Noninvasive functional and prognostic estimation of CAD in challenging pathological scenarios

Prof. Ana Djordjevic Dikic, MD, PhD, FACC, FESC
Cardiology Clinic, Medical School,
University of Belgrade, Serbia
How to assess ischaemia?

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

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

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

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

Unclear

Determine patient characteristics and preferences

2nd (imaging) stress test (if not done before)

Coronary CTA in suitable patient (if not done before)

ICA (with FFR when necessary)

Unclear

Ischaemia

No ischaemia

No stenosis

Stenosis

Consider functional CAD
Investigate other causes

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

Ischaemia testing using stress imaging if not done before
CONCLUSIONS—In symptomatic patients with suspected CAD who required noninvasive testing, a strategy of initial CTA, as compared with functional testing, did not improve clinical outcomes over a median follow-up of 2 years. (Funded by the National Heart, Lung, and Blood Institute; PROMISE ClinicalTrials.gov number, NCT01174550.)
PROMISE trial = Green is safe

Figure 3 Fagan nomogram. A hypothetical patient with a calculated pre-test probability of coronary artery disease of 56% (left-sided scales in A and B) undergoes: a stress electrocardiogram, coronary computed tomography angiography, or positron emission tomography when anatomically significant coronary artery disease is used as the reference standard (A), and single-photon emission computed tomography, coronary computed tomography angiography, or positron emission tomography when functionally significant coronary artery disease is used as the reference (B). In the middle scales, positive and negative likelihood ratios are identified and straight lines are drawn between the left and middle scales, and extended to reach the right-sided scales. (A and B) In the right-sided scales, the post-test probability of a positive and negative test result can be read. The grey bars represent the range of post-test probability in which coronary artery disease cannot confidently ruled-in or ruled-out (post-test probability 15–85%). (A) Stress electrocardiogram cannot rule-in or rule-out but the other two imaging tests can, (B) while single-photon emission computed tomography cannot rule-in or rule-out, coronary computed tomography angiography can only rule-out, and positron emission tomography can do both.
Echocardiography : 2 in 1

- Stress echocardiography = Motion analysis
- Transthoracic Doppler echocardiography = Coronary flow reserve
Expirience in Stress Echocardiography
Cardiology Clinic, Clinical Center Serbia
1986-2018
88337 tests
Transthoracic Doppler echocardiography: Coronary flow

CFR = hyperemic flow / basal flow
CFR increase the sensitivity of 2D stress echo

Picano E: Stress echocardiography 5th ed. 2009: 136
Relation between stenosis severity and flow in LAD, RCA I Cx

![Graph showing the relation between stenosis severity and flow in LAD, RCA I Cx. The graph includes data points for different groups with cut-off values and statistical significance indicated by p-values.]
TOPICS

• Prognostic value of transthoracic CFR in non-culprit stenosis of intermediate severity after primary PCI

• Noninvasive assessment of myocardial bridge

• CFR in angiographic and caly caly intermediate LM stenosis
DANAMI 3-PRIMULTI: FFR – based!

Difference in repeated revascularizations, not in all cause mortality and MI

Engstrom T al. Lancet 2015; 386:665-71
Primary percutaneous coronary intervention for myocardial reperfusion in ST-elevation myocardial infarction: procedural aspects (strategy and technique)

<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><strong>Strategy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine revascularization of non-IRA lesions should be considered in patients with multisessel disease before hospital discharge&lt;sup&gt;211-214&lt;/sup&gt;</td>
<td>IIa</td>
<td>A</td>
</tr>
<tr>
<td>CABG should be considered in patients with ongoing ischaemia and large areas of jeopardized myocardium if PCI of the IRA cannot be performed.</td>
<td>IIa</td>
<td>C</td>
</tr>
<tr>
<td>In cardiogenic shock, routine revascularization of non-IRA lesions is not recommended during primary PCI&lt;sup&gt;190&lt;/sup&gt;</td>
<td>III</td>
<td>B</td>
</tr>
<tr>
<td><strong>Technique</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine use of thrombus aspiration is not recommended.&lt;sup&gt;223-226,228&lt;/sup&gt;</td>
<td>III</td>
<td>A</td>
</tr>
</tbody>
</table>

CABG = coronary artery bypass grafting; IRA = infarct-related artery; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

<sup>a</sup>Class of recommendation.

<sup>b</sup>Level of evidence.
Prognostic value of transthoracic Doppler echocardiography coronary flow velocity reserve in patients with non-culprit stenosis of intermediate severity early after primary percutaneous coronary intervention

Tesic M, Djordjevic Dikic A et al.

Study population

- 210 pts (162 man)
- Culprit lesion treated with pPCI
- Non culprit intermediate stenosis (50-70%) in LAD or RCA
Event free survival (CFR>2 and CFR <2)

HIGHLIGHTS

- TDE CFVR provides useful information on the functional status of coronary arteries.
- We performed TDE CFVR of the intermediate (50%-70%) nonculprit coronary stenosis.
- TDE CFVR > 2 is associated with excellent long-term clinical outcomes.
- Findings contribute to ongoing debate over the best management of nonculprit lesions.

Tesic M, Djordjevic Dikic A et al. JASE 2018: 31: 880-887
TOPICS

• Prognostic value of transthoracic CFR in remaining non-culprit lesion of intermediate severity after primary PCI

• Noninvasive assessment of myocardial bridge
• CFR measurement during DOB might add important data on Functional significance of MB

• 44 pts with angiographic evidence of isolated MB
Noninvasive assessment of myocardial bridge

Highlights

• Non invasive CFR measurement during inotroping stimulation with Dobutamine in comparison to vasodilatation with adenosine, provides a more reliable functional significance of MB correspondent to stress echocardiography

• Doppler signal of diastolic flow velocity indicate the compromised flow during diastoly

• Data of prognostic implications are to be determined
TOPICS

- Prognostic value of transthoracic CFR in remaining non-culprit lesion of intermediate severity after primary PCI
- Noninvasive assessment of myocardial bridge
- CFR in angiographycaly intermediate LM stenosis
Prognostic value of preserved coronary flow velocity reserve by non-invasive transthoracic Doppler echocardiography in patients with angiographically intermediate left main stenosis

Djordjevic Dikic A et al. JASE in press
January 29, 2023

In patients with angiography intermediate and equivocal LM stenosis and preserved CFVR values of >2.0, revascularization can be safely deferred, suggesting that noninvasive Doppler echo CFVR might be used as valuable additional and alternative diagnostic tool in assessing functional significance of LM stenosis where there is a clinical question on revascularization in patients in whom FFR is not performed, or not available.

Djordjevic Dikic A et al. JASE in press
Concluding remarks

- Accumulating evidence indicates that CFR is a quantitative measurement of ischemia with integrated information on structure and function of the coronary artery at all levels.

- CFR has been shown to have strong prognostic value for hard cardiovascular events in number of patient cohorts.

- Quantitative measurement of CFR serve as a marker of disease progression and a tool for evaluation of potential effects of intervention.

- Comparative merit of noninvasive CFVR by Doppler 2D echocardiography evaluation includes wide availability, feasibility, reproducibility, safety, and clinical possibility to repeat CFVR evaluation regularly without additional risk for the patients.
### TABLE II. Using Fractional Flow Reserve to Guide Unprotected Left Main Intervention

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Defining iLM (%)</th>
<th>FFR cutoff</th>
<th>Follow-up (mo)</th>
<th>Defer</th>
<th>Revascularization of LM</th>
<th>Survival defer (%)</th>
<th>Survival revascularization (%)</th>
<th>RR CI [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bech et al. [17]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>54</td>
<td>40–60</td>
<td>0.75</td>
<td>29 ± 15</td>
<td>24</td>
<td>30 CABG</td>
<td>100</td>
<td>97</td>
<td>0.80 [0.05–12.13]</td>
</tr>
<tr>
<td>Jiménez-Navarro et al. [18]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>27</td>
<td>30–50</td>
<td>0.75</td>
<td>26 ± 12</td>
<td>20</td>
<td>7 CABG</td>
<td>100</td>
<td>86</td>
<td>7.87 [0.35–173.98]</td>
</tr>
<tr>
<td>Legutko et al. [19]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>38</td>
<td>30–60</td>
<td>0.75</td>
<td>24 (12–36)</td>
<td>20</td>
<td>12 CABG, 5 PCI, 1 OMT</td>
<td>100</td>
<td>89</td>
<td>5.526 [0.28–107.96]</td>
</tr>
<tr>
<td>Suemaru et al. [20]</td>
<td>15</td>
<td>25–75</td>
<td>0.75</td>
<td>32.5 ± 9.7</td>
<td>8</td>
<td>7 CABG</td>
<td>100</td>
<td>Excluded</td>
<td></td>
</tr>
<tr>
<td>Lindstaedt et al. [21]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>51</td>
<td>40–80</td>
<td>0.75–0.80</td>
<td>29 ± 16</td>
<td>24</td>
<td>27 CABG</td>
<td>100</td>
<td>81</td>
<td>8.03 [0.45–141.94]</td>
</tr>
<tr>
<td>Courtis et al. [22]&lt;sup&gt;b&lt;/sup&gt;</td>
<td>142</td>
<td>30–60</td>
<td>0.75</td>
<td>14 ± 11</td>
<td>82</td>
<td>54 CABG, 6 PCI</td>
<td>96</td>
<td>95</td>
<td>1.36 [0.28–6.53]</td>
</tr>
<tr>
<td>Hamilos et al. [23]&lt;sup&gt;a&lt;/sup&gt;</td>
<td>213</td>
<td>30–70</td>
<td>&lt;0.80</td>
<td>36 (6–99)</td>
<td>138</td>
<td>75 CABG</td>
<td>89.8</td>
<td>85.4</td>
<td>1.84 [0.67–5.04]</td>
</tr>
<tr>
<td>Total</td>
<td>540</td>
<td>316</td>
<td>224</td>
<td></td>
<td></td>
<td></td>
<td>96</td>
<td>90</td>
<td>2.28 [1.12–4.60]&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Route of adenosine—IV.

<sup>b</sup>Route of Adenosine—IC.

<sup>c</sup>Heterogeneity $\chi^2 = 2.85$ (df = 5), $P = 0.723$ I-squared (variation in RR attributable to heterogeneity) = 0.0%. Test of RR = 1: $z = 2.30, P = 0.022$.

iLM, intermediate left main; FFR, fractional flow reserve; IVUS, intravascular ultrasound; IC, intracoronary; IV, intravenous; MLA, minimum luminal area; MLD, minimum luminal diameter; PCI, percutaneous coronary intervention; pLM, protected left main; LAD, left anterior descending; LCx, left circumflex; CABG, coronary artery bypass grafting; ND, not defined; NA, not applicable; RR, relative risk; CI, confidence interval.
Multivessel disease

- Primary PCI:
  - Only “culprit” lesion?
  - Or: non culprit at the same procedure?
  - Or: Staged intervention at same hospitalization?
  - Or: Second hospitalisation?
  - Or: Conservative treatment?
<table>
<thead>
<tr>
<th>2013 Recommendation</th>
<th>2015 Focused Update Recommendation</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Class III: Harm</strong></td>
<td><strong>Class IIb</strong></td>
<td></td>
</tr>
<tr>
<td>PCI should not be performed in a noninfarct artery at the time of primary PCI in patients with STEMI who are hemodynamically stable (11-13). <em>(Level of Evidence: B)</em></td>
<td>PCI of a noninfarct artery may be considered in selected patients with STEMI and multivessel disease who are hemodynamically stable, either at the time of primary PCI or as a planned staged procedure (11-24). <em>(Level of Evidence: B-R)</em></td>
<td>Modified recommendation (changed class from “III: Harm” to “IIb” and expanded time frame in which multivessel PCI could be performed).</td>
</tr>
</tbody>
</table>
Functional testing for risk stratification in patients with chronic total occlusion of right coronary artery and intermediate stenosis of left coronary artery

- Correct estimation of functional severity of LAD stenosis is important for risk stratification of these patients and decision making.

- Special issue is selecting the optimal non-invasive test in this setting since, presence of CTO will preclude occurrence and detection of ischemia in other coronary regions.
**Overall Comparisons**

<table>
<thead>
<tr>
<th>Chi-Square</th>
<th>df</th>
<th>Sig.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Log Rank (Mantel-Cox)</td>
<td>7.356</td>
<td>1</td>
</tr>
</tbody>
</table>

Event free survival time: CFR>2 vs CFR<2: 18.8±1.5m vs 9±2.7m ; p<0.05

CFR <2 had 5.5 increased risk for CV event: 95% CI 0.047-0.713) p=0.014

A. Djordjevic Dikic et al., Eur J CVI 2016; suppl
LBBB, CAD, ECHO and CFR

Sn= 88%
Sp= 84%
Acc= 86%

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=18)</th>
<th>Group 2 (n=25)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline DV (m/s)</td>
<td>0.31 ± 0.03</td>
<td>0.34 ± 0.05</td>
<td>0.037</td>
</tr>
<tr>
<td>Stress DV (m/s)</td>
<td>0.55 ± 0.11</td>
<td>0.76 ± 0.15</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CFR</td>
<td>1.65 ± 0.21</td>
<td>2.31 ± 0.28</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Intermediate LAD or RPD stenosis (50-70%) on coronary angiography (n=241 patients)

Non-invasive CFVR (n=230)

CFVR > 2 (n = 174)  
**Group 1**

- Medical treatment
  - Follow up (n=210)

CFVR ≤ 2 (n = 56)

Exercise test or fractional flow reserve

Negative (n = 36)  
**Group 2**

Positive (n = 20)  
Excluded from the study

Revascularization

Excluded from the study:  
4 patients due to cancer disease  
7 patients due to technical inability to perform CFVR

Djordjevic Dikic A et al. JASE in press