Challenges in evaluation of coronary artery disease in patients with diabetes

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Scope of the problem

- 9% world population DM; 50-80% suffers from CV diseases

- this estimate is going to increase, with expected mortality rate of >50%

- the question of evaluation and diagnosis of CV diseases in patients with DM, where a significant number of patients are asymptomatic, is of paramount importance
Diabetes - definition of CV risk

<table>
<thead>
<tr>
<th>Very high-risk</th>
<th>Subjects with any of the following:</th>
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<tbody>
<tr>
<td></td>
<td>• Documented CVD, clinical or unequivocal on imaging. Documented clinical CVD includes previous AMI, ACS, coronary revascularization and other arterial revascularization procedures, stroke and TIA, aortic aneurysm and PAD. Unequivocally documented CVD on imaging includes significant plaque on coronary angiography or carotid ultrasound. It does NOT include some increase in continuous imaging parameters such as intima–media thickness of the carotid artery.</td>
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<td>• DM with target organ damage such as proteinuria or with a major risk factor such as smoking or marked hypercholesterolaemia or marked hypertension.</td>
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<td>• Severe CKD (GFR &lt;30 mL/min/1.73 m2).</td>
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<td>• A calculated SCORE ≥10%.</td>
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<td>• Markedly elevated single risk factors, in particular cholesterol &gt;8 mmol/L (&gt;310 mg/dL) (e.g. familial hypercholesterolaemia) or BP ≥180/110 mmHg.</td>
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<td>• Most other people with DM (with the exception of young people with type 1 DM and without major risk factors that may be at low or moderate risk).</td>
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<td></td>
<td>• Moderate CKD (GFR 30–59 mL/min/1.73 m2).</td>
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<td></td>
<td>• A calculated SCORE ≥5% and &lt;10%.</td>
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| Total CV risk (SCORE) | LDL-C levels |  |  |  |  |  |
|-----------------------|--------------|------------------|------------------|------------------|------------------|------------------|------------------|------------------|
|                       | <70 mg/dL    | 70 to <100 mg/dL | 100 to <155 mg/dL | 155 to <190 mg/dL | ≥190 mg/dL   |
|                       | <1.8 mmol/L | 1.8 to <2.6 mmol/L | 2.6 to <4.0 mmol/L | 4.0 to <4.9 mmol/L | ≥4.9 mmol/L |
| <1                   | Lifestyle advice | Lifestyle advice | Lifestyle advice | Lifestyle advice | Lifestyle advice, consider drug if uncontrolled |
| Class²/Level² | I/C | I/C | I/C | I/C | Ila/A |
| ≥1 to <5            | Lifestyle advice | Lifestyle advice | Lifestyle advice, consider drug if uncontrolled | Lifestyle advice, consider drug if uncontrolled | Lifestyle advice, consider drug if uncontrolled |
| Class²/Level² | I/C | I/C | Ila/A | Ila/A | I/A |
| ≥5 to <10, or high-risk | Lifestyle advice | Lifestyle advice, consider drug if uncontrolled | Lifestyle advice and drug treatment for most | Lifestyle advice and drug treatment | Lifestyle advice and drug treatment |
| Class²/Level² | IIa/A | IIa/A | IIa/A | I/A | I/A |
| ≥10 or very high-risk | Lifestyle advice, consider drug | Lifestyle advice and concomitant drug treatment | Lifestyle advice and concomitant drug treatment | Lifestyle advice and concomitant drug treatment | Lifestyle advice and concomitant drug treatment |
| Class²/Level² | IIa/A | IIa/A | I/A | I/A | I/A |

Recent meta-analysis evaluated 17 risk scores (15 with dominant caucasian population, 2 chinese) and concluded that there is not enough evidence to recommend application of risk scores specific for diabetes for assessment of CV diseases
General algorhytm for evaluation of CVD in DM

Cardiovascular disease (CVD) and Diabetes mellitus (DM)

Main diagnosis DM + CVD

CVD unknown
ECG
Echocardiography
Exercise test
Holter monitoring

CVD known
ECG
Echocardiography
Exercise test
Holter monitoring
if positive–cardiology
consultation

Abnormal
Cardiology consultation
Ischaemia treatment:
Non-invasive or invasive

Normal
Follow-up

Main diagnosis CVD + DM

DM unknown
HbA1c, FPG,
if needed OGGT
Blood lipids
if MI or ACS aim for
reasonable glycaemic control

DM known
Screen for
microangiopathy
if poor glycaemic
control
Diabetology consultation

Normal
Follow-up

Newly detected
DM or IGT
Diabetology consultation

Evidence?
ESC Algorithm for diagnosing CAD

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\textsuperscript{a}, CMR\textsuperscript{b}, SPECT\textsuperscript{c}, PET\textsuperscript{d}) if local expertise and availability permit

Stress imaging\textsuperscript{a} (echo\textsuperscript{b}, CMR\textsuperscript{c}, SPECT\textsuperscript{c}, PET\textsuperscript{d}); ECG exercise stress testing possible if resources for stress imaging not available

Coronary CTA\textsuperscript{a} in patients at low intermediate PTP (15% - 50%)
- If suitable candidate\textsuperscript{d}
- If adequate technology and local expertise available

2nd (imaging) stress test (if not done before)\textsuperscript{a}
Coronary CTA in suitable patient (if not done before)\textsuperscript{a}
ICA (with FFR when necessary)

Unclear
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
Guidelines for DM: Asymptomatic patients

- ACC/AHA guidelines (2014) classify asymptomatic patients with DM as high risk and recommend exercise stress test; imaging modalities and CT “may be” recommended

- ADA guidelines from 2014 does not recommend stress testing to screen asymptomatic patients due to DIAD study (2009) where there was no decrease in mortality and MI with routine screening (the event rate was low)
Why functional testing is important?

>12000 pts with CAD

Non-invasive imaging: Additional prognostic value of stress echo in + exercise ECG

- 935 patients (131 DM) with + exercise stress test
- Mean FU 26 months MACE

-Significantly more diabetic pts had + stress echo
- diabetics with + stress echo have different, and worse Prognosis compared to non-diabetics

Prognostic value of CFR in negative stress echo

- 1130 patients (207 DM) with negative dipyridamole stress echo
  - FU mean 16 months for MACE

-Preserved CFR is associated with much lower event rate!

Ca score and CFR in asymptomatic patients with DM

- 200 asymptomatic pts (101 with DM, 99 non-DM)
- Follow-up 12 months, MACE: 24 (19DM and 5 non-DM)

- Multivariable predictors of MACE: hipercholesterolemia, CFR and Ca score

Invasive evaluation: Does FFR affects outcome?

- Jan 2008 - Dec 2011 application of FFR increased from 2% to 51% in Corea
  - total 5097 pts; 2699 before and 2398 after routine FFR
  - stent implantation deferred in 475 pts

- mediana od PCI decreased from 2 to 1 (particularly RCA) (p<0.001)
- rate of primary events decreased after 1 year on mainly on behalf of less MI and revascularizations

FAME study

- 1005 pts, multivessel disease, randomized to angio-guided and FFR-guided PCI

**Graph:**

- **Angio-guided PCI (n=496)**
  - Cumulative (death, MI, CABG, rePCI): 13.2%
  - Death: p=0.02
  - Death or MI: p=0.04
  - CABG or rePCI: 9.5%

- **FFR-guided PCI (n=509)**
  - Cumulative (death, MI, CABG, rePCI): 18.4%
  - Death: p=0.19
  - Death or MI: 7.3%
  - CABG or rePCI: 6.5%

**“FFR-guided” vs angio-guided in pts with DM**

- 294 pts: 205 (70%) FFR - (drugs) vs 89 (30%) FFR + (revasc.)
- Follow-up 33 months for MACE

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**Deferred revascularization in pts with DM on the basis of negative FFR is not associated with good outcome, in fact it is worse**

- Death/MI (HR 2.02, p=0.03), rehosp. for ACS (HR 2.06, p=0.04) and revascularization (HR 3.38, p=0.02), previous IM cofounder

Clinical outcome in -FFR in DM and non-DM

- 250 pts with -FFR deferred for revacs.: 122 DM, 128 nonDM
- FU 40 months for TLF (TLR+MI)

- TLR 16% vs. 6% (HR 3.65, p<0.01), MI 6% vs 2% (HR 3.34. p=0.15)

Preserved and decreased CFR PET mortality in DM and non-DM

- 2783 pts (1172 DM) CFR with PET
- FU 1.4 years, primary aim mortality

CFR PET independent predictor of risk stratification

Long term follow-up discordance of FFR and CFVR

- FFR and CFVR in 158 intermediate lesions in which PCI was deferred on basis on negative FFR or CFVR (10 years inclusion)
- Long term FU (median 11.7 years) for death, MI and TVR

Discordance between FFR and CFVR occurred in 31% and 37% of stenoses at the 0.75, and 0.80 FFR cut-off value
Discordance may be less frequent with rest derived data (iFR) and less susceptible to high flow false positive FFR

Remarks on functional evaluation of pts with DM

1. Majority of data on functional evaluation of CAD in DM are derived from secondary analysis.

2. Non-invasive functional evaluation of CAD in pts with diabetes should include stress echo and ultimately CFR, with stronger diagnostic and prognostic power in comparison to exercise stress testing.

3. The role of FFR for prognosis is not ideal, not the same as in non-DM pts, and requires further evaluation (disease progression is different, and probably less mechanistic).

4. Combination of complementary functional and imaging modalities might be particularly beneficial in patients with DM and not known CAD (COMBINE OCT FFR).

CVD in DM and CICD ESC guidelines 2019
COMBINE OCT and FFR non-culprit lesions in DM

Factors associated with deferred lesion failure following fractional flow reserve assessment in patients with diabetes mellitus.
Kennedy MW$^{1,2}$, Fabris E$^{1,2}$, Hermanides RS$^1$, Kaplan E$^1$, Borren N$^1$, Berta B$^{1,2}$, Koopmans PC$^2$, Ottervanger JP$^1$, Suryapranata H$^{1,2}$, Kedhi E$^1$.

**Abstract**

**OBJECTIVE:**
To explore the predictors of deferred lesion failure (DLF) in patients with diabetes mellitus (DM) and lesions with a fractional flow reserve (FFR) >0.80 and to examine whether a predictive relationship between negative FFR values (>0.80-1.00) and DLF exists.

**BACKGROUND:**
DM is associated with rapidly progressive atherosclerosis and predictors of DLF in FFR negative lesions in this high-risk group are unknown.

**METHODS:**
All DM patients who underwent FFR-assessment between 1/01/2010 and 31/12/2013 were included, and followed until 1/7/2015. Patients carrying ≥1 FFR negative lesion(s) were assessed for DLF, and multivariate models used to identify independent factors associated with DLF.

**RESULTS:**
A total of 205 patients with 252 FFR >0.80 lesions were identified. At a mean follow-up of 3.1 ± 1.4 years, DLF occurred in 29/205 (14.1%) patients, 31/252 (12.3%) lesions. Using marginal Cox regression multivariate analysis, insulin requiring DM [HR 2.24 (95%CI: 1.01-4.95), P = 0.046] and prior revascularization [HR 2.70 (95%CI 1.21-6.01), P = 0.015] were identified as being associated with a higher incidence of DLF. Absolute FFR values in FFR negative lesions in DM patients are not predictive of DLF (receiver operating characteristics curve analysis: area under the curve: 0.57 ± 0.06, 95%CI 0.46-0.69).

**CONCLUSIONS:**
In DM patients with FFR negative lesions, insulin requiring DM and prior revascularization are predictors for DLF. In contrast to non-DM patients, no predictive relationship between absolute negative FFR values (ranging >0.80-1.00) and the risk of DLF exists in DM patients. © 2017 Wiley Periodicals, Inc.
Indikacije za imidžing (eho, CMR) i stres test

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
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<tbody>
<tr>
<td><strong>During hospital stay (after primary PCI)</strong></td>
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<td>Routine echocardiography to assess resting LV and RV function, detect early post-MI mechanical complications, and exclude LV thrombus is recommended in all patients.</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>Emergency echocardiography is indicated in haemodynamically unstable patients.</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>When echocardiography is suboptimal/inconclusive, an alternative imaging method (CMR preferably) should be considered.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>Either stress echo, CMR, SPECT, or PET may be used to assess myocardial ischaemia and viability, including in multivessel CAD.</td>
<td>IIb</td>
<td>C</td>
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Preporuke

- multi-disciplinaran pristup
- centralno promena načina života, TT i fizička aktivnost
- intenzivna trepija hiperglikemije smanjuje mikrovaskularne komplikacije
- intezivno lečenje KP (140 prema 130 mmHg granica)
- ključno smanjenje holesterola za smanjenje KV bolesti
- svi preko 40 godina treba da uzimaju statine
- oni koji već imaju DM i KB, SGLT2 inhibitori smanjuju mortalitet, KB i HF bez neželjenih efekata
Algoritam funkcionalnog ispitivanja kod asimptomatskih pacijenata

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class^a</th>
<th>Level^b</th>
<th>Ref.</th>
<th>C</th>
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<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>
<td>-</td>
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<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>
<td>221-225</td>
<td></td>
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<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>
<td>226, 227</td>
<td></td>
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<tr>
<td>In asymptomatic adults without hypertension or diabetes a resting ECG may be considered.</td>
<td>IIb</td>
<td>C</td>
<td>-</td>
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<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>
<td>228, 229</td>
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<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>
<td>-</td>
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<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>
<td>-</td>
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-Ne od velike pomoći kod asimptomatskih pacijenata pošto su IIa i većina IIb sve preporuke (EKG u miru!, dijabates CT?)

Historical perspective of functional parameters


FFR (2005)

iFR (2015)

Hybrid FFR/CFR/iFR (future)
CT perfusion imaging vs. CT FFR vs FFR: meta-analysis

- CT angio, CT perfusion, and CT-FFR compared to gold standard FFR
- 18 studies with 1535 pts

The CTP protocol involved more radiation (3.5 mSv CCTA vs 9.6 mSv CTP) and a higher volume of iodinated contrast (145 ml).