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Some Characteristic Effects of Diabetes Mellitus on Acute Coronary Syndrome: A Narrative Review

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Abstract

Unlike the declining prevalence of several cardiovascular risk factors such as high blood pressure and high cholesterol, the public health burden of diabetes is increasing. The increased risk of diabetic patients after acute coronary syndrome (ACS) creates a management challenge. This risk is conferred by several metabolic alterations at the level of the vascular endothelium, of the thrombotic cascade as well as at the inflammatory level. This diabetic population may be the one that benefits the most from various therapies, such as significant platelet inhibition, and an early invasive strategy. Despite the documented efficacy and the evidence from the recommendations, diabetic patients with ACS remain treated less frequently than patients without diabetes.

Keywords: Acute coronary syndrome; Diabetes mellitus; Reperfusion therapy; Coronary angiography; Coronary heart disease

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Introduction

This is a narrative review it's a narrative review where I will describe my theme in the following order:

- Acute coronary syndromes and diabetes association
- Particularity of coronary heart disease in diabetic patients
- Reperfusion strategy in diabetic patients
- Indication for ESC revascularization 2018
- Antiplatelet therapy
- Aspirin resistance
- Conclusion

Literature Review

Diabetes mellitus is a rapidly growing pandemic affecting more than 350 million patients worldwide [1]. About 1.8 million people have diabetes in Algeria, with a national diabetes prevalence set at 6.9%, according to data from the new 2017 report from the International Diabetes Federation. In detail, the statistical margin of uncertainty for people with diabetes in Algeria is between 1.25 and 2.45 million, corresponding to a national prevalence rate of between 4.9% and 9.5% [2]. In addition, diabetes is one of the main risk factors for coronary heart disease, since more than 40% of patients with acute coronary syndrome (ACS) have diabetes [3].

Acute coronary syndromes and the Diabetes Association

In my daily practice I have several diabetic patients who have had an acute coronary syndrome followed for several years the mortality in patients with ACS is twice as high in diabetic patients compared to non-diabetic patients [4], undiagnosed diabetics and patients with glucose intolerance have an increase in mortality at 30 days after treatment. SCA compared to non-diabetics [5]. Long-term studies in diabetic patients with ACS have shown a 1.8-fold increase in the incidence of cardiovascular mortality and a 1.4-fold increase in myocardial infarction after 2 years of follow-up than in non-diabetics [6]. The presence of diabetes increases the risk of death at 1 year by 70% in ST-elevated ACS and by 20% in no ST- elevated ACS. Clinically, atypical forms of epigastric site with variable intensity and accompanying digestive signs (nausea, vomiting) are frequent in diabetics. Specifically, diabetics with ST-elevated ACS compared to non-diabetics generally receive late reperfusion and exhibit more hemodynamic instability and associated comorbidities [7]. The recurrence rate of myocardial infarction and stroke is lower in patients after primary angioplasty. Diabetics with ACS

have a late onset of reperfusion, a longer time to ischemia, and a delayed onset of treatment due to atypical symptoms [7]. They are more likely to develop complications such as heart failure, kidney failure and major bleeding [8].

Particularity of coronary heart disease in diabetic patients

Diabetics represent 15 to 20% of patients undergoing myocardial revascularization. The anatomical profile of coronary artery disease in patients with diabetes clearly influences their prognosis and response to revascularization. Angiographic studies have shown that diabetics are more likely to have larger main stem and multiple vessel disease with more diffuse disease involving the smaller vessels. In addition, these patients have a greater atherosclerotic load and increased lipid count, rich plaques that tend to rupture, while those with unstable angina have more fissured plaques and intracoronary thrombus and contribute significantly to reduction of the luminal region and coronary flow [8].

Reperfusion strategy in diabetic patients

From a therapeutic point of view, diabetic patients compared to non-diabetic patients present a reduced antiplatelet response and less favorable results after interventional (PCI) and surgical (CABG) revascularization [9]. Specifically the reperfusion therapy in diabetic patients with multivascular coronary disease remains uncertain due to the lack of randomized studies comparing different strategies. The best results were obtained by comparing PCI and CABG in patients with stable multivascular coronary disease. The selection of the reperfusion strategy in diabetic patients would be based on many factors such as the evaluation of the clinical state (hemodynamic/electrical instability, current or residual ischemia, etc.), echocardiographic evaluation of LV function, filling pressures, RV function, global and segmental kinetics and systolic pulmonary artery pressure; angiographic data; evaluation of accessibility to complex coronary lesions during angioplasty and to distal anastomoses during coronary artery bypass grafting, and finally other comorbidities [10]. In addition, various coronary lesion assessment and mortality risk prediction scores after surgery such as SYNTAX and EUROSCORE II [11] are used for revascularization decision making. The presence of diabetes should favor an invasive strategy in no ST elevated ACS, the benefit being greater than in non-diabetic patients. Coronary angiography will be performed within the first 24 hours in high-risk patients with a GRACE score greater than 140 (troponin elevation, ST shift). It can be performed within the first 72 hours in lower risk diabetics [12]. In the FRISC II study, the invasive strategy reduced in absolute value the risk of death from infarction at 1 year by 9.3% in diabetics with ACS ST-, 3 times more than in non-diabetics (3.1% reduction risk at 1 year). In the TACTICS-TIMI 18 study, the invasive strategy reduced the risk of death from infarction to new hospitalization for ACS at 6 months in diabetics by 7.6% in absolute value (*vs.* 1.8% in non-diabetics). Among the 3,488 coronary heart patients in the Euro Heart Survey, one-third had diabetes, and two-thirds had ACS. No benefit of revascularization was found in non-diabetics. Conversely, revascularization reduced mortality at 1 year in diabetics (5.7% *vs.* 8.6%) in the absence of revascularization), as well as the rate of death, infarction and stroke (9, 9% *vs.* 16.9% in the absence of revascularization). In the absence of extracardiac contraindication related to the site, an invasive strategy for revascularization is therefore recommended in all diabetics with ACS [12]. Choosing the most appropriate strategy to revascularize high-risk patients is crucial for improving clinical outcomes. Several studies, randomized trials and meta-analyzes have compared the short- and long-term outcomes after coronary artery bypass grafting and percutaneous coronary intervention in diabetic patients with coronary artery disease. The CARDIA (Coronary Artery Revascularization in Diabetes) study concluded that coronary angioplasty was not inferior to coronary artery bypass grafting in diabetic coronary patients after five years of follow-up [13]. The FREEDOM study At 5 years, the absolute difference between the primary outcome rate of the PCI group and that of the CAP group was similar in the three SYNTAX score subgroups. The use of bio-absorbable stents remains an alternative of choice in diabetic patients, especially with a vessel diameter <2.5 mm [14]. The practice guidelines for the treatment of ACS propose the same treatment strategies in diabetic and non-diabetic patients. In the presence of non-ST segment elevation ACS, early invasive strategies with revascularization, if possible, provide diabetic patients with a reduction in mortality and ischemic recurrence (follow-up period of up to 5 years) equal to or greater than that obtained in the general population. The ACC/AHA non-ST segment elevation ACS guidelines recommend that early invasive strategies be favored over selective (traditional) invasive strategies. In diabetics who have undergone non-ST segment elevation ACS, who have multivascular disease and for whom revascularization is indicated, coronary artery bypass grafting with internal mammary artery may provide greater benefit than angioplasty. Angioplasty (with a drug-impregnated stent if possible) may however be suitable in patients with less extensive disease (only one vessel affected) [15].

In the presence of ACS with ST-segment elevation, an immediate reperfusion strategy (using fibrinolysis or primary angioplasty) provides similar benefits in diabetic and non-diabetic patients. Compared to fibrinolysis, primary angioplasties provide greater benefit in diabetics, and in a similar manner to what is observed in non-diabetics (mortality in diabetic patients, primary PCI *vs.* fibrinolysis, odds ratio [OR] ¼ 0.49; 95% CI ¼ 0.31 to 0.79). However, fibrinolysis should be performed if PCI cannot be administered in a timely manner. Eye bleeding in patients with diabetic retinopathy is extremely rare and should not limit the use of fibrinolysis in cases where it is indicated [16-22].

The latest recommendations from ESC 2018 Coronary bypass surgery are an indication for grade IA in diabetics with tritronascular disease and Syntax score between 0 and 22 [23].

Indication for ESC Revascularization 2018

Antiplatelet therapy: Regarding antiplatelet therapy, it must be the same in diabetic and non-diabetic patients (same drugs and same doses). However, the new P2Y12 inhibitors, prasugrel and ticagrelor appear to be superior compared to clopidogrel in diabetic patients with ACS in the TRITON-TIMI 38 and PLATO

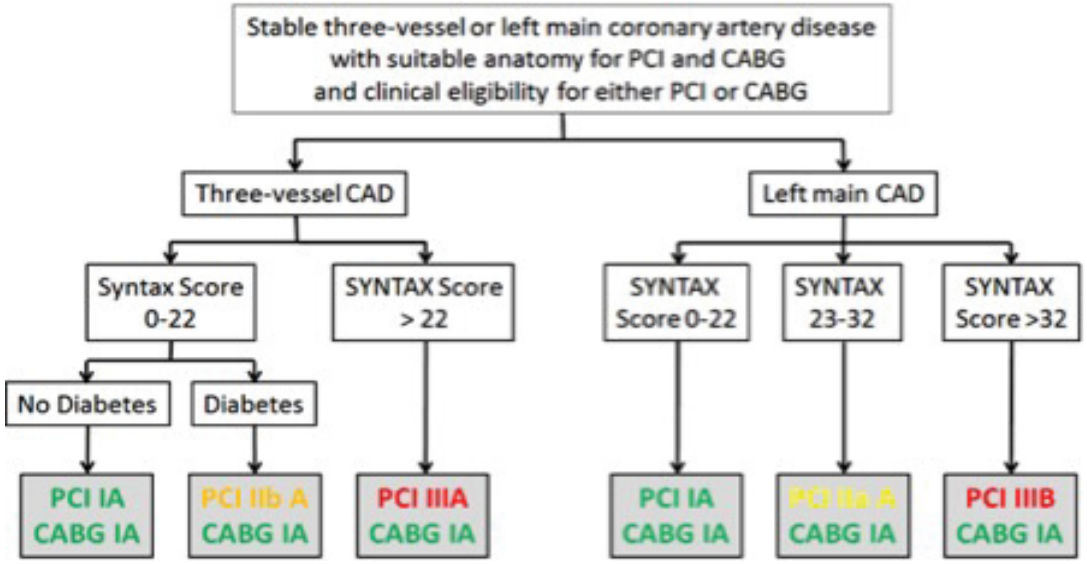

Figure 1 Indication for ESC revascularization 2018.

studies [17]. Anti-GPIIBIIIA have shown a reduction in mortality in diabetics with ACS without ST segment elevation but their role should be further elucidated. Antiplatelet drugs such as thienopyridines are used less often in diabetic patients than in non-diabetics [17]. Antiplatelet therapy reduces the risk of serious events and death in the diabetic after ACS, although the residual risk may be attributed to poor adherence, varying inhibition, and multiple pathways of platelet activation or response to optimal to aspirin which is called resistance to aspirin [17]. Diabetes increases the risk of stent thrombosis by 2 to 3 compared to non-diabetic. This increased risk of thrombosis should prompt the use of prasugrel or ticagrelor in combination with aspirin in diabetics with acute coronary syndrome. In TRITON-TIMI 38 (angioplasty for acute coronary syndrome), prasugrel decreases at 15 months the cumulative risk of cardiac death, infarction, cerebrovascular accident (9.9% on prasugrel *vs.* 12.1% on clopidogrel). The benefit is twice as important in diabetics than in non-diabetics (30% reduction in the event with prasugrel in diabetics *vs.* 14% in non-diabetics). In the predefined subgroup of 4,662 diabetic patients with acute coronary syndrome in the PLATO study, comparing ticagrelor and clopidogrel, ticagrelor reduced the risk of death by 18% and the risk of stent thrombosis by 35%. In the absence of a specific study in stable coronary artery disease, the use of ticagrelor or prasugrel remains "off label" in diabetics revascularized by angioplasty for stable angina [17] **(Figure 1).**

Aspirin resistance: Its prevalence differs widely due to the doses used, it is greater in obese people and when carbohydrate metabolism is disturbed [18]. Insufficient absorption is a potential cause of the unresponsiveness of aspirin, delayed or reduced absorption may be more common, and the platelet inhibitory response more variable for enteric-coated aspirin than for immediate-release aspirin [19]. Clinical resistance to aspirin is defined as any recurrence of atherothrombotic disease in a patient on aspirin. Obviously, this definition is very broad because the causes are multifactorial. Platelet aggregation tests, carried out in certain expert centers, measuring the inability of aspirin to inhibit the production of thromboxane A2 by platelets, provide a better understanding of this resistance to aspirin. Diabetes is a major risk factor for aspirin resistance. In diabetic coronary patients with one of the following criteria (active smoking, platelet count> 270 g/l, inflammatory syndrome), biological resistance can reach 40%. This could explain the negative results of studies of prevention of ischemic events in diabetic patients with arterial disease such as in the POPADAD study [19]. In practice, for the clinician, any new thrombotic event in a patient on aspirin should raise suspicion of resistance to aspirin. Compliance problems and competition with anti-inflammatory drugs should be systematically investigated. In some patients, especially those with inflammatory syndrome, PAD and/or diabetes, aspirin is often lacking. The duration of the biological effect of aspirin has been overestimated in these populations. The presence of an accelerated platelet turnover does not allow a single daily dose of aspirin to exert its antiplatelet pharmacodynamic effect. This could lead to proposing to increase the number of daily aspirin intakes in the future, but no clinical evidence currently exists and studies are ongoing [20-23].

Conclusion and Recommendations

Some practical recommendations for diabetic patients with ACS:

- Screening for diabetes should be performed by measuring fasting blood sugar, HbA1c or blood sugar after ingestion of 75 g of glucose.
- All patients with diabetes and ACS should receive the same treatments recommended for non-diabetic patients with ACS, as they provide equivalent benefit.
- Patients with diabetes and ACS undergoing angioplasty should receive antiplatelet therapy with prasugrel (in

patients who have never been treated with clopidogrel, aged less than 75 years, weighing more than 65 kg and not having no history of stroke) [Class IA] or ticagrelor [Class IB], rather than clopidogrel, to further reduce recurrent ischemic events.

- Patients with diabetes and non-ST segment elevation ACS, with characteristics that put them at higher risk and requiring selective invasive intervention should be treated with ticagrelor rather than clopidogrel [Class IIB].
- In patients with diabetes and non-ST segment elevation ACS and with features that put them at high risk, an early invasive revascularization strategy should be adopted, rather than a selective invasive approach, in order to reduce the risk. Risk of recurrent coronary events, except in cases of contraindication.
- In patients with diabetes and ST-segment elevation ACS, the presence of retinopathy should not be a contraindication for fibrinolysis [Class IIB].
- The management of diabetes in a hospital setting, in patients with ACS, should include strategies to avoid both hyperglycemia and hypoglycemia: Blood glucose should be measured at the time of hospitalization, and it should be monitored throughout the stay.
- In patients who have undergone ACS and whose blood glucose is greater than 11.0 mmol/L during hospitalization, blood glucose control will aim for values of 7.0 to 10.0 mmol/L, and will be followed by strategies aimed at achieving recommended target values.
- Insulin therapy may be necessary to reach these targets.
- A similar approach can be taken in diabetic patients with a blood glucose level of 11.0 mmol/L or less at the time of hospitalization.
- An appropriate protocol should be developed and staff should be trained to ensure safe and effective initiation of treatment and to minimize the risk of hypoglycemia
- While all diabetic coronaries should benefit from intensive correction of risk factors, the indication and choice of revascularization mode depends on many parameters including the clinical situation, coronary anatomy, patient-related factors and comorbidities.
- The specifics of myocardial revascularization in diabetic patients were the subject of ESC/EACTS recommendations in 2014. New antiplatelet drugs, bioabsorbable stents, new surgical techniques reducing the risk of stroke and sternal infection will justify further studies and other recommendations in our complex and high risk patients.

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