GENERAL REVIEW


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# Four varieties of diabetes mellitus in acute myocardial infarction

## Četiri tipa šećerne bolesti u akutnom infarktu miokarda

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**Ključne reči:**
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### Introduction

It is believed that 387 million patients (> 8% of the global population) have diabetes mellitus (DM), and almost one half of them are unaware of their diagnosis [1]. DM is very important risk factor for acute myocardial infarction (AMI) [2]. The patients with DM have a two- to four-fold increased risk of developing cardiovascular (CV) disease [3], three-fold for the acute coronary syndrome (ACS) [4], and they experience the CV events 15 years earlier than the general population [4, 5]. The patients with DM were believed to have as the high risk for the new AMI as the patients with previous myocardial infarction (MI), the "coronary artery disease (CAD) equivalent" [6–8]. This is an overestimation as shown by the meta-analysis [9]. The Euro Heart Survey and other registries/studies found that a majority of ACS patients had dysglycaemia, including DM, which was not previously diagnosed [1, 8, 10, 11]. The patients with MI have the incidence of insulin resistance twice as often as the individuals with no history of myocardial infarction. Therefore, some authors consider a MI to be a pre-DM equivalent [1, 8], or a DM risk equivalent [12], or a pre-DM risk eqiuvalent [13]. Out of 2,036 DM-naïve CAD patients who were followed up for at least one year, AMI significantly increased the risk of "new-onset" DM after adjusting the covariates [hazard ratio (HR), 1.54; 95% confidence interval (CI), 1.14–2.07; $p < 0.01$] [14].

Nevertheless, a short- term [4] and a long-term mortality risk in the AMI patients with DM is almost doubled in comparison with the nondiabetic AMI patients [2, 4, 7]. A systematic review and meta-regression of 1,614,174 AMI, or ACS patients showed that the patients with DM (n = 432,066) had the odds ratio (OR) [95% CI] of 1.66 [1.59–1.74] ($p < 0.0001$) for early mortality, and of 1.86 [1.75–1.97] ($p < 0.0001$) for 6–12 months mortality in comparison with 1,182,108 nondiabetic patients [2]. The mortality risk after a 10-year follow-up in the patients with CAD and DM exceeds 70% [15]. Glycemia on admission of 108–126 mg/dL (6–7 mmol) in the AMI patients with DM is associated with 3 times higher mortality vs. the AMI patients without DM [16, 17]. In AMI, the risk for the repeated myocardial infarctions, heart failure, cardiogenic shock and stroke is also greater in the patients with concomitant DM, as compared to the AMI patients without DM [4, 18]. Increased mortality in the AMI patients vs. those without DM has remained constant over time (from 1970 to 2011), despite the important therapeutic advantages [2]. The survival curves were persistently diverging for 20 years between the AMI patients with and without DM and the median survival was less than 3.3 years ($p < 0.0001$) in the DM patients following the AMI [5]. DM confers increased in-hospital mortality risk both in the ST-elevation myocardial infarction (STEMI) and the non-STEMI (NSTEMI) patients [19].

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Moreover, this dismal prognosis of patients with AMI and DM is not related to the body mass index, i.e., „obesity paradox“ is not relevant to them (in contrast to the AMI patients without DM) [20]. Indeed, a meta-analysis of 21,759 DM patients (~29% of them were insulin-treated) revealed that both short-term and long-term mortality, and the incidence of new AMI, target lesion revascularization, major adverse cardiac effect (MACE), and stent thrombosis were significantly more frequent in the insulin-treated DM patients [21]. Also, among 243,861 patients with AMI the in-hospital mortality risk was higher in the insulin-treated DM patients (n = 20,051) vs. the DM patients who did not require insulin (n = 25,364) [19]. DM is prevalent in AMI, with usuallly quoted figures between 20%–30% [7, 22–24], or 30%–40% [25], and the incidence and the prevalence of DM are expected to grow further [2, 26]. Another 300 million individuals are at a risk of developing DM [26]. Even higher actual prevalence was published and a few recent papers reported almost doubled DM prevalence in AMI (47%) [27].

**Diagnosing DM in AMI has been clearly suboptimal**

In a recent research paper, of the 3,778 AMI patients who had no history of DM before admission, 18.7% had the criteria for DM during hospitalization: fasting glucose level of at least 126 mg/dL (7 mmol/L), random plasma glucose (RPG) of at least 200 mg/dL (11.1 mmol/L), or glycated hemoglobin [HbA1c] level of at least 6.5%. Out of the AMI patients with the criteria for a new-onset DM, only 30% were clinically diagnosed (as having DM) in the hospital and were treated instantly [27]. Similarly, in a study of 1,566 patients, insulin, or oral agents were prescribed at discharge for 80% of patients with known DM and only 25.4% of patients with newly diagnosed DM [1]. Therefore, the great majority of newly diagnosed DM remained without an appropriate hypoglycemic treatment, which is very important finding. Indeed, the AMI patients who met the criteria for DM, but were not diagnosed, had a significantly higher risk for a MACE, 1 year following discharge, compared with the patients without previous diagnosis of DM (OR, 1.5; 95% CI, 1.3–1.7; $p < 0.0001$). On the other hand, there was no a statistically significant difference between the patients with properly newly diagnosed DM and the patients without DM (OR, 1.3; 95% CI, 0.9–1.7; $p = 0.15$) [27]. The authors divided their DM patients into only three groups: 1) with a history of DM (34%); 2) without a history of DM, diagnosed during hospitalization (4%); with the criteria for DM, but undiagnosed during their intrahospital stay (9%) [27].

**How many kinds of DM can be observed in AMI?**

We believe that it is important to recognize that there were actually four kinds of DM in ACS: A) Previously diagnosed DM [1]; B) Newly diagnosed (previously present, but not diagnosed until this admission) DM with HbA1c > 6.5% [1, 28]; C) New-onset DM with HbA1c < 6.5% and with either C1. Fasting blood glucose (FBG) ≥ 126 mg/dL (7 mmol/L), or C2. A RPG ≥ 200 mg/dL (11.1 mmol/L), or C3. The positive oral glucose tolerance test (OGTT) before discharge with 2-hr plasma glucose (PG) ≥ 200 mg/dL (11.1 mmol/L) [1]; D) Undetected DM, i.e., some of the four 2016 American Diabetes Association (ADA) criteria [in terms of FBG ≥ 126 mg/dL (7 mmol/L), or a RPG ≥ 200 mg/dL (11.1 mmol/L) or HbA1c ≥ 6.5% (48 mmol/mol), or 2-hr PG ≥ 200 mg/dL (11.1 mmol/L) during OGTT (75 g)] not fulfilled and the other analysis not performed [29].

**Some frequent mistakes in categorizing DM and stress hyperglycemia in AMI**

The forth group (D) is missing in the aforementioned work [27] and with this group, the number of DM patients in AMI would be even higher. Consequently, as these patients were neither diagnosed nor treated – the real number of adequately diagnosed and treated DM patients in AMI may be therefore even lower than 30%. This should call to action. Regarding the terminology used in writing on this topic, there is a mistake with labeling “newly diagnosed” DM as “new-onset”. In AMI, the patients without known (previously diagnozed) DM can be considered as having “new-onset”, which frequently is not true, because they may have unrecognized DM for some time. It is not difficult to distinguish “new onset DM” from undiagnosed DM, because HbA1c is normal in the first and elevated in the second case.

Common methodological error for decades was to use the same cut-off in the AMI patients for the subgroup with the glycometabolic disease (DM) and without it. This single cut-off was arteficially low for the DM patients (and high for non-DM ones) and decreased somewhat the predicitive accuracy of stress hyperglycemia (SH). It is particularly true for the DM patients, because they are less represented in AMI, so that their cut-off value for SH is more remote from the artificial single cut-off of the whole AMI group [30]. Hyperglycemia is common, valid both for risk stratification and treatment initiation and adjustments, but is often the underestimated parameter in critical illnesses, including AMI [31]. The importance of hyperglycemia in AMI stems from two facts: AMI is one of the most common lethal diseases and glycemia is undoubtely one of the basic parameters in general and in AMI [17]. Hyperglycemia in AMI has different cut-offs for the prognostic and therapeutic purposes. The common mistake is to take therapeutic treshold e.g., 11 mmol/L (198 mg/dl) for the prognostic one, because the AMI patients without DM have far less prognostic cut-off ~8 mmol/L (144 mg/dl) [32]. Post-prandial hyperglycaemia contributed more to the CAD genesis as compared to fasting hyperglycemia [33]. No less than 84% of AMI patients with abnormal glucose tolerance had normal plasma glucose (FPG) [34].

**Comparison of the most important tools to detect DM in AMI (in addition to FPG and RPG)**

HbA1c is a marker of an increased CV risk in the patients with and without DM [35]. ADA recommended the HbA1c with a threshold of 6.5%, to diagnose DM, due to its preanalytical stability, convenience (fasting not required),

and less day-to-day variability [28]. Moreover, HbA1c is currently used to guide the management decisions [4]. The ACS patients with HbA1c of 6.0%–6.4% should have an OGTT 6–8 weeks after discharge [4]. HbA1c reflects the average glycemia, including postprandial spikes during last 3 months [36]. The relation of postprandial hyperglycemia and a risk of CV diseases was demonstrated in a meta-analysis of 95,783 individuals [3, 37]. HbA1c has a low intraindividual variability and is not influenced by the stress caused by ACS [25, 36]. A single measurement of HbA1c is not sufficient to diagnose DM [38]. Using HbA1c, FPG, and RPG newly diagnosed DM was found in ~1/5 of all AMI patients and pre-DM in 14% [39].

OGTT has been often recommended for the AMI patients [23, 25, 26]. But neither from ADA [28] nor from NICE [40], OGTT is a valid screening tool for both DM and a high CV risk [41]. OGTT in the patients with ACS has comparable accuracy to that in the general population. Therefore, it is sound to perform OGTT in the ACS patients to improve search for such an important disease as DM [42]. Bronisz et al. [43] reported that a substantial proportion of AMI patients with the abnormal result of OGTT soon after AMI, can have a normal glucose tolerance 3 months after AMI. To the contrary, a meta-analysis found that < 10% of ACS patients diagnosed with DM by means of an OGTT before discharge will have a different result at the follow-up OGTT [42]. Moreover, HbA1c is more expensive, it is not availabile so widely, and does not correlate adequately with the average glycemia in certain individuals [44].

Comparing all three glycemic parameters, FPG, OGTT and HbA1c simultaneously for mortality and CV disease risk reveals that the association is strongest for 2-hour plasma glucose concentration (2hPG) in OGTT [26]. In addition to FPG and HbA1c, OGTT reveals much more cases of DM, both in the general population and CAD [45]. A portion of AMI patients with new-diagnosed AMI by means of OGTT was not negligible [8]. The OGTT showed that 27.4% of CAD patients without known DM at admission actually had DM. Moreover, 33.5% were found to have impaired glucose tolerance (IGT) and another 11.2% were found to have both IGT and impaired fasting glucose (IFG) [46]. On one hand, HbA1c ≥ 6.5% can predict the DM values on OGTT (2hPG value ≥ 11.1 mmol/L) with the positive predictive value of no less than 100% and could, therefore, replace OGTT to diagnoze DM following ACS [25]. To the contrary, OGTT or HbA1c may not diagnose the same patients; evidence of discrepancies between the two modalities to classify abnormal glycoregulation accumulated [25]. OGTT is likely needed, but there is a dilemma when to perform it, during the initial hospitalization, or later (e.g., within 30 days, or at three months).

Variable practice reflects directly the lack of consensus – some authors used to perform OGTT: as early as on the day one of hospitalization [47], on the day three from the admission [34, 48, 49]; on the day four of hospitalization [50] (the ESC guidelines also recommend delaying the test for 4 to 5 days after ACS to minimize the false positive results [51, 52] ,because the results of OGTT could be somewhat falsified by stress hyperglycemia [52]); from one to 3 days following the hospital discharge [53]; from 7 to 28 days after ACS [25]; or 3 months after discharge [42, 46].

OGTT at the discharge performed in the patients with AMI detected a high proportion of patients with previously unknown abnormal glycoregulation that was significantly and independently related to a dismal long-term prognosis [41]. Within 7 days following AMI, OGTT can detect many patients with previously unknown either newly detected DM or IGT, indicating a high risk for the CV events in the next decade. OGTT was a better prognosticator as compared to FBG or HbA1c [41].

Characteristics of most important methods detection of DM in AMI patients are given in Table 1.

### The combination of HbA1c and OGTT to diagnose DM in the AMI patients

To obtain the diagnosis of DM as soon as possible, HbA1c and FBG should be analysed during the first days of hospitalization, but both of them will leave an undetected group of patients with glucometabolic abnormalities [41]. Indeed, OGTT should be performed when HbA1c and FPG are inconclusive [51]. Moreover, a combination of tests (both HbA1c and OGTT) in addition to simple FBG can be used to the better risk-stratification of AMI patients. The OGTT is more sensitive than fasting plasma glucose and HbA1c. The AMI patients categorized as newly diagnosed DM by OGTT, although HbA1c < 6.5%, have a poor long-term prognosis compared to the patients with HbA1c < 6.5%, and an IFG, or normal glucose tolerance (NGT)/IGT by OGTT [37]. The combination of HbA1c and OGTT seems sound. For example, in the AMI patients treated invasively with IGT and newly diagnosed DM (detected by OGTT), an increase of HbA1c was one of the strongest independent risk markers of death [54].

**Table 1**

**Detection of diabetes mellitus (DM) in the acute myocardial infarction patients**

| Method | Advantage |
|---|---|
| RPG > 11.1 mmol/L | routine, always available [1, 27] |
| FBG > 7 mmol/L | routine, always available [1, 46] |
| HbA1C > 6.5% | widely available, within 24 hours [1, 28] |
| OGTT 2-hr PG ≥ 11.1 mmol/L | improves DM detection additionally [26, 45] |
| All above | provides optimal result in DM detection [36, 41, 51] |

**RPG – random plasma glucose; FBG – fasting blood glucose; HbA1C – glycated haemoglobin A1c; OGTT – oral glucose tolerance test; PG – plasma glucose.**

OGTT in a combination with HbA1c provides the additional prognostic information on all-cause mortality, as this identifies a group of high-risk patients, who would remain undetected if using an OGTT, or HbA1c only [38]. Regretably, in practice, the HbA1c levels were not available in about 3/4 of AMI patients without DM [19]. Moreover, the frequency of performing HbA1c varied widely; it was quite different among hospitals (capturing from 7.7% to 87.6% of hospitalized patients) [55].

The real world underutilization of evidence-based therapies for DM may contribute to worse outcome of patients with DM and ACS [7]. Early diagnosis and treatment of dysglycemia may slow down, or even reverse the adverse effects on the CV system [11]. Improved glycaemic control in the DM patients following the AMI results in the reduced long-term mortality [55]. A greater benefit could be obtained from treating the ACS patients with newly diagnosed DM more intensively [4]. Some of the important advantages of measuring HbA1c and performing OGTT are timely detection of abnormal glucose regulation (during the AMI hospitalization, or shortly after it) which could give rise to the prevention strategies, such as lifestyle and pharmacological interventions that can help to prevent DM [45, 46] , and the detection of pre-DM which can be used to avoid drugs known to impair glucoregulation, such as diuretics, non-vasodilatory and non-selective beta blockers, some types of statins, etc. [56–58]. When DM is diagnosed, the appropriate diet, anti-DM drugs, exercise programs, etc., can be planed to improve quality of life and prognosis [29]. Moreover, in the newly diagnozed DM, the prevention of CV diseases can be improved, such as introduction/intensification of treatment (e.g., renin-angiotensin system inhibitor, statin, aspirin, etc.), as a risk category changes substantially with the diagnosis of DM. Timely made DM diagnosis can improve even the mode of reperfusion, as the diabetic status influence the choice between a coronary artery by-pass graft (CABG) and a stent, and further – the choice of stent, as well as antiplatelet therapy. For example, < 20% of the patients with dysglycemia, detected by OGTT, received drug-eluting stents, since they were treated as the non-diabetic patients at the time of percutaneous coronary intervention (PCI) [1, 11]. In the multivariate analysis, the ACS patients with pre-DM (OR, 1.58, 95%:1.08–2.31) and undiagnosed DM (OR, 1.51, 95%:1.01–2.26) also had reduced kidney function more frequently, in comparisson with the AMI patients who had normal glycoregulation [23].

Consequently, the detection of pre-DM and previously undiagnozed DM could enable us to pay more attention to the kidney function and prevent its deteoration. It may be useful to have information about pre-DM and newly detected DM prior to imaging techniques requiring contrast, in order to better prevention of contrast induced nephropathy, i.e., acute kidney injury. Moreover, an additional care should be taken to avoid potentially nephrotoxic drugs, such as, e.g., aminoglycosides.

## Conclusion

There are four different DM varieties in ACS. The real number of the DM patients in AMI, who are adequately diagnosed and treated, could be even less then 30%. It is important to measure HbA1c on admission to detect the unrecognized patients with glycometabolic abnormalities. OGTT before discharge, or within the next 3 months is recommended in the majority of guidelines, but not in all. It is reasonable not to omit OGTT at least if HbA1c is not conclusive. DM and pre-DM are important prognostically, they can be prevented, or treated only if detected. There is no excuse to avoid at least one of such routine tests as it frequently occurred in practice with probable serious clinical consequence (see Table 1).

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