DIABETES AND CHRONIC CORONARY ARTERY DISEASE

ΓΙΩΡΓΟΣ ΜΑΚΑΒΟΣ
ΚΑΡΔΙΟΛΟΓΟΣ
ΑΚΑΔΗΜΑΙΚΟΣ ΥΠΟΤΡΟΦΟΣ
Β’ ΠΑΝ.ΚΑΡΔΙΟΛΟΓΙΚΗ ΚΛΙΝΙΚΗ
Γ.Π.Ν.«ΑΤΤΙΚΟΝ»
DM Definition, Classification

- **DM** is a condition defined by an elevated level of blood glucose.
- **Type 1 diabetes**: deficiency of insulin due to destruction of pancreatic beta-cells.
- **Type 2 diabetes**: a combination of *insulin resistance* and *beta-cell failure*. Impaired first-phase insulin secretion causing postprandial hyperglycaemia at early stage of T2DM followed by a deteriorating second-phase insulin response and persistent *hyperglycaemia in the fasting state*.
- **Gestational diabetes**: during pregnancy.
- **Other specific types of diabetes**: (i) single genetic mutations that lead to rare forms of DM such as maturity-onset the young; (ii) DM secondary to other pathological conditions or diseases (pancreatitits, trauma or surgery of the pancreas); (iii) drug- or chemically induced DM.
Disorders of glucose metabolism -‘Pre-Diabetes’

- Natural history of progression from normoglycaemia to T2DM
- Impaired fasting glucose (IFG) (110–125 mg/dL)
- Impaired glucose tolerance (IGT)
  OGGT: 2-hour post-load plasma glucose (2hPG) ≥7.8 and <11.1 mmol/L (≥140 and < 200 mg/Dl)
**Table 3** Comparison of 2006 World Health Organization (WHO) and 2003/2011 and 2012 American Diabetes Association (ADA) diagnostic criteria

<table>
<thead>
<tr>
<th>Diagnose/ measurement</th>
<th>WHO 2006²/2011⁷</th>
<th>ADA 2003 and 2012⁵⁶</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diabetes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HbA₁c</td>
<td>Can be used</td>
<td>Recommended</td>
</tr>
<tr>
<td></td>
<td>If measured ≥6.5% (48 mmol/mol)</td>
<td>≥6.5% (48 mmol/mol)</td>
</tr>
<tr>
<td></td>
<td>Recommended</td>
<td></td>
</tr>
<tr>
<td>FPG</td>
<td>≥7.0 mmol/L (≥126 mg/dL)</td>
<td>≥7.0 mmol/L (≥126 mg/dL)</td>
</tr>
<tr>
<td>or</td>
<td>≥11.1 mmol/L (≥200 mg/dL)</td>
<td>or</td>
</tr>
<tr>
<td></td>
<td></td>
<td>≥11.1 mmol/L (≥200 mg/dL)</td>
</tr>
<tr>
<td>IGT</td>
<td>&lt;7.0 mmol/L (&lt;126 mg/dL)</td>
<td>&lt;7.0 mmol/L (&lt;126 mg/dL)</td>
</tr>
<tr>
<td>FPG</td>
<td></td>
<td>Not required</td>
</tr>
<tr>
<td>2hPG</td>
<td>≥7.8–&lt;11.1 mmol/L (≥140–&lt;200 mg/dL)</td>
<td>If measured 7.8–11.0 mmol/L (140–198 mg/dL)</td>
</tr>
<tr>
<td>IFG</td>
<td>6.1–6.9 mmol/L (110–125 mg/dL)</td>
<td>5.6–6.9 mmol/L (100–125 mg/dL)</td>
</tr>
<tr>
<td>FPG</td>
<td></td>
<td>--</td>
</tr>
<tr>
<td>2hPG</td>
<td></td>
<td>--</td>
</tr>
</tbody>
</table>
### Burden of DM and FINnish Diabetes Risk Score (FINDRISC) for 10-year risk of T2DM

**ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD**

<table>
<thead>
<tr>
<th>Variable</th>
<th>2011</th>
<th>2030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total population (millions)</td>
<td>896</td>
<td>927</td>
</tr>
<tr>
<td>Adults (20–79 years; millions)</td>
<td>651</td>
<td>670</td>
</tr>
<tr>
<td>DM (20–79 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>European prevalence (%)</td>
<td>8.1</td>
<td>9.5</td>
</tr>
<tr>
<td>Number with DM (millions)</td>
<td>52.6</td>
<td>64.0</td>
</tr>
<tr>
<td>IGT (20–79 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional prevalence (%)</td>
<td>9.6</td>
<td>10.6</td>
</tr>
<tr>
<td>Number with IGT (millions)</td>
<td>62.8</td>
<td>71.3</td>
</tr>
<tr>
<td>Type 1 DM in children (0–14 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number with type 1 DM (thousands)</td>
<td>115.7</td>
<td>–</td>
</tr>
<tr>
<td>Number newly diagnosed/year (thousands)</td>
<td>17.8</td>
<td>–</td>
</tr>
<tr>
<td>DM mortality (20–79 years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of deaths; men (thousands)</td>
<td>281.3</td>
<td>–</td>
</tr>
<tr>
<td>Number of deaths; women (thousands)</td>
<td>316.5</td>
<td>–</td>
</tr>
<tr>
<td>Healthcare expenditure due to DM (20–79 years, Europe)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total expenditure (billion of €)</td>
<td>75.1</td>
<td>90.2</td>
</tr>
</tbody>
</table>
Disorders of glucose metabolism and CVD

- Increased mortality was observed in people with DM and IGT, identified by 2hPG, but not in people with IFG.
- A high 2hPG predicted all-cause and CVD mortality after adjustment for other major cardiovascular risk factors.
- The highest excess CVD mortality was in people with IGT, especially those with normal FPG.
- The relationship between 2hPG and mortality was linear, but this relationship was not observed with FPG.

DECODE study

Lancet 1999;354:617–621
Glycaemic continuum and CVD

- Impaired glucose tolerance
- Frank diabetes
- Microvascular complications
- Macrovascular complications

- Insulin resistance
- Hepatic glucose production
- Endogenous insulin
- Postprandial blood glucose
- Fasting blood glucose

- Time
- Years to decades

Typical diagnosis of diabetes
DM and CVD pathophysiology

- Atherothrombotic risk
  - Endothelial dysfunction
  - Vascular inflammation
  - Adipose tissue
  - Cytokines
  - FFA

- Hypertension
  - PKC
  - ROS
  - NO

- Hyperglycaemia
  - AGE
  - Diabetic cardiomyopathy
  - PAI-1/tPA
  - Factor VII, XII
  - Fibrinogen
  - Platelet reactivity

- Insulin resistance
  - SR-B
  - Triglycerides
  - HDL-C
  - Small/dense LDL

- Macrophage dysfunction
  - Foam cell
  - PPARγ

- Hyperinsulinaemia

- Atherothrombotic risk
Diagnosis and management of CVD in DM patients

European Heart Journal (2013) 34, 3035–3087
CAD diagnosis in DM patients

- **CAD often silent** (up to 60% of MI may be asymptomatic), diagnosed only by systematic ECG screening.

- **Silent myocardial ischaemia (SMI)** may be detected by ECG stress test, MPI or stress echo.

- SMI 20–35% of DM patients who have additional risk factors, and 35–70% of patients with SMI have **significant coronary stenoses** in the others, SMI may result from alterations of coronary endothelium function or coronary microcirculation.

- SMI is a major cardiac risk factor, especially when associated with coronary stenoses on angiography.

- **D.D. CAD**-Diabetic cardiomyopathy
Risk engines for assessment of CVD in DM

- The United Kingdom Prospective Diabetes Study (UKPDS)
- The Swedish National Diabetes Register (NDR)
- The Framingham Study. Stroke
- The UKPDS for stroke
- The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE)

There was little evidence to suggest that using risk scores specific to DM provides a more accurate estimate of CVD risk. Risk scores for the evaluation of DM have good results in the populations in which they were developed, but validation is needed in other populations.

Risk assessment based on biomarkers and imaging

- In patients with T2DM

- **Albuminuria** is a risk factor for future CV events, CHF and all-cause, even after adjusting for other risk factors

- **NT-proBNP** is also a strong predictor of excess overall and CV mortality, independent of albuminuria and conventional risk factors

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

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

- **Ankle-brachial index (ABI)**

- **Carotid intima-media thickness** and detection of carotid plaques

- **Arterial stiffness by PWV**

- **Cardiac autonomic neuropathy (CAN)** by standard reflex tests may be considered as useful cardiovascular markers, adding predictive value to the usual risk estimate.
In asymptomatic patients, routine screening for CAD is controversial. It is not recommended by the ADA, since it does not improve outcomes as long as CV risk factors are treated.

Screening may be performed in patients at a particularly high risk, such as those with evidence of peripheral artery disease (PAD) or high CAC score or with proteinuria, and in people who wish to start a vigorous exercise programme, cardiovascular target organ damage, including low ABI, increased carotid intima-media thickness, artery stiffness or CAC score.

CAN and SMI may account for a part of the cardiovascular residual risk that remains. The detection of these disorders contributes to a more accurate risk estimate and should lead to a more intensive control of modifiable risk factors, particularly including a stringent target for LDL-cholesterol.

In patients with SMI, medical treatment or coronary revascularization may be proposed on an individual basis.
2013 ESC guidelines on the management of stable coronary artery disease

Table 12: Characteristics of tests commonly used to diagnose the presence of coronary artery disease

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise ECG</td>
<td>45–50</td>
<td>85–90</td>
</tr>
<tr>
<td>Exercise stress echocardiography</td>
<td>80–85</td>
<td>80–88</td>
</tr>
<tr>
<td>Exercise stress SPECT</td>
<td>73–92</td>
<td>63–87</td>
</tr>
<tr>
<td>Dobutamine stress echocardiography</td>
<td>79–83</td>
<td>82–86</td>
</tr>
<tr>
<td>Dobutamine stress MRI</td>
<td>79–88</td>
<td>81–91</td>
</tr>
<tr>
<td>Vasodilator stress echocardiography</td>
<td>72–79</td>
<td>92–95</td>
</tr>
<tr>
<td>Vasodilator stress SPECT</td>
<td>90–91</td>
<td>75–84</td>
</tr>
<tr>
<td>Vasodilator stress MRI</td>
<td>67–84</td>
<td>61–85</td>
</tr>
<tr>
<td>Coronary CTA</td>
<td>95–99</td>
<td>64–83</td>
</tr>
<tr>
<td>Vasodilator stress PET</td>
<td>81–97</td>
<td>74–91</td>
</tr>
</tbody>
</table>

Table 13: Clinical pre-test probabilities in patients with stable chest pain symptoms

<table>
<thead>
<tr>
<th>Age</th>
<th>Typical angina</th>
<th>Atypical angina</th>
<th>Non-anginal pain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
</tr>
<tr>
<td>30–39</td>
<td>59</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>40–49</td>
<td>69</td>
<td>37</td>
<td>38</td>
</tr>
<tr>
<td>50–59</td>
<td>77</td>
<td>47</td>
<td>49</td>
</tr>
<tr>
<td>60–69</td>
<td>84</td>
<td>58</td>
<td>59</td>
</tr>
<tr>
<td>70–79</td>
<td>89</td>
<td>68</td>
<td>69</td>
</tr>
<tr>
<td>&gt;80</td>
<td>93</td>
<td>76</td>
<td>78</td>
</tr>
</tbody>
</table>
2013 ESC guidelines on the management of stable coronary artery disease

ALL PATIENTS
- Assess symptoms
  - Perform clinical examination
- Symptoms consistent with unstable angina
- Follow specific NSTE-ACS guidelines

ECG
Bio-Chemistry
Resting echocardiography
CXR in selected patients

Consider comorbidities and QoL
- Comorbidities or QoL make revascularization unlikely
  - Medical therapy
- Cause of chest pain other than CAD?
  - Yes
    - Treat as appropriate
  - No
    - LVEF <50%?
      - No
        - Assess pre-test-probability (PTP) (see Table 13) for the presence of coronary stenoses
        - Low PTP (<15%)
          - Investigate other causes
            - Consider functional coronary disease
        - Intermediate PTP, eg 15-85%
          - Non-invasive testing for diagnostic purposes
            - See Fig. 2 for decisions based on non-invasive testing and choice between stress testing and coronary CTA
        - High PTP (>85%)
          - Diagnosis of SCAD established
            - Proceed to risk stratification (see Fig. 3). In patients with severe symptoms or clinical constellation suggesting high risk coronary anatomy initiate guideline-directed medical therapy and offer ICA
      - Yes
        - Typical angina?
          - Yes
            - Offer ICA if revascularization suitable
          - No
            - See Fig. 2 for selection of test
2013 ESC guidelines on the management of stable coronary artery disease

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

Consider:
- Patient criteria/suitability for given test
- Availability
- Local expertise

Stress testing for ischaemia

PTP 15-65% and LVEF ≥50%

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

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

Stress imaging<sup>a</sup> (echo<sup>b</sup>, CMR<sup>c</sup>, SPECT<sup>a</sup>, PET<sup>a</sup>); ECG exercise stress testing possible if resources for stress imaging not available

Coronary CTA<sup>a</sup> in patients at low intermediate PTP (15% - 50%)
- If suitable candidate<sup>d</sup>
- If adequate technology and local expertise available

Unclear

Determine patient characteristics and preferences<sup>b</sup>

Ischaemia

No ischaemia

No stenosis

Stenosis

Unclear

Consider functional CAD
Investigate other causes

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

Ischaemia testing using stress imaging if not done before<sup>f</sup>
Exercise ECG is of limited value in diabetic patients because exercise capacity is often impaired by peripheral vascular disease, neuropathic disease, and obesity. Test specificity on electrocardiographic criteria is less than ideal due to high prevalence of hypertension and microvascular disease.
Stress myocardial perfusion imaging in DM

- Stress MPI has been shown to have significant prognostic power for future cardiac events in the symptomatic diabetic population, the number of abnormal segments (fixed or ischemic) was related to worse outcome.


- The coexistence of epicardial coronary artery stenosis with microangiopathy can explain the low specificity of perfusion imaging compared to stress echocardiography in the detection of CAD in asymptomatic and symptomatic diabetic patients [ ]
Cardiac Outcomes After Screening for Asymptomatic Coronary Artery Disease in Patients With Type 2 Diabetes
The DIAD Study: A Randomized Controlled Trial

Cardiac event rates were low and were not significantly reduced by MPI screening for myocardial ischemia over 4.8 years. Of those in the screened group, 409 participants with normal results and 50 with small MPI defects had lower event rates than the 33 with moderate or large MPI defects; 0.4% per year vs 2.4% per year (HR, 6.3; 95% CI, 1.9-20.1; P=.001).

Young et al. JAMA. 2009;301(15):1547-1555
In diabetic patients, stress echo has shown a higher specificity than MPI but suffers from higher rate of false positive results, possibly due to the coexistence of cardiomyopathy in many patients.
Ischemia at s.echo is a strong and independent predictor of total mortality in diabetic as well as non-diabetic patients and the level of risk is related to the extent of the inducible abnormality as expressed by peak WMSI.

Multivariable indicators of mortality: age, RWMA's and ischemia at stress echo.

Normal study is a marker of low risk however in the diabetic group the risk is higher.
Coronary Flow Reserve Doppler

CFR < 2.0 for the detection of diameter stenosis >75%
Sensitivity 86%, Specificity 70%

CFR cannot distinguish between microvascular and macrovascular coronary disease

Picano E. Stress echocardiography. 6th ed. 2015.
CFR in DM without WMAs during Stress Echo

- CFR yields useful **prognostic information** in several clinical subsets, such as diabetics with **unchanged wall motion** during stress.


In diabetic patients, a normal CFR is associated with **tighter glycemic control** and **better long-term event-free survival** both considering unselected patients and patients with angiographically normal coronary arteries.

CAC SCREENING IN PERSONS WITH METABOLIC SYNDROME AND DIABETES

Wong et al. J Am Coll Cardiol 2003;41:1547–1553

CAC for CHD

Malik et al., Diabetes Care 2011; 34:2285–2290

Wong et al., JACC Cardiovasc Imaging 2012;5:358–366
# 2013 ESC guidelines on the management of stable coronary artery disease

## Table 2.1  Testing in asymptomatic patients at risk for stable coronary artery disease

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>In asymptomatic adults with hypertension or diabetes a resting ECG should be considered for CV risk assessment.</td>
<td>IIA</td>
<td>C</td>
</tr>
<tr>
<td>In asymptomatic adults at intermediate risk (see SCORE for definition of intermediate risk - <a href="http://www.heartscore.org">www.heartscore.org</a>) 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.</td>
<td>IIA</td>
<td>B</td>
</tr>
<tr>
<td>In asymptomatic adults with diabetes, 40 years of age and older, measurement of coronary calcium using CT may be considered for CV risk assessment.</td>
<td>IIB</td>
<td>B</td>
</tr>
<tr>
<td>In asymptomatic adults without hypertension or diabetes a resting ECG may be considered.</td>
<td>IIB</td>
<td>C</td>
</tr>
<tr>
<td>In intermediate-risk asymptomatic adults (see SCORE for definition of intermediate risk - <a href="http://www.heartscore.org">www.heartscore.org</a>), (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.</td>
<td>IIB</td>
<td>B</td>
</tr>
<tr>
<td>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.</td>
<td>IIB</td>
<td>C</td>
</tr>
<tr>
<td>In low- or intermediate-risk (based on SCORE) asymptomatic adults stress imaging tests are not indicated for further CV risk assessment.</td>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>
### Stratification for risk of events

#### Definitions of risk for various test modalities

<table>
<thead>
<tr>
<th>Test Modality</th>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise stress ECG</td>
<td>CV mortality &gt;3%/year. CV mortality between 1 and 3%/year. CV mortality &lt;1%/year.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischaemia Imaging</td>
<td>Area of ischaemia &gt;10% (&gt;10% for SPECT; limited quantitative data for CMR – probably ≥2/16 segments with new perfusion defects or ≥3 dobutamine-induced dysfunctional segments; ≥ 3 segments of LV by stress echo).</td>
<td>Area of ischaemia between 1 to 10% or any ischaemia less than high risk by CMR or stress echo. No ischaemia.</td>
<td></td>
</tr>
<tr>
<td>Coronary CTA</td>
<td>Significant lesions of high risk category (three-vessel disease with proximal stenoses, LM, and proximal anterior descending CAD).</td>
<td>Significant lesion(s) in large and proximal coronary artery(ies) but not high risk category. Normal coronary artery or plaques only.</td>
<td></td>
</tr>
</tbody>
</table>

**High risk: annual mortality > 3%**
Microvascular disease

Arterial hypertension, either with or without associated ventricular hypertrophy, is frequently encountered in the population with chest pain and ‘normal coronary arteries’

The consequence of coronary microvascular disease—which is still often called ‘hypertensive heart disease’ but is similarly encountered in patients with diabetes or a strong family history of vascular disease — is a reduced coronary flow reserve (CFR) and later interstitial and perivascular fibrosis, resulting in impaired diastolic dysfunction.

Even later in the course of the disease, epicardial plaques and stenoses may develop and eventually dominate the clinical picture.
Myocardial viability

Stunning: sustained improvement during stress
Hibernating: improve during early stress with subsequent deterioration at peak (biphasic response) indicative of a jeopardized region (hibernating myocardium) often improving after revascularization
dysfunctional but viable myocardium, regional function can be improved by the inotropic effect of low-dose (5–10 μg/kg/min.) dobutamine
Sensitivity and specificity of LDSE 86% and 90% for recovery of stunning) 84% and 81% for predicting functional recovery in hibernating
Compared to nuclear techniques, DSE has lower sensitivity, but higher specificity, with similar overall accuracy regarding recovery of function. In quantitative terms, contractile reserve evidenced by a positive dobutamine requires at least 50% viable myocytes

<table>
<thead>
<tr>
<th>Characteristics of clinical ‘hibernating’ and ‘stunned’ myocardium</th>
<th>Stunning</th>
<th>Hibernation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wall motion abnormalities</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Coronary blood flow</td>
<td>normal</td>
<td>reduced</td>
</tr>
<tr>
<td>Inotropic reserve</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Recovery potential</td>
<td>(spontaneous)</td>
<td>(revascularized)</td>
</tr>
</tbody>
</table>

Krawinkel et al European Heart Journal 1997; 18:111-116

Prediction of Recovery of Function

Shimoni et al Circulation. 2003;107:538-544
Viability in DM

In overt resting ischemic cardiomyopathy, the presence of myocardial viability recognized by dobutamine stress echo independently predicts improved outcome following revascularization in non-diabetics as well as in diabetic patients following revascularization.

Ischaemic LV dysfunction and a significant amount of viable myocardium (at least five segments or a wall motion score index >0.25)
- lower perioperative mortality
- greater improvements in regional and global LV function
- fewer heart failure symptoms
- improved long-term survival after revascularization than patients with large areas of non-viable myocardium

The viability sub-study of the STICH trial found viable myocardium in 487 of 601 patients (81%) and no viable myocardium in 114 (19%). Among patients without viability, 60 were allocated to CABG and 54 to medical therapy and, among the 487 patients with myocardial viability, 244 were assigned to CABG and 243 to medical therapy. The differences in baseline characteristics, between patients who underwent myocardial viability testing and those who did not, indicate some selection bias driven by clinical factors. Viability was arbitrarily defined using different cut-off values for the different tests used. By univariate analysis, there was a significant association between myocardial viability and outcome; however, this association was not significant on multivariable analysis that included other prognostic variables. It is likely that other variables, such as LV volumes and ejection fraction, are causally determined by the extent of viable myocardium. The lack of correlation between myocardial viability status and benefit from CABG in this study indicates that assessment of myocardial viability should not be the sole factor in selecting the best therapy for these patients.

short disease duration, long life expectancy, and no significant CVD, if it can be achieved without hypoglycaemia or other adverse effects.
Although there is a strong relationship between glycaemia and microvascular disease, macrovascular disorders is less clear.

A meta-analysis of cardiovascular outcomes based on VADT, ACCORD and ADVANCE suggested that an HbA1c reduction of 1% was associated with a 15% relative risk reduction (RRR) in non-fatal MI but without benefits on stroke or all-cause mortality.

However, patients with a short duration of T2DM, lower baseline HbA1c at randomization, and without a history of CVD seemed to benefit from more-intensive glucose-lowering strategies.

This interpretation is supported by ORIGIN, which did not demonstrate benefit or detriment on cardiovascular endpoints by early institution of insulin-based treatment, even though insulin glargine was associated with increased hypoglycaemia.

This suggests that intensive glycaemic control should be appropriately applied in an individualized manner, taking into account age, duration of T2DM and history of CVD.
ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood pressure control is recommended in patients with DM and hypertension to lower the risk of cardiovascular events.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>It is recommended that a patient with hypertension and DM is treated in an individualized manner, targeting a blood pressure of &lt;140/85 mmHg.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>It is recommended that a combination of blood pressure lowering agents is used to achieve blood pressure control.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>A RAAS blocker (ACE-I or ARB) is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro-albuminuria.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Simultaneous administration of two RAAS blockers should be avoided in patients with DM.</td>
<td>III</td>
<td>B</td>
</tr>
</tbody>
</table>
**Dyslipidemia control in DM**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin therapy is recommended in patients with T1DM and T2DM at very high-risk (i.e. if combined with documented CVD, severe CKD or with one or more CV risk factors and/or target organ damage) with an LDL-C target of &lt;1.8 mmol/L (&lt;70 mg/dL) or at least a ≥50% LDL-C reduction if this target goal cannot be reached.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Statin therapy is recommended in patients with T2DM at high risk (without any other CV risk factor and free of target organ damage) with an LDL-C target of &lt;2.5 mmol/L (&lt;100 mg/dL).</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Statins may be considered in T1DM patients at high risk for cardiovascular events irrespective of the basal LDL-C concentration.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>It may be considered to have a secondary goal of non−HDL-C &lt;2.6 mmol/L (&lt;100 mg/dL) in patients with DM at very high risk and of &lt;3.3 mmol/L (&lt;130 mg/dL) in patients at high risk.</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>Intensification of statin therapy should be considered before the introduction of combination therapy with the addition of ezetimibe.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>The use of drugs that increase HDL-C to prevent CVD in T2DM is not recommended.</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

SGLT2 inhibitor empagliflozin substantial reductions in CVD death (by 38%) and all-cause mortality (by 32%), as well as in hospitalisation for HF (by 35%), as compared with standard care, suggesting use of an SLGT2 inhibitor should come very early in the course of management of patients with DM and CVD.

The pattern of trial results whereby non-fatal MI and stroke were not reduced by active treatment, as well as the rapid separation of mortality curves, suggest that the mechanism of benefit was likely to relate more to cardio-renal haemodynamic effects than to atherothrombotic actions or effects of glucose lowering per se.
## 2016 European Guidelines on cardiovascular disease prevention in clinical practice

### Recommendations for management of diabetes

<table>
<thead>
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<tr>
<td>Lifestyle changes including smoking cessation, low fat diet, high fibre diet, aerobic physical activity, and strength training are recommended.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Reduction in energy intake is recommended to patients to help achieve lower weight or prevent weight gain.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>A target HbA1c for the reduction in risk of CVD and microvascular complications in DM of &lt;7.0% (&lt;53 mmol/mol) is recommended for the majority of non-pregnant adults with either type 1 or type 2 DM.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>For patients with a long duration of DM, the elderly, frail, or those with existing CVD, a relaxing of the HbA1c targets (i.e. less stringent) should be considered.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>A target HbA1c of ≤6.5% (&lt;48 mmol/mol) should be considered at diagnosis or early in the course of type 2 DM in patients, who are not frail and do not have CVD.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>When screening for DM in individuals with or without CVD, assessment of HbA1c (which can be done non-fasting) or fasting blood glucose should be considered. An oral glucose tolerance test can be offered when there is still doubt.</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>Metformin is recommended as first-line therapy, if tolerated and not contra-indicated, following evaluation of renal function.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Avoidance of hypoglycaemia and excessive weight gain should be considered and individual approaches (with respect to both treatment targets and drug choices) should be considered in patients with advanced disease.</td>
<td>IIa</td>
<td>A</td>
</tr>
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</table>

In patients with type 2 DM and CVD, the use of an SGLT2 Inhibitor should be considered early in the course of the disease to reduce CV and total mortality.

Lipid lowering agents (principally statins) are recommended to reduce CV risk in all patients with type 2 or type 1 DM above the age of 40 years.

Lipid lowering agents (principally statins) may be considered also in individuals below 40 years of age if at significantly elevated risk, based on the presence of microvascular complications or of multiple CV risk factors.

In DM patients at very high-risk (see table 5), a LDL-C target <1.8 mmol/L (<70 mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 1.8 and 3.5 mmol/L (70 and 135 mg/dL), is recommended.

In DM patients with high-risk (see table 5), LDL-C target <2.6 mmol/L (<100 mg/dL), or a reduction of at least 50% if the baseline LDL-C is between 2.6 and 5.1 mmol/L (100 and 200 mg/dL) is recommended.

BP targets in type 2 DM are generally recommended to be <140/85 mmHg, but a lower target of <130/80 mmHg is recommended in selected patients (e.g. younger patients at elevated risk for specific complications) for additional gains on stroke, retinopathy and albuminuria risk. Renin-angiotensin-aldosterone system blocker is recommended in the treatment of hypertension in DM, particularly in the presence of proteinuria or micro-albuminuria. Recommended BP target in patients with type 1 DM is <130/80 mmHg.

The use of drugs that increase HDL-C to prevent CVD in type 2 DM is not recommended.

Antiplatlet therapy (e.g. with aspirin) is not recommended for people with DM who do not have CVD.
Coronary revascularization in DM

CABG vs compared PCI for multivessel disease
Meta-analysis 10 randomized trials


FREEDOM trial 1900 patients—a majority with three-vessel disease—to treatment with CABG or PCI with sirolimus-eluting and paclitaxel-eluting stents.

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

### Coronary revascularization of patients with diabetes

<table>
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<tr>
<td>Optimal medical treatment should be considered as preferred treatment in patients with stable CAD and DM unless there are large areas of ischaemia or significant left main or proximal LAD lesions.</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>CABG is recommended in patients with DM and multivessel or complex (SYNTAX Score &gt;22) CAD to improve survival free from major cardiovascular events.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>PCI for symptom control may be considered as an alternative to CABG in patients with DM and less complex multivessel CAD (SYNTAX score ≤22) in need of revascularization.</td>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>Primary PCI is recommended over fibrinolysis in DM patients presenting with STEMI if performed within recommended time limits.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>In DM patients subjected to PCI, DES rather than BMS are recommended to reduce risk of target vessel revascularization.</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>Renal function should be carefully monitored after coronary angiography/PCI in all patients on metformin.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>If renal function deteriorates in patients on metformin undergoing coronary angiography/PCI it is recommended to withhold treatment for 48 h or until renal function has returned to its initial level.</td>
<td>I</td>
<td>C</td>
</tr>
</tbody>
</table>
ΣΥΜΠΕΡΑΣΜΑΤΑ

- Ο διαβήτης συνοδεύεται συχνά από σοβαρές μικρο- και μακροαγγειακές επιπλοκές πρώιμα ακόμη και πριν τη διάγνωσή του.

- Χρειάζεται εκτίμηση του κινδύνου και έγκαιρη ανίχνευση της στεφανιαίας νόσου και διαστρωμάτωση κινδύνου των ασθενών.

- Η αντιμετώπιση ΣΔ σε συνδυασμό με ΧΣΝ είναι πολυεπίπεδη τόσο σε πρωτογενή όσο και δευτερογενή πρόληψη και περιλαμβάνει τροποποίηση του τρόπου ζωής, φαρμακευτική αγωγή, αντιμετώπιση των λοιπών παραγόντων κινδύνου και των βλαβών οργάνων στόχων και επαναγγείωση ανάλογα με τα επιμέρους κριτήρια.
ΕΥΧΑΡΙΣΤΩ