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Mini Review

Challenges in Diagnosis of Cardiovascular Disease in Patients with Diabetes: Reflection to The Last 2019 ESC/EADS Guidelines for Diabetes, Pre-Diabetes and Cardiovascular Diseases

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Abstract

With increasing incidence of diabetes mellitus worldwide, particularly in some areas of Middle East where almost 50% of patients presenting with acute coronary syndrome have diabetes mellitus, the question of the best diagnostic approach to detect early coronary artery disease before complications develop are of paramount importance. In this mini review, we present and discuss main recommendations, directions and current issues for diagnosis of cardiovascular diseases according to the new 2019 ESC/EASD Guidelines for diabetes, pre-diabetes and cardiovascular diseases.

Introduction

Diabetes mellitus (DM), per se, carries at least 2-fold risk for cardiovascular diseases, with some areas in Middle East particularly vulnerable to high prevalence of DM and cardiovascular diseases (CVD) as complication of DM [1]. Although Type2 DM is far more common than Type1 DM, both patients populations carries adverse prognosis, particularly severe in the young onset female patients with Type1 DM, underlying the need for early diagnosis, CDV risk modification, strict adherence to non-drug and drug therapy and systematic follow-up. In fact, patients with known DM and baseline fasting blood glucose of ≥7mmol/L are at highest risk of coronary artery disease (CAD), whereas patients with DM and regulated glucose of <7mmol/L and patients without known DM and fasting blood glucose concentration of ≥7mmol/L carries the same risk for CAD [1]. CVD, particularly cardiac death and myocardial infarction (CAD) accompanied by stroke, is by far most severe complication of DM and diagnostic modalities to address this issue has been discussed by the new ESC/EASD guidelines for diabetes, pre-diabetes cardiovascular diseases from 2019 [2].

According to the new 2019 ESC/EASD guidelines for diabetes, pre-diabetes and cardiovascular diseases [2], the patients are stratified into 3 CVD risk categories including very high-risk, high risk and moderate risk for future adverse events. Very-high risk group (10-year risk of CVD death >10%) include individuals with DM and cardiovascular diseases (CVD), or DM with target organ damage, such as proteinuria or renal failure (estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m2), patients with DM with three or more major risk factors, or with a DM duration of >20 years, and Type1 DM at the age of 40 years with early onset (i.e. 1-10 years of age) and particularly female. Patients of the young age (<35 years) with type1 DM of short duration (<10 years), and patients with T2 DM aged <50 years with a DM duration of <10 years and without major risk factors, are at moderate risk (<5% 10 year risk of CVD).

Yet, the most of the patients remains to the high risk group (10 year risk of CVD death 5-10%) consisting of patients with

DM of more than 10 years and without previous CVD, without target organ damage and with at least one additional risk factor including age, hypertension, dyslipidemia, smoking and obesity [3]. According to the guidelines [2], the screening of these patients remains challenging as the guidelines only recommended resting ECG (Class I), whereas noninvasive functional imaging (radionuclide myocardial perfusion imaging, magnetic resonance imaging, or physical or pharmacological stress echocardiography) or CT angiography imaging may only be considered (Class IIb) in asymptomatic high-risk patients. In addition, the only other Class I recommendation refers to routine assessment of microalbuminuria as an indicator of risk of developing renal dysfunction or future CVD.

The addition of circulating biomarkers for CV risk assessment has limited clinical value and is not recommended by the guidelines (Class III) [2,3]. The reason for this suggestion is in the fact that in asymptomatic patients with DM, measurement of C-reactive protein or fibrinogen provides only minor incremental value to current risk assessment [2,3]. The addition of hsTnT to conventional risk factors has not shown incremental discriminative power in this group [3]. In individuals with type1 DM, elevated hsTnT was an independent predictor of renal decline and CV events [4], whereas prognostic value of N-terminal pro-B-type natriuretic peptide (NT-proBNP) in an unselected cohort of people with DM (including known CVD) showed that patients with low levels of NT-proBNP (<125pg/mL) have an excellent short-term prognosis [5]. Therefore, and despite some prognostic significance, routine clinical assessment of cardiac biomarkers is not recommended for CVD risk stratification in any patient group with DM [2].

Similarly, and once popular in risk evaluation, carotid ultrasound intima-media thickness should not be recommended for screening CV risk [2], whereas assessment of carotid and/or femoral plaque burden with arterial ultrasonography should be consider as risk modifier in asymptomatic patients with DM. So, arterial ultrasonography remains one of the imaging tests that should be performed in asymptomatic patients with DM not for stratification but comprehensive consideration in diagnostic algorithm.

Non-invasive estimation of the atherosclerotic burden, based on the coronary artery calcium score, can also be performed in asymptomatic patients for the risk assessment. In fact, patients with DM have a higher prevalence of coronary artery calcification compared to non-DM individuals [6] a CAC score of 0 (Agatston score) is associated with favorable prognosis, whereas incremental coronary artery calcium score from 1-99 (minimal to mild), 100-399 (moderate), and ≥400 (severe calcification) is associated with a substantial higher relative risk of mortality of 25-33% [3]. Therefore, coronary artery calcium score may be considered by the guidelines [2] as a risk modifier in CV assessment in asymptomatic patients with moderate risk.

The most of the controversies and challenges regarding diagnosis of CAD in asymptomatic patients carries evaluation of myocardial ischemia with noninvasive functional testing and/or noninvasive imaging of coronary arteries. Stress testing with myocardial perfusion imaging or stress echocardiography allows the detection of myocardial ischemia, particularly silent form which is more prevalent in patients with DM [7-9]. Randomized trials evaluating the impact of routine screening for CAD in asymptomatic DM and no history of CAD have shown no differences in the outcome (cardiac death and unstable angina) in those who underwent stress testing or CT angiography, or not [9-13]. In fact, four randomized trials (DIAD, DYNAMIT, FACTOR-64, DADDY-D) [9,11-13] including form 520 up to 1123 patients have shown no significant decrease in the rate of cardiac events, except for the last DADDY-D study [13] that demonstrated significant decrease in cardiac events in the subgroup of patients over 60 years undergoing routine exercise stress testing. In addition, study by Faglia et al. [14] using also exercise stress testing or stress echocardiography also demonstrated better outcome in patients undergoing functional testing for myocardial ischemia. Taken together, the studies showed obvious disparities in the testing modality, patient population, the rate of invasive coronarography following positive testing (15-93%!), treatment strategy following testing (usually left to discretion of the treating physician), whereas the annual rate of major adverse cardiac events was very low ranging from 0.6-1.9%. In fact, this rate annual rate of adverse events correspondents to moderate to high risk group of asymptomatic patients with DM.

In addition, a meta-analysis including 3299 asymptomatic subjects with DM showed that non-invasive imaging for CAD did not significantly reduce event rates of non-fatal MI (relative risk 0.65; p=0.062) and hospitalization for HF (relative risk 0.61; p=0.1) [10]. Accordingly, routine screening of CAD in asymptomatic DM is not recommended [2]. However, CTCA or functional imaging (radionuclide myocardial perfusion imaging, stress cardiac magnetic resonance imaging, or exercise or pharmacological stress echocardiography) may be considered in asymptomatic (presumable high risk) patients with DM for screening of CAD (Class IIb), whereas stress testing or CT angiography may be indicated in very high-risk asymptomatic individuals (with peripheral arterial disease (PAD), a high CAC score, proteinuria, or renal failure) [2,15].

2019 ESC guidelines for management and treatment of patients with chronic coronary syndrome [16], proposed unique diagnostic algorithm guiding revascularization in patients with anginal symptoms, and without any relevant differences for patients with diabetes. In brief, myocardial revascularization is now strongly based on functional evaluation of coronary stenosis, unless coronary stenosis is critical defined as more than 90% luminal stenosis, or in case or poor left ventricular ejection fraction (EF<35%). In addition, in case of clear previous evidence of myocardial ischemia correspondent to the territory with intermediate coronary lesions

revascularization is indicated, however in patients with multi-vessel coronary artery stenoses, invasive functional testing is warranted and should be performed to interrogate each coronary lesion of intermediate significance. Regarding invasive functional parameters, the guidelines recommend both fractional flow reserve (FFR) or instantaneous wave-free flow reserve (iFR) with cut-off points of 0.80 and 0.89, respectively, and without any particular notion about possible interaction in patients with diabetes, or differences between FFR and iFR. In fact, previous large randomized studies (FAME, iFR SwedeHeart, Define Flair) have shown no difference in the outcome between patients with and without DM [17-19].

On the other hand, some studies focused on diabetic population, have shown that the outcome of patients with and without DM may not be the same, i.e. DM patients with negative FFR had inferior and almost 2 times higher event rate [20] than non-diabetic patients. However, none of these studies have been powered enough to evaluate differences in the outcome between diabetes and non-diabetic patients. Regarding comparison of functional parameters, although there was no difference in the outcome between FFR and iFR group, iFR group had consistently demonstrated less stenting [18,19]. On the other hand, the data on iFR in diabetic patients, which is not a surrogate of FFR, but incorporates the hemodynamic status of microcirculation, which is particularly vulnerable in DM patients, are limited.

Conclusion

With emerging role of CT angiography and advanced functional imaging techniques (magnetic resonance imaging, strain, coronary flow reserve), on one hand, and exciting new therapeutic drug options, diagnosis of CAD is particularly challenging in moderate and particularly high risk diabetic patients, and relies on the capacity of the health care system, as well as imaging capacities and expertise, having in mind prevalence of diabetic patients in the population. On the other hand, diabetic patients with known CVD and symptomatic patients are per se high risk group and should promptly undergo functional imaging testing and invasive evaluation with functional interrogation of intermediate coronary stenosis. The threshold for revascularization remains the same as in non-diabetic patients, including comprehensive evaluation of each patient.

Acknowledgment

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Conflict of Interest

The author has no conflict of interest related to this publication.

References

1. Emerging Risk Factors Collaboration, Sarwar N, Gao P, Seshasai SR, Gobin R, S Kaptoge, et al. (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375(9733): 2215-2222.
2. Cosentino F, Grant PJ, Aboyans V, Bailey CJ, Ceriello A, et al. (2019) ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD. Eur Heart J 41(2): 255-323.
3. Price AH, Weir CJ, Welsh P, McLachlan S, Strachan MWJ, et al. (2017) Comparison of non-traditional biomarkers, and combinations of biomarkers, for vascular risk prediction in people with type 2 diabetes: the Edinburgh Type 2 Diabetes study. Atherosclerosis 264: 67-73.
4. Galsgaard J, Persson F, Hansen TW, Jorsal A, Tarnow L, et al. (2017) Plasma high-sensitivity troponin T predicts end-stage renal disease and cardiovascular and all-cause mortality in patients with type 1 diabetes and diabetic nephropathy. Kidney Int 92(5): 1242-1248.
5. Huelsmann M, Neuhold S, Strunk G, Moertl D, Berger R, et al. (2008) NT-proBNP has a high negative predictive value to rule-out short-term cardiovascular events in patients with diabetes mellitus. Eur Heart J 29: 2259-2264.
6. Valenti V, Hartaigh BO, Cho I, Schulman Marcus J, Gransar H, et al. (2016) Absence of coronary artery calcium identifies asymptomatic diabetic individuals at low near-term but not long-term risk of mortality: a 15-year follow-up study of 9715 patients. Circ Cardiovasc Imaging 9(2): e003528.
7. Wackers FJ, Young LH, Inzucchi SE, Chyun DA, Davey JA, et al. (2004) Detection of Ischemia in Asymptomatic Diabetics Investigators. Detection of silent myocardial ischemia in asymptomatic diabetic subjects: the DIAD study. Diabetes Care 27(8):1954-1961.
8. Zellweger MJ, Maraun M, Osterhues HH, Keller U, Muller Brand J, et al. (2014) Progression to overt or silent CAD in asymptomatic patients with diabetes mellitus at high coronary risk: main findings of the prospective multicenter BARDOT trial with a pilot randomized treatment substudy. JACC Cardiovasc Imaging 7(10): 1001-1010.
9. Lievre MM, Moulin P, Thivolet C, Rodier M, Rigalleau V, et al. (2011) Detection of silent myocardial ischemia in asymptomatic patients with diabetes: results of a randomized trial and metaanalysis assessing the effectiveness of systematic screening. Trials 12: 23.
10. Clerc OF, Fuchs TA, Stehli J, Benz DC, Grani C, et al. (2018) Non-invasive screening for coronary artery disease in asymptomatic diabetic patients: a systematic review and meta-analysis of randomised controlled trials. Eur Heart J Cardiovasc Imaging 19(8): 838-846.
11. Young LH, Wackers FJ, Chyun DA, Davey JA, Barrett EJ, et al. (2009) DIAD Investigators. Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with type 2 diabetes: the DIAD study: a randomized controlled trial. JAMA 301(15): 1547-1555.
12. Muhlestein JB, Lappe DL, Lima JA, Rosen BD, May HT, et al. (2014) Effect of screening for coronary artery disease using CT angiography on mortality and cardiac events in high-risk patients with diabetes: the FACTOR-64 randomized clinical trial. JAMA 312(21): 2234-2243.
13. Turrini F, Scarlini S, Mannucci C, Messora R, Giovanardi P, et al. (2015) Does coronary Atherosclerosis Deserve to be Diagnosed earlY in Diabetic patients? The DADDY-D trial. Screening diabetic patients for unknown coronary disease. Eur J Intern Med 26(6): 407-413.
14. Faglia E, Manuela M, Antonella Q, Michela G, Vincenzo C, et al. (2005) Risk reduction of cardiac events by screening of unknown asymptomatic coronary artery disease in subjects with type 2 diabetes mellitus at high cardiovascular risk: an open-label randomized pilot study. Am Heart J 149(2): e1-e6.
15. Ryden L, Grant PJ, Anker SD, Berne C, Cosentino F, et al. (2013) ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD: The Task Force on diabetes, pre-diabetes, and cardiovascular diseases of the European Society of Cardiology (ESC) and developed in collaboration with the European Association for the Study of Diabetes (EASD). Eur Heart J 34(39): 3035-3087.
16. Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, et al. (2019) 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC).

17. Tonino PA, De Bruyne B, Pijls NH, Siebert U, Ikeno F, et al. (2009) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention. N Engl J Med 360(3): 213-224.

18. Gotberg M, Christiansen EH, Gumundsdottir IJ, Sandhall L, Danielwicz M, et al. (2017) For the iFR – SWEDEHEAR investigators. Instantaneous wave-free ratio vs. fractional flow reserve to guide PCI. N Engl J Med 376: 1813-1823.

19. Davies JE, Sen S, Dehbi HM, Al Lamee R, Petraco R, et al. (2017) Use of Instantaneous wave-free ratio or fractional flow reserve in PCI. N Engl J Med 376: 1824-1834.

20. Kennedy MW, Kaplan E, Hermanides RS, Fabris E, Hemradj V, et al. (2016) Clinical outcomes of deferred revascularisation using fractional flow reserve in patients with and without diabetes mellitus. Cardiovasc Diabetol 15: 100.