnal cough Wheezing Bloated feeling Loss of appetite Confusion (especially in the elderly) Depression Palpitations Dizziness Syncope Bendopnea[53]	Weight gain (>2 kg/week) Weight loss (in advanced HF) Tissue wasting (cachexia) Cardiac murmur Peripheral oedema (ankle, sacral, scrotal) Pulmonary crepitations Reduced air entry and dullness to percussion at lung bases (pleural effusion) Tachycardia Irregular pulse Tachypnoea Cheyne Stokes respiration Hepatomegaly Ascites Cold extremities Oliguria Narrow pulse pressure

HF = heart failure.



Heart failure diagnosis (AF screening)

Table 3.1 Definition of heart failure with preserved (HFpEF), mid-range (HFmrEF) and reduced ejection fraction (HFrEF)

Type of HF		HFrEF	HFmrEF	HFpEF
CRITERIA	1	Symptoms ± Signs[a]	Symptoms ± Signs[a]	Symptoms ± Signs[a]
	2	LVEF <40%	LVEF 40–49%	LVEF ≥50%
	3	–	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).	1. Elevated levels of natriuretic peptides[b]; 2. At least one additional criterion: a. relevant structural heart disease (LVH and/or LAE), b. diastolic dysfunction (for details see Section 4.3.2).

BNP = B-type natriuretic peptide; HF = heart failure; HFmrEF = heart failure with mid-range ejection fraction; HFpEF = heart failure with preserved ejection fraction; HFrEF = heart failure with reduced ejection fraction; LAE = left atrial enlargement; LVEF = left ventricular ejection fraction; LVH = left ventricular hypertrophy; NT-proBNP = N-terminal pro-B type natriuretic peptide.
[a]Signs may not be present in the early stages of HF (especially in HFpEF) and in patients treated with
[b]BNP >35 pg/ml and/or NT-proBNP >125 pg/mL.

Screening for AF by pulse palpation should be considered in patients aged >65 years with DM and confirmed by ECG, if any suspicion of AF, as AF in patients with DM increases morbidity and mortality.[501,513–517]	IIa	C

Key structural alterations

Left Atrial Volume Index (LAVI) > 34 ml/m²

Left Ventricular Mass Index (LVMI) ≥115 g/m² for males and ≥95 g/m² for females

Diastolic dysfunction

E/e' ≥ 13 and a mean e' septal and lateral wall ,9 cm/s

(Longitudinal strain or tricuspid regurgitation velocity)

LEAD screening and diagnosis

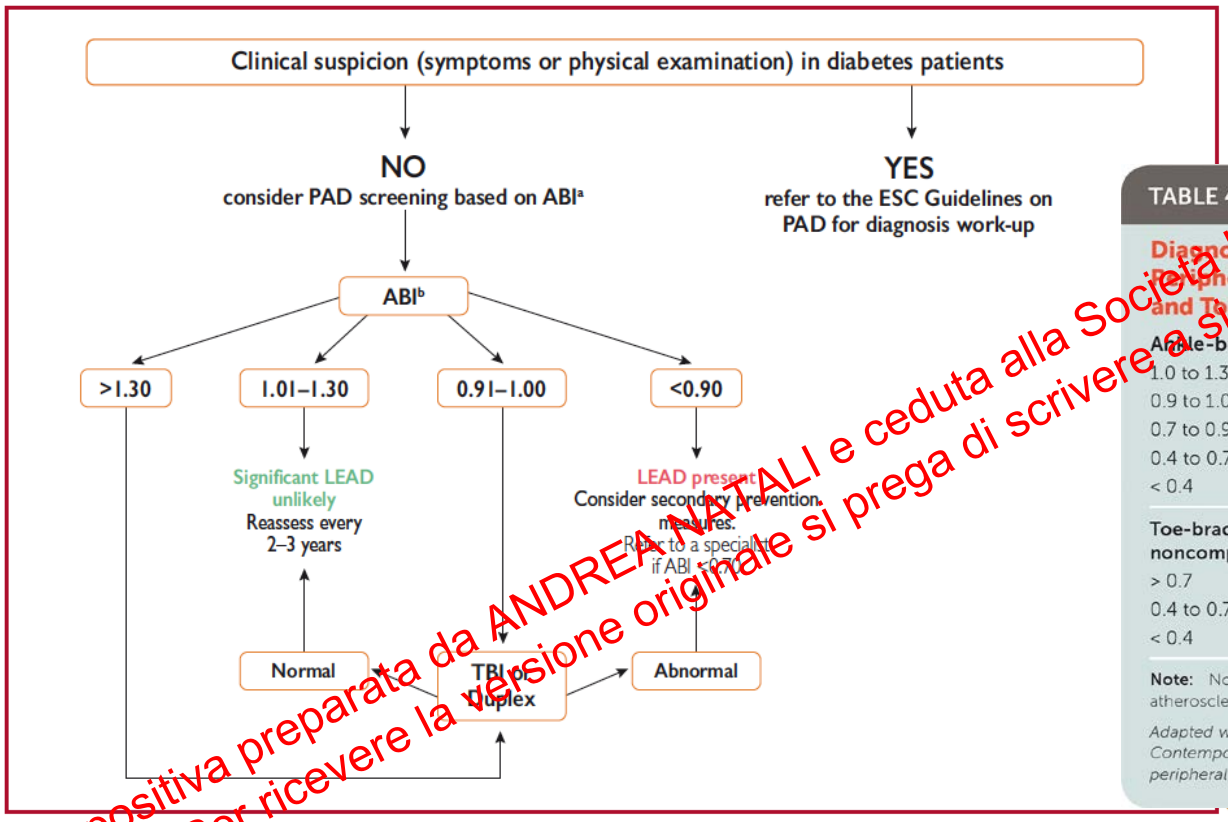


Figure 3 Screening for lower extremity artery disease in patients with diabetes. ABI = ankle–brachial index; DM = diabetes mellitus; ESC = European Society of Cardiology; LEAD = lower extremity artery disease; PAD = peripheral arterial disease; TBI = toe–brachial index. [a]ABI-based screening should be performed once when DM is diagnosed, and then after 10 years of DM if the results from the initial examination were normal (can be considered after 5 years of diagnosis if other risk factors such as smoking exist). Patients should be assessed every year for symptoms and pulses should be checked. ABI-based screening is proposed in the absence of any clinical suspicion of PAD. [b]In case of borderline results (e.g. 0.89), repeat the measurement and average the results to increase accuracy. If TBI is available, this can be done in conjunction with the ABI.

TABLE 4

Diagnostic Criteria for Lower Extremity Peripheral Artery Disease on Ankle- and Toe-Brachial Testing

Ankle-brachial index	
1.0 to 1.3	Normal
0.9 to 1.0	Borderline
0.7 to 0.9	Mild
0.4 to 0.7	Moderate
< 0.4	Severe

Toe-brachial index (used when ankle-brachial index is noncompressible; > 1.3)	
> 0.7	Normal
0.4 to 0.7	Abnormal
< 0.4	Severe

Note: Noncompressible vessel atherosclerosis.

Adapted with permission from Fo Contemporary evaluation and r peripheral artery disease. Heart. 2

Diagnosis and management of PAD

Low-dose rivaroxaban 2.5 mg b.i.d. plus aspirin 100 mg o.d. may be considered in patients with DM and symptomatic LEAD

Cerobrovascular Disease

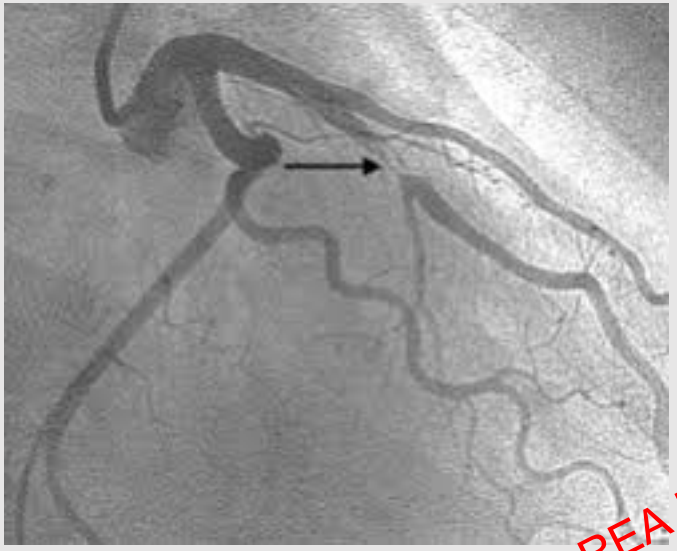
In patients with DM without a history of cerebrovascular disease, there is no evidence that carotid screening improves outcomes and systematic screening is not recommended (ESC-EASD 2019)

Reverse screening (CVD ➢ Diabetes)

13 'What to do' and 'what not to do' messages from the Guidelines

Diagnosis of disorders of glucose metabolism		
Recommendations	**Class[a]**	**Level[b]**
It is recommended that screening for potential T2DM in patients with CVD is initiated with HbA1c and FPG, and that an OGTT is added if HbA1c and FPG are inconclusive.[13–18]	I	A
It is recommended that an OGTT is used to diagnose IGT.[2–4,16–22]	I	A
It is recommended that the diagnosis of DM is based on HbA1c and/or FPG, or on an OGTT if still in doubt.[1–4,9,10,16–22]	I	B

CAD Vediamo le linee guida



ESC European Society of Cardiology
European Heart Journal (2019) 00, 1–69
doi:10.1093/eurheartj/ehz486
ESC GUIDELINES

2019 ESC Guidelines on diabetes, pre-diabetes, and cardiovascular disease developed in collaboration with the EASD

The Task Force for diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD)

Authors/Task Force Members: Francesco Cosentino* (ESC Chairperson) (Sweden), Peter J. Grant* (EASD Chairperson) (United Kingdom), Victor Aboyans (France), Clifford J. Bailey[1] (United Kingdom), Antonio Ceriello[1] (Italy), Victoria Delgado (Netherlands), Massimo Federici[1] (Italy), Gerasimos Filippatos (Greece), Diederick E. Grobbee (Netherlands), Tina Birgitte Hansen (Denmark), Heikki V. Huikuri (Finland), Isabelle Johansson (Sweden), Peter Jüni (Canada), Maddalena Lettino (Italy), Nikolaus Marx (Germany), Linda G. Mellbin (Sweden), Carl J. Östgren (Sweden), Bianca Rocca (Italy), Marco Roffi (Switzerland), Naveed Sattar[1] (United Kingdom), Petar M. Seferović (Serbia), Miguel Sousa-Uva (Portugal), Paul Valensi (France), David C. Wheeler[1] (United Kingdom)

Asymptomatic CAD (ESC-EASD 2019)

Screening for asymptomatic CAD in patients with DM remains controversial. With computed tomography (CT), non-invasive esti-

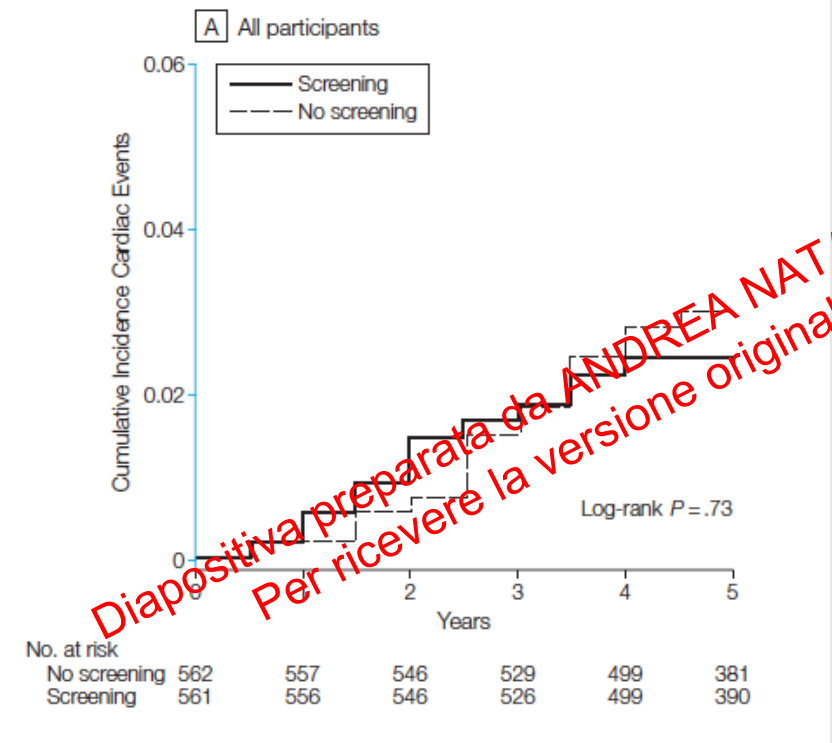
Table 8 Overview of randomized controlled trials

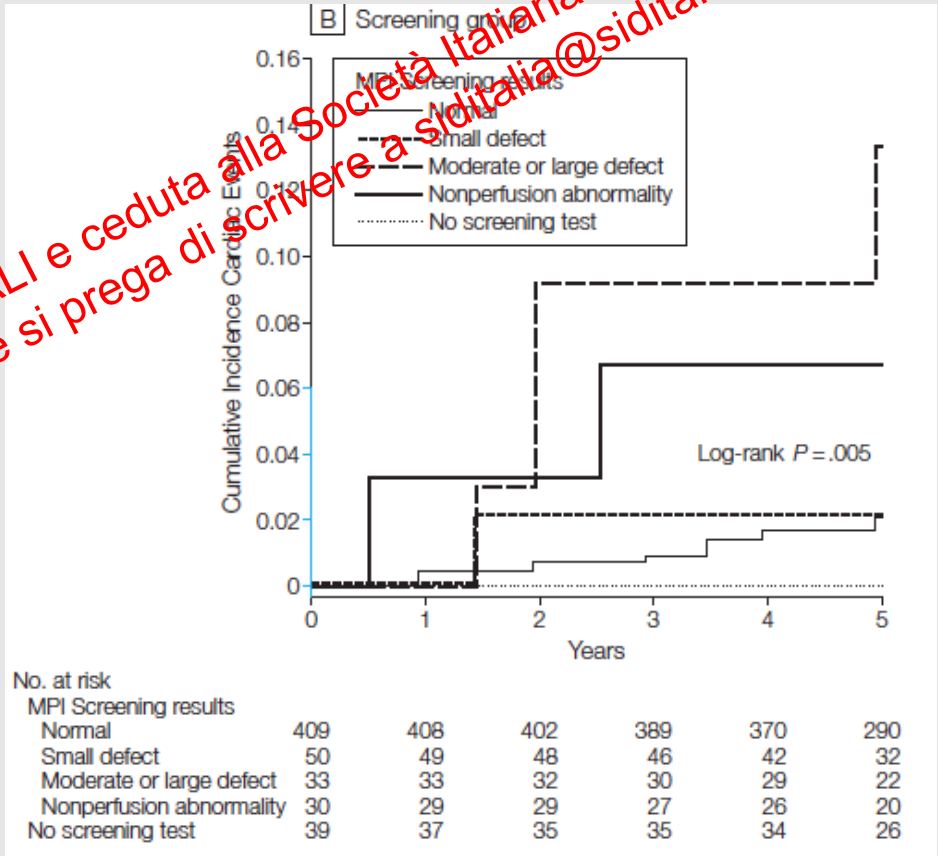
Study/author	Faglia et al.[69]	DIAD[68]	DYNAMIT[64]	FACTOR-64[67]	DADDY-D[70]
Year of publication	2005	2009	2011	2014	2015
Patients (*n*)	141 (+1)[a]	1123	615	899	520
Inclusion criteria	T2DM	T2DM	T2DM	T1DM or T2DM	T2DM
	45–76 years	50–75 years	50–75 years	♂ aged ≥50 years/ ♀ aged ≥55 years, DM for ≥3 years	50–75 years
	≥2 other CVRFs		≥2 other CVRFs	♂ aged ≥40 years/ ♀ aged ≥45 years, DM for ≥5 years	CV risk ≥10%
					Sinus rhythm
					Able to do EET
Mean age (years)	60.1	60.8	63.9	61.5	61.9
Male sex (%)	55.6	53.5	54.5	52.2	80.0
Screening test	EET and SE	MPI	EET or MPI	CTCA and CAC score	EET
Positive screening test (%)	21.1	5.9 moderate or large defects	21.5 positive or uncertain	11.9 moderate; 10.7 severe	7.6
Treatment strategy	ICA and cardiac follow-up if any test was positive	At the referring physician's discretion	According to the cardiologist's decision	Recommendation based on stenosis severity and CAC score	ICA if EET positive
ICA performed after positive test (%)	93.3	15.2	55.9	47.3	85.0
Mean follow-up (years)	4.5	4.8	3.5	4.0	3.6
Annual rate of major CEs (%)	1.9	0.6	1.0	0.8	1.4
Main results of screening	Significant ↓ of major and all CEs	Non-significant ↓ of major CEs	Non-significant ↓ of MI; no effect on combined CEs	Non-significant ↓ of combined CEs	Non-significant ↓ of major CEs, but significant ↓ in those aged >60 years

DIAD study

N=610 No screening

N= 510 screening (MPS ADO+EX): 21% Pos; 4.4% angio; 1.4% rivasc





Asymtomatic CAD (ESC-EASD 2019)

Accordingly, routine screening of CAD in asymptomatic DM is not recommended.

However, stress testing or CTCA may be indicated in very high-risk asymptomatic individuals [with PAD, a high CAC score (>400), proteinuria (?), or renal failure (<30)]

Recommendations for the use of laboratory, electrocardiogram, and imaging testing for cardiovascular risk assessment in asymptomatic patients with diabetes

Recommendations	Class[a]	Level[b]
Routine assessment of microalbuminuria is indicated to identify patients at risk of developing renal dysfunction or at high risk of future CVD.[27,38]	I	B
A resting ECG is indicated in patients with DM diagnosed with hypertension or with suspected CVD.[38,39]	I	C
Assessment of carotid and/or femoral plaque burden with arterial ultrasonography should be considered as a risk modifier in asymptomatic patients with DM.[60–62]	IIa	B
CAC score with CT may be considered as a risk modifier in the CV risk assessment of asymptomatic patients with DM at moderate risk.[63]	IIb	B
CTCA or functional imaging (radionuclide myocardial perfusion imaging, stress cardiac magnetic resonance imaging, or exercise or pharmacological stress echocardiography) may be considered in asymptomatic patients with DM for screening of CAD.[47,48,64,65,67–70]	IIb	B
ABI may be considered as a risk modifier in CV risk assessment.[76]	IIb	B
Detection of atherosclerotic plaque of carotid or femoral arteries by CT, or magnetic resonance imaging, may be considered as a risk modifier in patients with DM at moderate or high risk CV.[c] [75,77]	IIb	B
Carotid ultrasound intima–media thickness screening for CV risk assessment is not recommended.[62,73,78]	III	A
Routine assessment of circulating biomarkers is not recommended for CV risk stratification.[27,31,35–37]	III	B
Risk scores developed for the general population are not recommended for CV risk assessment in patients with DM.	III	C

ABI = ankle–brachial index; CAC = coronary artery calcium; CAD = coronary artery disease; CT = computed tomography; CTCA = computed tomography coronary angiography; CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus; ECG = electrocardiogram.

Asymptomatic CAD (ADA 2018)

1) **In pazienti asintomatici lo screening per CAD non è raccomandato dal momento che non migliora l'outcome allorquando i FR vegano trattati aggressivamente. (BARI 2D, COURAGE, DIAD). A**

2) Fate indagini per CAD se

a) sono presenti sintomi (dispnea non spiegata, precordialgie)

b) segni e sintomi di MV (soffi carotidei, TIA, stroke, claudicatio, ECG anormale). E

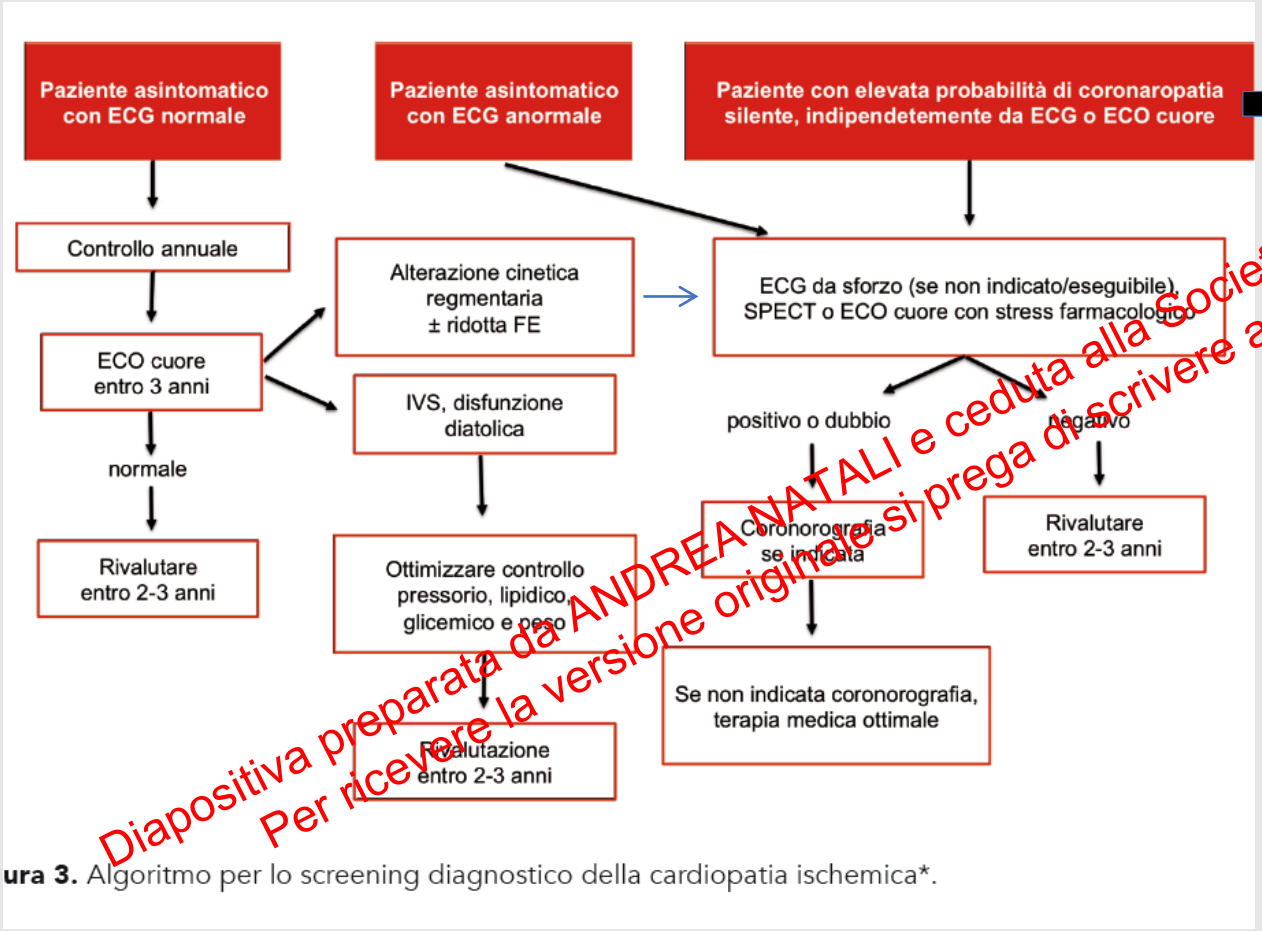
- Test iniziale: ECG da sforzo con o senza eco, se ≥ 40 aa anche CAC

- Test di secondo livello: Scintigrafia o ECO stress se ECG bas. alterato (BB, ST-T) o se non possibile esercizio.

Sebbene l'angio TC sia in grado di predirre gli eventi cardiaci in p. sintomatici (1) il vantaggio di questo approccio (costo/beneficio) in p. asintomatici non è dimostrato.

1) Hadamitzky M, Diabetes Care 2010

Asymptomatic CAD (SID 2018)



ura 3. Algoritmo per lo screening diagnostico della cardiopatia ischemica*.

Macroangiopatia non coronarico avanzata/molto avanzata

Sintomatica

- Precedenti eventi aterotrombotici
- Interventi di rivascolarizzazione

Non sintomatica

- Arteriopatia periferica con ABI <0,9
- Stenosi carotidea asintomatica >50%
- Aneurisma aortico

Score di rischio coronarico (UKPDS) >30% a 10 anni

Score di rischio coronarico (UKPDS) >20% a 10 anni + almeno <u>uno</u> dei seguenti:

- Placche ateromasiche determinanti stenosi ≥20%
- GFR <30 ml/min per 1,73 m²
- Neuropatia autonomica cardiaca
- Disfunzione erettile
- Familiarità di 1° grado positiva per cardiopatia ischemica in giovane età (<55 anni maschi; <65 anni femmine)

Score di rischio coronarico (UKPDS) >20% a 10 anni + almeno <u>due</u> dei seguenti: ≤

- GFR <30 ml/min per 1,73 m²
- Micro- o macroalbuminuria
- Retinopatia laser-trattata/proliferante

My way

Primary screening

Reverse screening

Convinco i cardiologi
HbA1 in all patients

Cerco i sintomi
CAD, LEAD, CVD & FA, CVD

Cerco i segni
CAD, LEAD, CVD & FA, CVD

Misuro/verifico
Smoking
BP, HR
ECG (US)
Retina
AlbU
Lipids
eGFR

Secondary screening/diagnosis

Se sospetto malattia

CAD: CTCA or EET or MPI
HF: BNP, Echocardiography
LEAD: ABI, US
FA: 24/48h-ECG
CVD: Carotid US, 24h-ECG, TC

Se high/very-high risk

Carotid US (>2 mm), ABI, CAC (or EET)

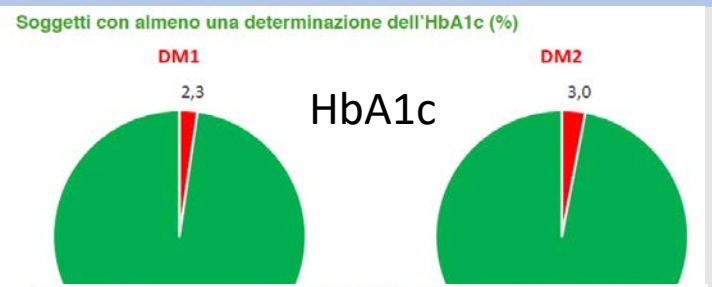
Se moderate risk

Follow-up

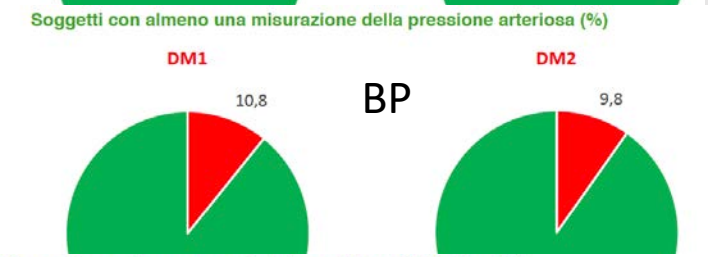
Referr to specialist

Intensify/Revise theraphy

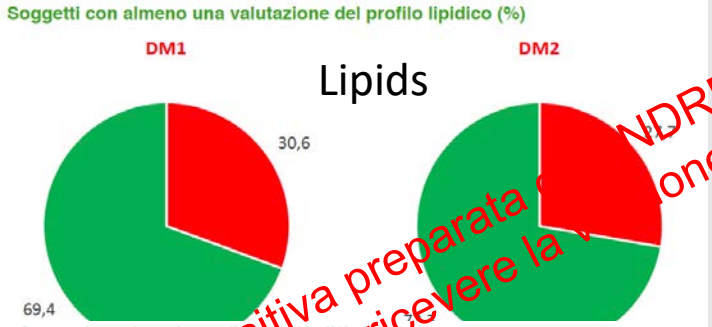
Real world



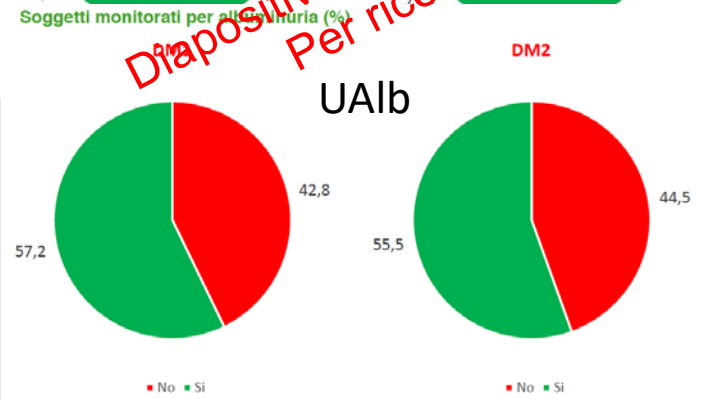
HbA1c



BP

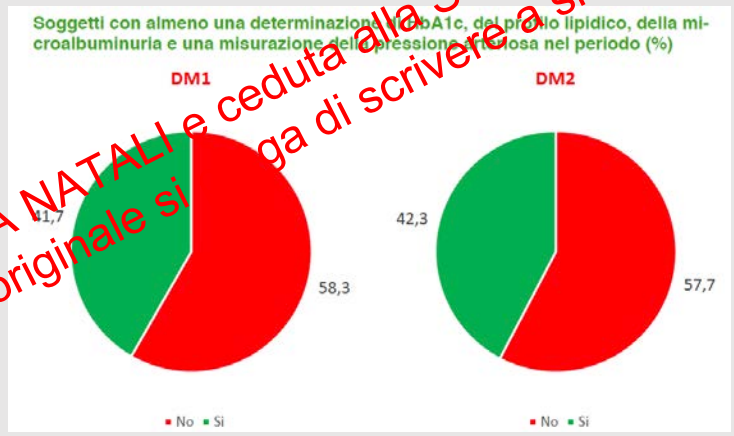


Lipids

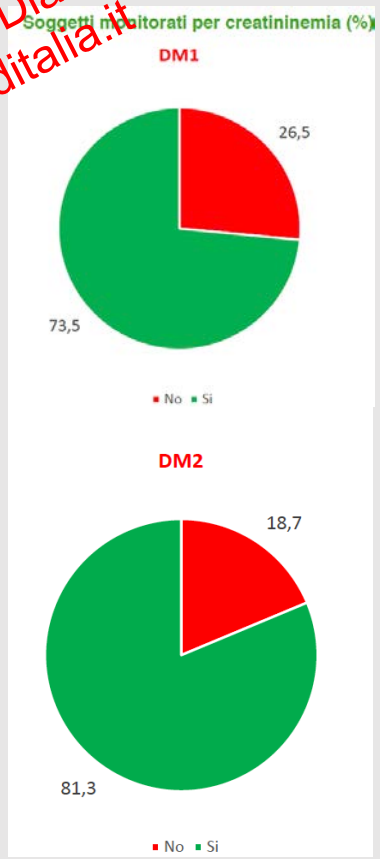


UAlb

HbA1c BP Lipids UAlb



Creatinine

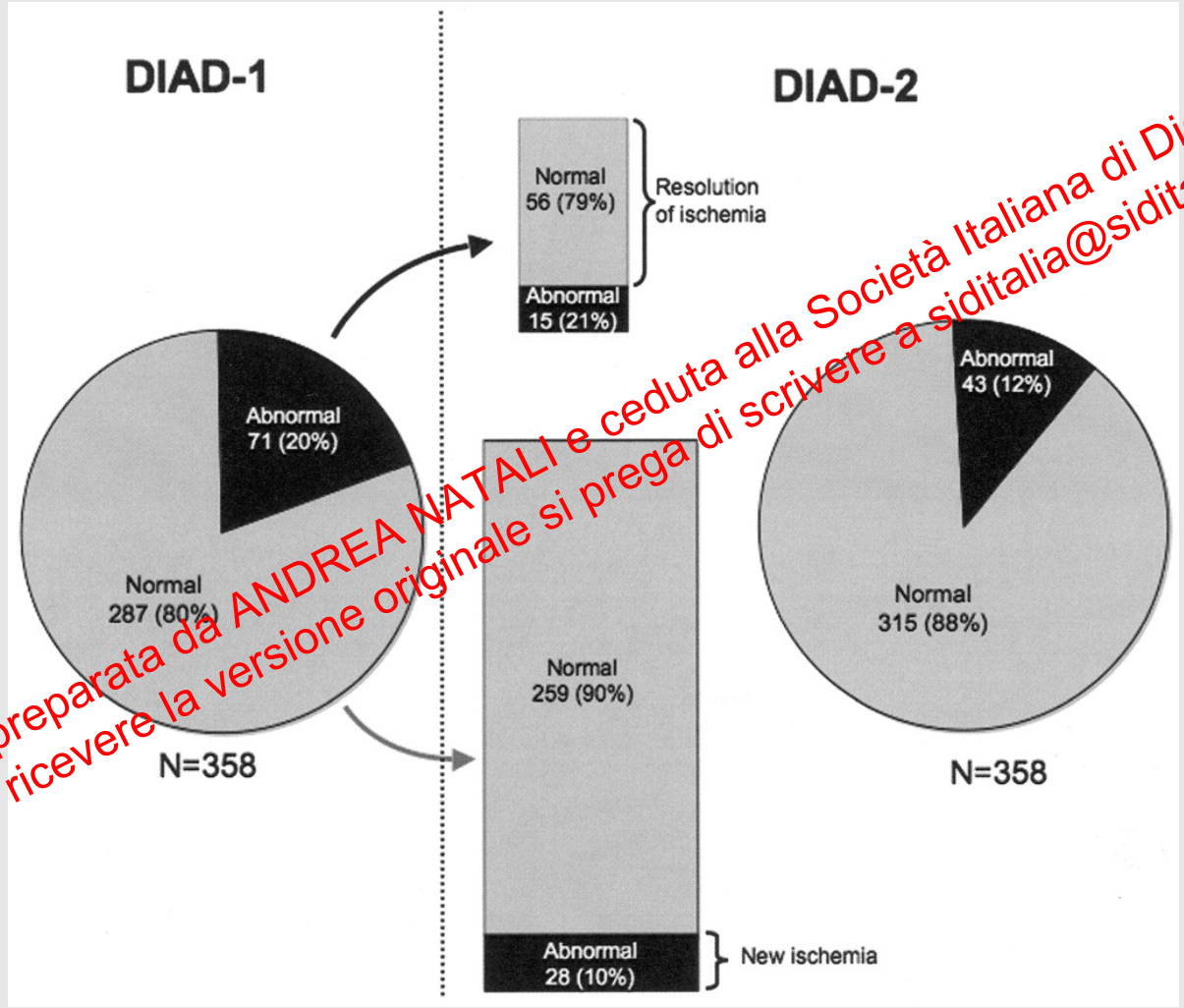


Open questions

- **Definition of proteinuria**
- **Gender**
- **Ethnicity**
- **Carotid plaque definition and characterization**
- **CAC < 100 to exclude or CAC > 400 to suspect ?**
- **What exactly is a risk modifyer ?**
- **Cost effectivenes**

Scintigrafia

ASA	42%
STAT	38%
ACE	34%



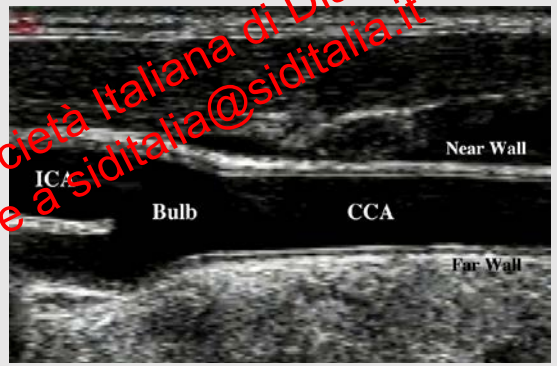
ASA	69%
STAT	59%
ACE	42%

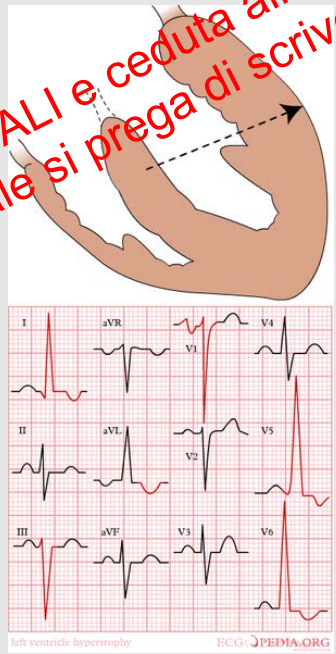
Fattori di rischio non classici ed imaging

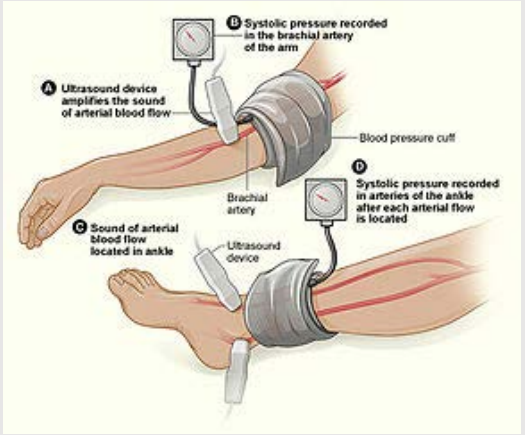
Fattori di rischio non classici

BMI
waist-to-hip ratio
heart rate
sport activity
residual FEV_1
Keys score
cigarette packs-years
creatinine
lipoprotein(a)
apolipoprotein AI
apolipoprotein B
albumin
fibrinogen
factor VII
WBC
factor VIII
von Willebrand factor
multiple risk factors†

Imaging indiretto

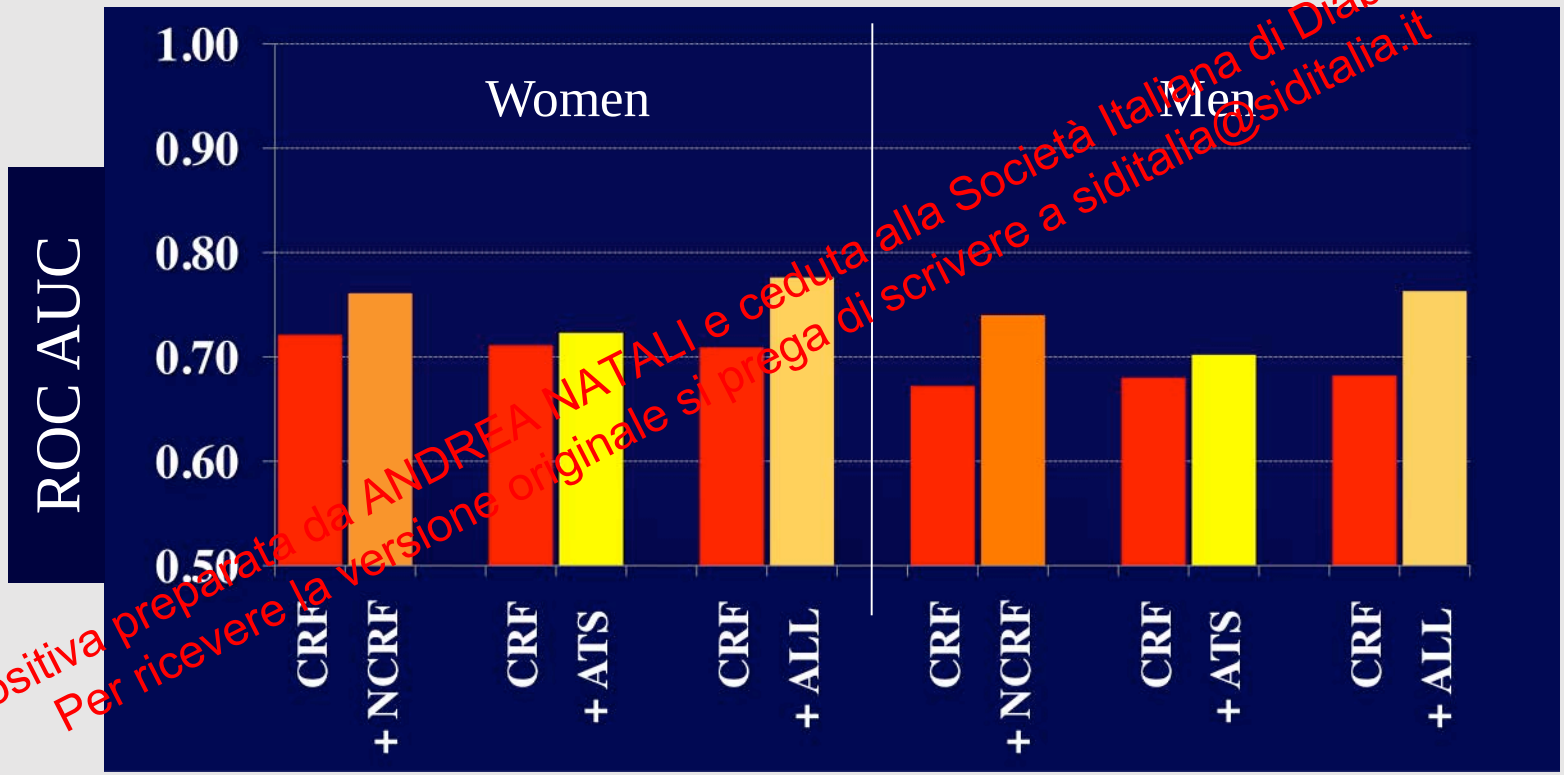






Rivediamo le linee guida

ARIC study. 1,500 asymptopmatic type 2 diabetics FU 10 yrs, 225 <u>first</u> CHD events



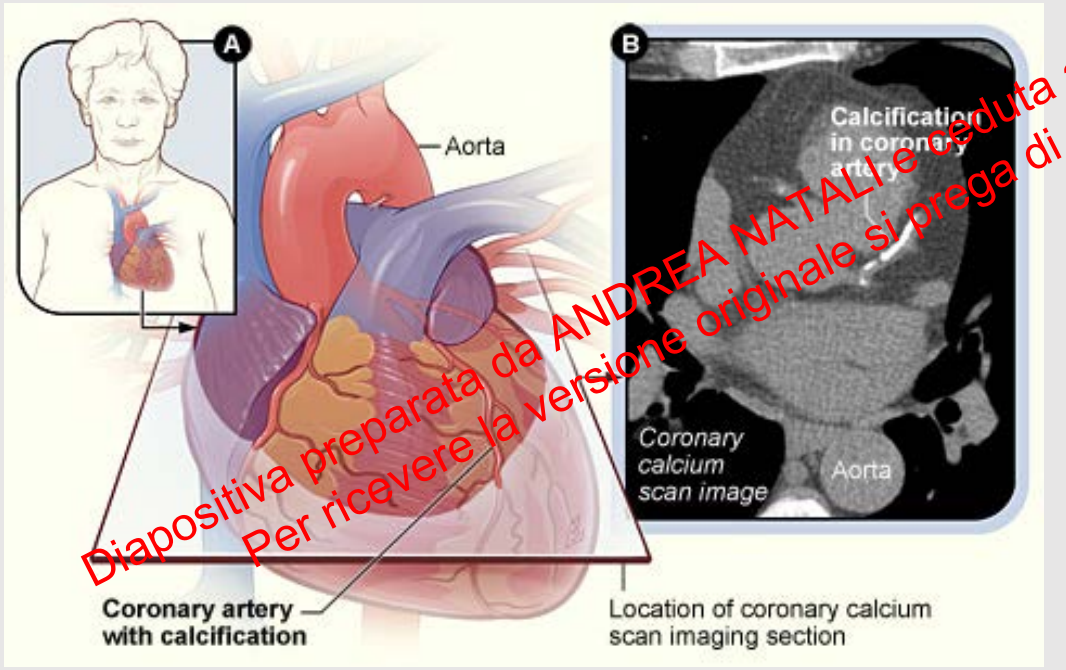
NCRF = BMI, waist-to-hip ratio, lipoprotein(a), albumin, creatinine, WBC, fibrinogen, factor VIII, sport activity, Keys score, and pack-years

ATS = ECG LVH, IMT (ABI)

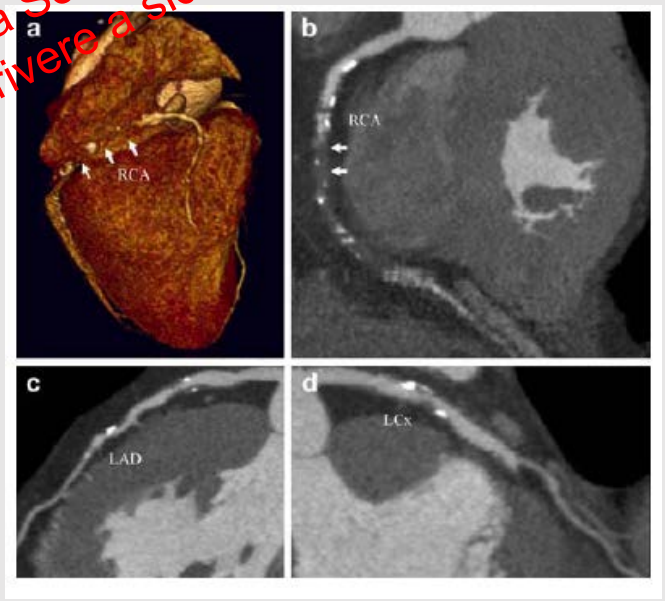
Folsom A, Diab Care 2003

Imaging diretto

CAC scores



MSCT angiography



CCS and CCTA in asymptomatic Pts

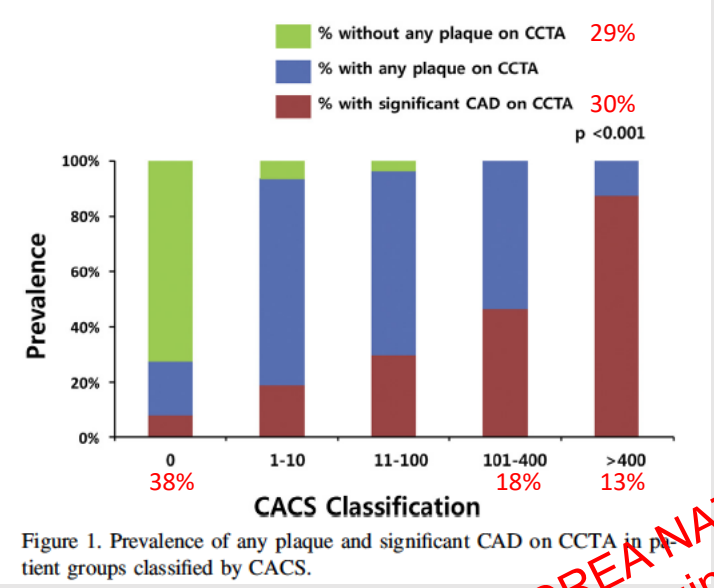


Figure 1. Prevalence of any plaque and significant CAD on CCTA in patient groups classified by CACS.

Indep predictors of signif CAD:

Age
Diab duration
Family history of premature CAD
Previous stroke
Higher UKPDS 10-year risk scores
Neuropathy
Retinopathy

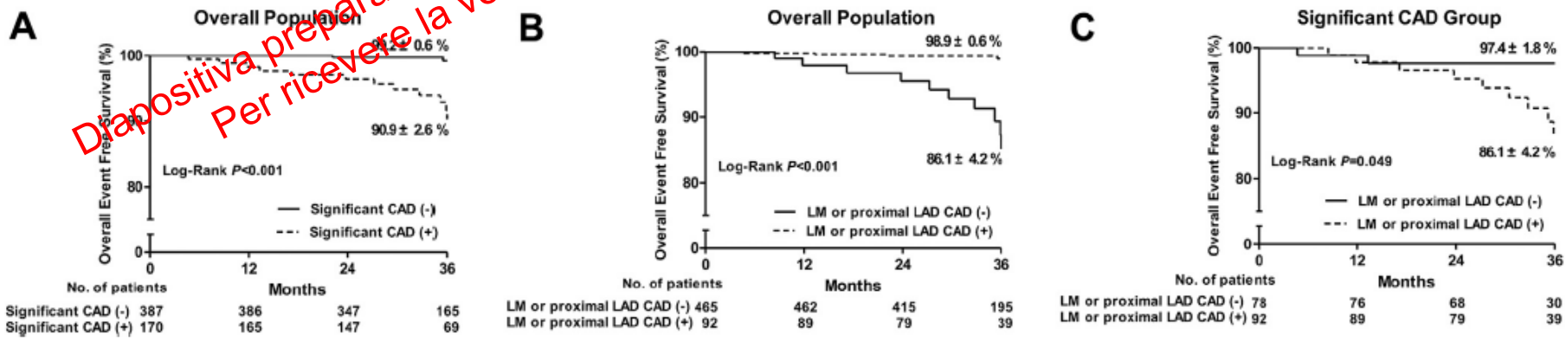
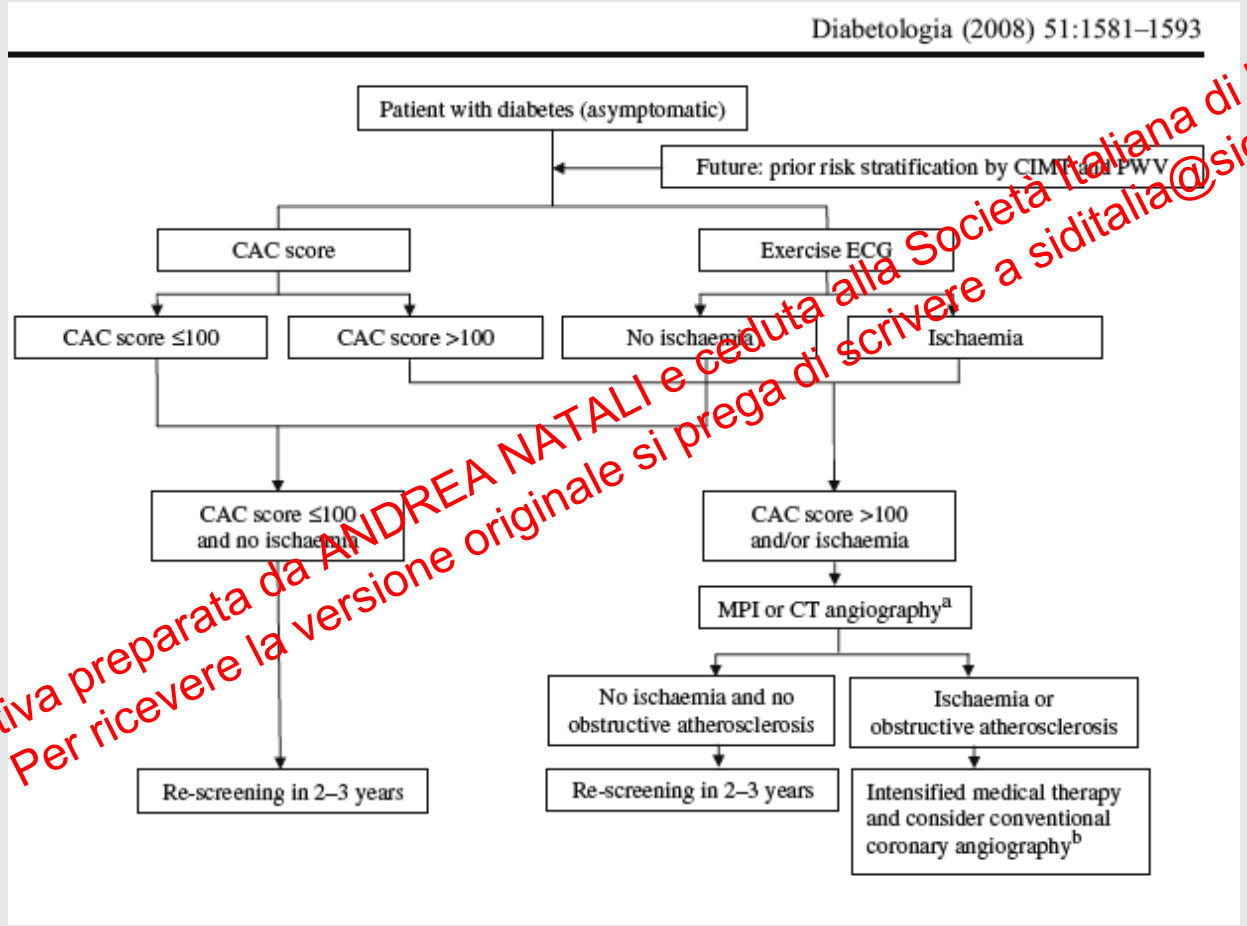


Figure 2. Kaplan-Meier event-free survival curves of 3-year cardiac event outcomes. The numbers in each figure represent the 3-year event-free survival rates.

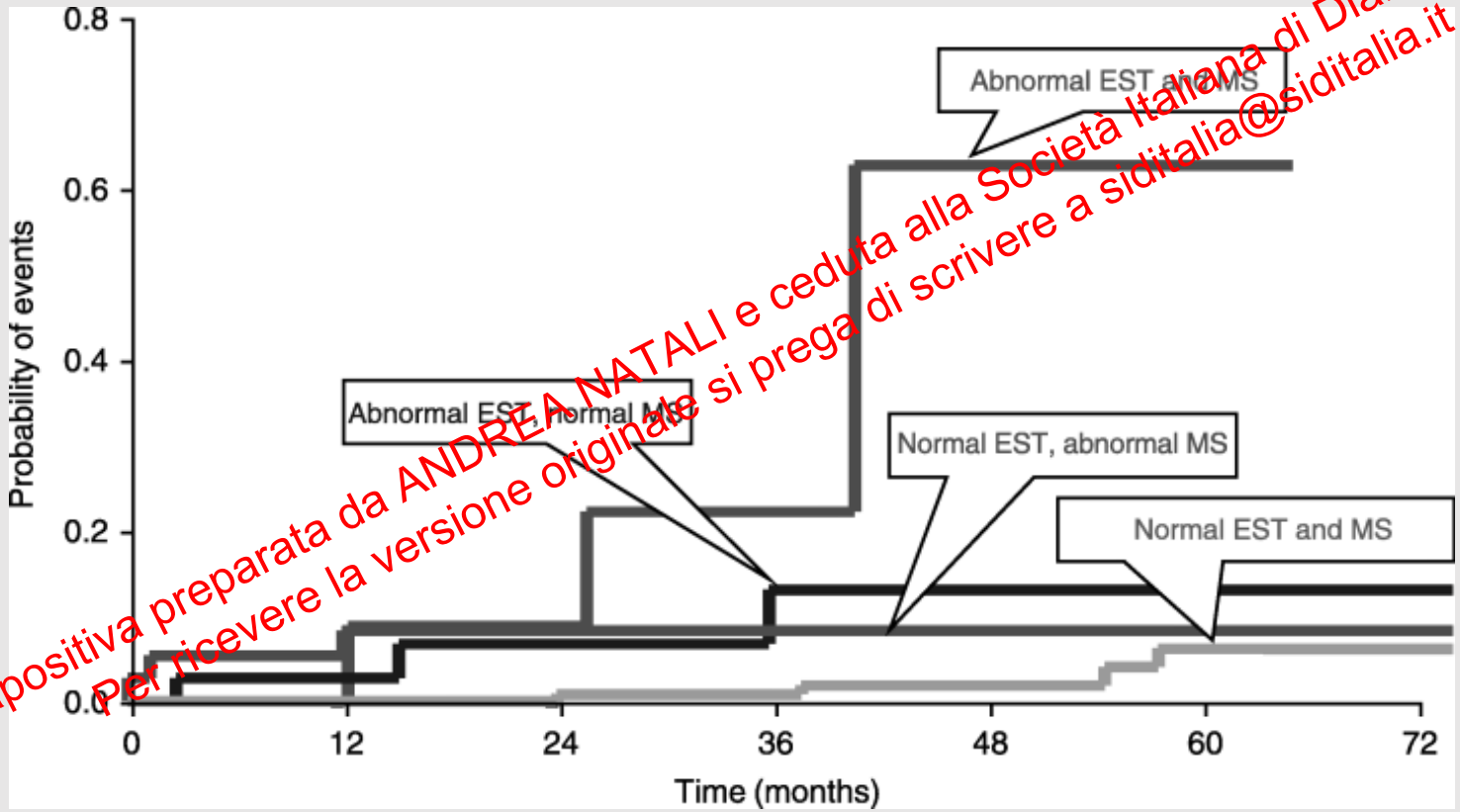
Algoritmo



E’ meglio l’ECG da sforzo o la scintigrafia ?

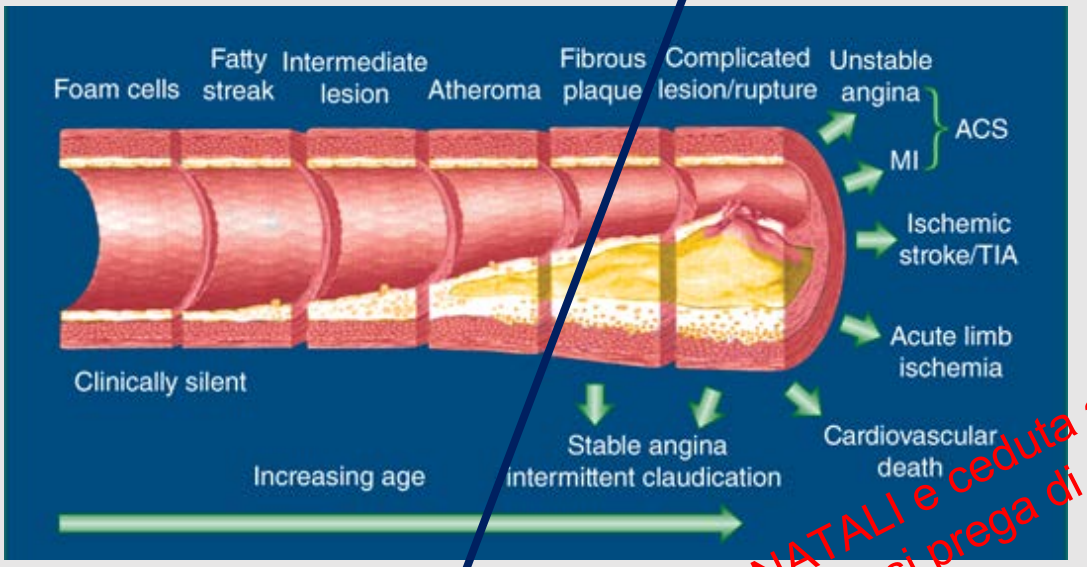
Cosson E, Diabetic Medicine 2004

262 IDDM&NIDDM asintomatici



L’ECG da sforzo ha un ottimo valore predittivo negativo

1) Per intensificare la terapia ?



C	
IIa	An HbA1c target of <7.0% (or <53 mmol/mol) should be considered for the prevention of macrovascular complications in individuals with DM.

Recommendations for lifestyle modifications in patients with diabetes and pre-diabetes

Recommendations	Class[a]	Level[b]
Smoking cessation guided by structured advice is recommended in all individuals with DM and pre-DM.[27,117]	I	A
Lifestyle intervention is recommended to delay or prevent the conversion of pre-DM states, such as IGT, to T2DM.[85,86]	I	A
Reduced calorie intake is recommended for low-energy, excessive body weight in individuals with pre-DM and DM.[22,89,90]	I	A
Moderate to vigorous physical activity, notably a combination of aerobic and resistance exercise, for ≥150 min/week is recommended for the prevention and control of DM, unless contraindicated, such as when there are severe comorbidities or a limited life expectancy.[d 110,111–113,119]	I	A
A Mediterranean diet, rich in polyunsaturated and monounsaturated fats, should be considered to reduce CV events.[96,97]	IIa	B
Vitamin or micronutrient supplementation to reduce the risk of DM, or CVD in patients with DM, is not recommended.[79,120]	III	B

2013	2019
BP targets	
BP target <140/85 mmHg is recommended for all	Individualized BP targets are recommended SBP to <130 mmHg and, if well tolerated, <130 mmHg, but not <120 mmHg In older people (>65 years) target SBP to a range of 130-139 mmHg DBP to <80 mmHg but not <70 mmHg
	On-treatment SBP to <130 mmHg should be considered for patients at high risk of cerebrovascular events or diabetic kidney disease

In patients with T2DM at moderate CV risk,[c] an LDL-C target of <2.6 mmol/L (<100 mg/dL) is recommended.[210–212]	I	A
In patients with T2DM at high CV risk,[c] an LDL-C target of <1.8 mmol/L (<70 mg/dL) and LDL-C reduction of at least 50% is recommended.[d 210–212]	I	A
In patients with T2DM at very high CV risk,[c] an LDL-C target of <1.4 mmol/L (<55 mg/dL) and LDL-C reduction of at least 50% is recommended.[d 200,201,210]	I	B
In patients with T2DM, a secondary goal of a non-HDL-C target of <2.2 mmol/L (<85 mg/dL) in very high CV-risk patients, and <2.6 mmol/L (<100 mg/dL) in high CV-risk patients, is recommended.[d,213,214]	I	B