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TREATMENT OF ACS IN THE DIABETIC PATIENT: WHAT THE EVIDENCE SHOWS

TRATAMENTO DA SCA NO PACIENTE DIABÉTICO: O QUE MOSTRAM AS EVIDÊNCIAS

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ABSTRACT

Diabetes mellitus (DM) is a frequent comorbidity among patients with acute coronary syndrome (ACS), affecting about 20% to 37% of these patients. Besides being an independent risk predictor, it is also related to a higher prevalence of atypical presentations of ACS. Despite this, it is important to emphasize that in the case of ACS the majority of patients with DM have the same clinical presentation as patients without the disease. Just as for non-diabetic patients, risk scores should be applied. However, this comorbidity per se predicts a greater severity. Also, it is preferable to use an early invasive strategy for these patients. Regarding the medicinal treatment of ACS, there are no significant differences between the treatment of patients with DM and those without DM. In relation to reperfusion therapy, much of it is extrapolated from knowledge of stable angina, in which surgical treatment takes precedence over percutaneous treatment for patients with DM, despite the lack of evidence in the acute context. Finally, there is no definitive body of evidence to indicate the best strategy to control hyperglycemia, but it is known that both hyperglycemia and hypoglycemia during hospitalization are associated with worse outcomes. Thus, it is important to avoid glycemia values above 180 mg/dL and below 90 mg/dL, restricting the strategy of strict glycemic control with intravenous insulin to selected patients.

Keywords: Diabetes mellitus; Acute coronary syndrome; Comorbidity; Reperfusión.

RESUMO

O diabete mellitus (DM) é uma comorbidade muito frequente entre os pacientes com síndrome coronariana aguda (SCA), acometendo, aproximadamente, 20 a 37% desses. Além de ser um preditor de risco independente, também está relacionado a uma maior prevalência de quadros atípicos de SCA. Apesar disso, é importante ressaltar que no caso da SCA, a maioria dos pacientes com DM apresenta o mesmo quadro clínico que os pacientes sem a doença. Assim como para os pacientes não diabéticos, os scores de risco devem ser aplicados. Entretanto, essa comorbidade por si própria já prediz uma maior gravidade. Inclusive é mais aconselhável utilizar para esses pacientes uma estratégia invasiva precoce. Em relação ao tratamento medicamentoso da SCA, não há alterações significativas no tratamento dos pacientes com DM para os pacientes sem DM. Já no que diz respeito à terapia de reperfusão, muito se extrapola dos conhecimentos em angina estável, em que há uma superioridade do tratamento cirúrgico sobre o percutâneo para os pacientes com DM, ainda que haja falta de evidências no contexto agudo. Finalmente, o conjunto de evidências não é definitivo para indicar a melhor estratégia para o controle da hiperglicemia, entretanto, sabe-se que tanto a hiperglicemia quanto à hipoglicemia durante a internação está relacionada aos piores desfechos. Portanto, é importante evitar valores de glicemia superiores a 180 mg/dL e inferiores a 90 mg/dL, ficando a estratégia de controle rigoroso de glicemia com insulina intravenosa restrita aos pacientes selecionados.

Descritores: *Diabetes mellitus; Síndrome coronariana aguda; Comorbidade; Reperfusão.*

INTRODUCTION

It is estimated that there are over 170 million patients with diabetes worldwide, and this number may increase up to 165% over the next 12 years.[1] Approximately 20% to 37% of patients with acute coronary syndrome (ACS) have diabetes mellitus (DM), and many remain unaware of the diagnosis until the onset of coronary heart disease. Usually, a patient with DM is older, and DM has a higher prevalence rate in women with comorbidities and aggregates such as hypertension, obesity, chronic kidney disease, and dyslipidemia.[1-5]

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In the presence of ACS, most patients with DM have the same clinical presentation as those without the disease. However, patients with DM are more likely to present atypical symptoms of coronary artery disease, such as epigastric pain, pinprick pain, indigestion, pleuritic pain, syncope, and dyspnea.[2,6-11] Thus, the absence of classic symptoms of coronary artery disease may compromise the diagnosis of ACS in patients with DM, especially when the electrocardiogram finding is normal or presents some previous alteration that causes difficulty in interpretation.[2,10]

Some specific therapeutic recommendations for this population should be considered and will be further discussed below.

THERAPEUTIC CONSIDERATIONS

1. Risk stratification

The same risk scores for non-ST elevation ACS applied in patients without DM, such as *TIMI* and *GRACE risk scores*, can be used in patients with DM. However, DM is in itself a predictor of mortality in patients with ACS, resulting in a risk two to three times greater than that of the general population.[2,4,5,12-15] Thus, a patient with DM can be considered a high-risk patient regardless of the score utilized, in which case an optimized early invasive strategy should be preferred.[2,12-18]

Although they admittedly present a higher risk of death and events in the short and long term, patients with DM and ACS are usually treated in a non-optimal manner. In European records, use of invasive strategy and reperfusion therapy and administration of thienopyridine and glycoprotein IIb/IIIa inhibitors (IGP IIb/IIIa) may lower the rates in patients without DM, and this is clearly reflected in morbidity and mortality.[2,4,19]

2. Antiplatelet therapy

Drug treatment in the acute phase of ACS and the decision regarding application of noninvasive or stratification invasive tests and/or revascularization should be similar in patients with or without DM.[2,12,15,18,20-25]

a. Acetylsalicylic acid (ASA)

The use of ASA is universally recommended in patients with DM and coronary artery disease, with a benefit of up to 23% reduction of events. The same dose is indicated for patients with DM, in both the acute and chronic phases of the disease.[1,26,27]

b. Clopidogrel

In a subanalysis of the *CURE study*, which analyzed the acute phase of non-ST elevation ACS and compared the uses of ASA in isolation and ASA plus clopidogrel (300 mg for the attack and 75 mg for maintenance), 2,840 patients with DM were included. In this study, a combined outcome reduction when clopidogrel was added (14.2% × 16.7%) was observed, but no statistical significance was noted. Nevertheless, due to the small number of patients with DM and the fact that there is a high level of events in the group with DM (14.2% × 7.9%), the routine use of clopidogrel in non-ST elevation ACS is recommended, similar to the approach used for patients without DM.[1,28]

In ST elevation ACS, the benefit of using clopidogrel is less convincing vis-à-vis than that in non-ST elevation ACS. In the *COMMIT* study, the prevalence of DM was not disclosed. This made the subanalysis of that population impossible.[1] As for the *CLARITY-TIMI 28* study, patients were randomized to receive fibrinolytic medications or not in addition to clopidogrel (300 mg for the attack, followed by 75 mg for maintenance). The study included 575 patients with DM. Among those who underwent primary angioplasty, the group that received clopidogrel showed a 39% reduction in events at 30 days, but, again, no statistical significance was observed (due to the small sample size).[1,29,30]

Moreover, a probable rebound effect has been observed after early discontinuation of clopidogrel (before one year of use) in patients with DM, with an increase in the number of events compared to that in patients without DM. The results are still conflicting, but they do show a significant trend. It is believed that there is a greater activation/platelet reactivity in patients with DM vis-à-vis those without the disease.[31,32]

c. Prasugrel

Similar to clopidogrel, there are no differences in the use of prasugrel in patients with or without DM in non-ST elevation ACS. In the *TRITON-TIMI 38* study, prasugrel was superior to clopidogrel in reducing composite outcome (cardiovascular death, AMI, or stroke) without an increased risk of bleeding. In patients with DM, the benefit obtained with the use of prasugrel was greater than that in the general population of the study, with reduction of incidence of events from 17% to 12.2%. No specific studies have been performed in patients with DM; however, the same recommendation for the general population should be applied to this specific group.[2,12,18,22]

d. Ticagrelor

The use of ticagrelor in patients with DM follows the same approach as mentioned above with regard to clopidogrel and prasugrel. It must be prescribed without significant modifications. In the *PLATO* study, the use of ticagrelor in patients with non-ST elevation ACS reduced coronary events and mortality rate compared to the use of clopidogrel, regardless of the patient's glycemic *status,* without significant increase in bleeding. Specifically, in patients with glycated hemoglobin level greater than 6.0%, ticagrelor has also been shown to reduce all-cause mortality.[2,23]

e. IGP IIb/IIIa

Several studies were carried out on IGP IIb/IIIa, including those in patients with DM. The main meta-analysis of six large studies showed favorable outcomes with the use of IGP IIb/IIIa in patients with DM and ACS (reduction of mortality from 6.2% to 4.6%, $p = .007$). In patients with DM who underwent coronary angioplasty, the benefit was shown to be even greater, with reduction of mortality rate at 30 days from 4% to 1.2%.[26]

However, the studies included in this meta-analysis were conducted before the application of platelet antiaggregation therapy. Some studies have evaluated whether the use of IGP IIb/IIIa in the presence of dual platelet antiaggregation therapy prior to invasive stratification would have a proven clinical benefit. Its routine use, as *upstream* treatment, did not confirm this benefit in the *ISAR-SWEET* and *EARLY-ACS* studies. With the use of dual platelet antiaggregation drugs, especially at high doses, in patients with DM, there is no

evidence in the literature regarding the benefit from the routine addition of IGP IIb/IIIa.[33-35]

In contrast, the *ISAR-REACT 2* study showed the reduction of combined outcomes in patients with DM with non-ST elevation ACS and elevated troponin levels who received a clopidogrel attack dose of 600 mg 2 h before coronary angioplasty was performed. However, abciximab was the IGP IIb/IIIa used and administered only during the procedure in the hemodynamic room.[1,16]

3. Anticoagulant therapy

There were no differences regarding the use of anticoagulant medications in patients with or without DM, in ACS either with or without ST elevation. Initially, all routinely prescribed medications (enoxaparin, heparin, fondaparinux, and non-fractional bivalirudin) can and should be used if there is no precise indication. Specifically in non-ST elevation ACS, in the *SYNERGY* and *A to Z* studies (which evaluated the use of unfractionated heparin vs. enoxaparin), the groups of patients with or without DM showed the same levels of benefit with regard to reduction of combined outcomes, with no significant difference between the two medications.[2,26,27,36-38]

4. Invasive versus conservative strategy

Although no large study has been designed to evaluate the best strategy in patients with DM with non-ST elevation ACS, performing an early invasive strategy is the best measure to be adopted, mainly due to the fact that patients with DM are considered high-risk patients.[2,17,18,39,40]

In the *FRISC-II study,* it was demonstrated that the benefit of invasive strategy in patients with DM (OR = .72; CI 95%: -.54–.95) is similar to that in high-risk patients without DM (OR = .61; CI 95%: .36–1.04), with reduction in the number of AMI and deaths in the one-year follow-up.[2,15]

In the *TACTICS-TIMI-18* study, patients with DM showed greater benefit than those without DM, owing to the adoption of early invasive strategy, with a relative risk reduction of 27% and 13%, respectively.[1,12,41]

5. Reperfusion therapy in patients with ST elevation ACS

A meta-analysis involving all major studies on ST elevation ACS comparing thrombolysis and a placebo showed greater survival after 35 days of evolution in patients with DM (n = 2,236) who were administered fibrinolytic medications (3.7 × 1.5 lives saved per 100 patients treated, respectively).[42]

Although no studies have specifically compared thrombolysis and primary angioplasty in patients with DM, a subanalysis of 11 randomized studies demonstrated a reduction in death and re-infarction rate in 30 days after performing primary angioplasty compared to that after performing thrombolysis (9.2% × 19.3%, p < .05). Additionally, the benefit of primary angioplasty was higher in the diabetic group than in the non-diabetic group (number needed to treat: 10 vs. 16, respectively).[43] Thus, primary angioplasty, when available, should be preferred.

6. Coronary revascularization surgery versus coronary angioplasty

In patients with triarterial coronary artery disease and DM, myocardial revascularization surgery seems to be better than percutaneous coronary intervention. In a meta-analysis of 10 randomized trials with 7,812 patients, surgery resulted in a lower mortality rate in a 5.9-year follow-up compared to angioplasty in patients with DM (23% vs. 29%, p = .05).[2,44,45]

Similar results were observed in the *BARI-2D* study, which compared clinical treatment + surgical revascularization/angioplasty and optimized clinical treatment in patients with stable angina. In the five-year follow-up, the group of patients with DM who underwent revascularization presented lower mortality rates than did those who underwent clinical treatment (21.1% vs. 29.2%, p < .01), as well as lower death rates from cardiac/AMI causes (15.8% vs. 21.9%, p < .03). No difference was observed between the angioplasty and clinical treatment groups.[46,47]

In the *SYNTAX study*, when surgical revascularization was compared to angioplasty with pharmacological *stent* in patients with multiarterial coronary artery disease and DM or those with left coronary trunk lesion, no difference in the number of deaths or AMI was observed. However, there was a higher revascularization rate in the angioplasty group after 18 months of follow-up.[48]

In the last published study on patients with DM with stable and triarterial angina, without ventricular dysfunction, angioplasty with drug-eluting *stent* was compared with myocardial revascularization surgery in 1,900 patients. Again, surgery showed better results, in relation to mortality, when compared to angioplasty (10.9% vs. 16.3%, p = .049).[49]

However, all these studies included only patients with stable angina. It is not known whether these data can be extrapolated to patients with ACS.

The *AWESOME* study was the only study that compared myocardial revascularization and coronary angioplasty in patients with DM and ACS. The three-year survival rate among patients with DM was 72% versus 81%, respectively, with no statistical significance. However, careful interpretation of the results is necessary, since the internal thoracic artery was used in only 70% of the patients, *stent* in 54%, and IGP IIb/IIIa in 11%.[1,50]

7. Conventional versus drug-eluting stent

A recent meta-analysis compared the use of a drug-eluting and conventional *stent*, showing similar safety profiles in the first six months, provided that the dual platelet antiaggregation therapy was properly performed.[2,9,51] The number of re-interventions was significantly lower when the drug-eluting *stent* was used, in comparison to the use of a conventional *stent* (OR = .29 for sirolimus; OR = .38 for paclitaxel). It is assumed that these data can be extrapolated to patients with DM and ACS, since there are no specific studies evaluating such intervention. Moreover, because of the increased risk of intra*stent* restenosis in this group of patients, it has even been speculated that there is greater benefit from the use of drug-eluting *stent*s in patients with DM even with the presence of ACS.[1,52-54] Currently, the use of state-of-the-art drug-eluting *stents* in patients with DM is being recommended.[26]

8. Glycemic control during hospitalization

Data on glycemic control in patients with DM are inconclusive so far. In patients with ST elevation ACS, the *DIGAMI* study showed a 30% reduction in mortality in one year with intravenous insulin use and strict glycemic control.[2,55]

In contrast, these same data were not found in the *DIGAMI-2* study. More recent studies on critical patients, not necessarily with ACS, have shown that in hemodynamically stable patients with DM, the use of intravenous insulin associated with restricted glycemic control may cause an increase in adverse events, mainly related to episodes of hypoglycemia. It is not known whether hypoglycemia is the direct cause of increased mortality rate in the intensive group in some of these studies. There is a lack of specific studies in patients with ACS to define the best strategy to be adopted. Thus, it is currently recommended that hyperglycemia (blood glucose level > 180 mg/dL) as well as hypoglycemia (blood glucose level < 90 mg/dL) should be avoided and strict glycemic control with intravenous insulin should be implemented and used only in specific cases.[2,56-65] Similarly, there is no evidence that insulin infusion with glucose and potassium will be beneficial to patients; it may even be deleterious.[66]

PROGNOSIS

As mentioned above, DM is an independent predictor of mortality in patients with ACS. Similar data have also been observed even in patients with glucose intolerance compared to individuals with normal glucose metabolism.[2,5,19,67-72]

In patients without DM, the development of hyperglycemia on admission or during hospitalization is an independent risk predictor of ACS.[1,2]

Although an explanation for the mechanism underlying such findings is still unclear, the patient usually presents with a higher prevalence rate of other cardiac risk factors, inflammation, tendency for thrombosis, and increased platelet aggregation.[73]

Other predictors of mortality as a maximum value of troponin or markers of inflammation with C-reactive protein and/or leukocytosis are also valid in patients with DM, although most of the studies have not specifically assessed this group of patients.[1,2,74]

CONFLICTS OF INTEREST

The author declares that he has no conflicts of interest in this work.

REFERENCES

1. Amin AP, Marso SP. Acute Coronary Syndrome in the Patient with Diabetes: Is the Management Different? Curr Cardiol Rep. 2010;12:321–9.
2. Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, et al. 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persis*tent* ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persis*tent* ST-Segment Elevation of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(3):267-315.
3. Bartnik M, Malmberg K, Norhammar A, Tenerz A, Ohrvik J, Ryden L. Newly detected abnormal glucose tolerance: an important predictor of long-term outcome after myocardial infarction. Eur Heart J. 2004;25:1990–7.
4. Dotevall A, Hasdai D, Wallentin L, Battler A, Rosengren A. Diabetes *mellitus*: clinical presentation and outcome in men and women with acute coronary syndromes. Data from the Euro Heart Survey ACS. Diabet Med. 2005;22:1542–50.
5. Donahoe SM, Stewart GC, McCabe CH, Mohanavelu S, Murphy SA, Cannon CP, et al.: Diabetes and mortality following acute coronary syndromes. JAMA. 2007;298:765–75.
6. Canto JG, Fincher C, Kiefe CI, Allison JJ, Li Q, Funkhouser E, et al. Atypical presentations among Medicare beneficiaries with unstable angina pectoris. Am J Cardiol. 2002;90:248–53.
7. Culic V, Eterovic D, Miric D, Silic N. Symptom presentation of acute myocardial infarction: influence of sex, age, and risk factors. Am Heart J. 2002;144:1012–7.
8. Brieger D, Eagle KA, Goodman SG, Steg PG, Budaj A, White K, et al. Acute coronary syndromes without chest pain, an underdiagnosed and undertreated high-risk group: insights from the Global Registry of Acute Coronary Events. Chest. 2004;126:461–9.
9. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2010;31:2501–55.
10. Nicolau JC, Timerman A, Marin-Neto JA, Piegas LS, Barbosa CJDG, Franci A, et al. Sociedade Brasileira de Cardiologia. Diretrizes da Sociedade Brasileira de Cardiologia sobre Angina Instável e Infarto Agudo do Miocárdio sem Supradesnível do Segmento ST. Arq Bras Cardiol. 2014; 102(3Supl.1):1-61.
11. Nicolau JC, Barbosa CJ, Franci A, Baracioli LM, Franken M, Lima FG, et al. Do diabetic patients with acute coronary syndromes have a higher threshold for ischemic pain? Arq Bras Cardiol. 2014;103(3):183-91.
12. Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE Jr, et al. 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non–ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2012;126:875–910.
13. Institute of Medicine: Clinical Practice Guidelines We Can Trust. Washington, DC: The National Academies Press; 2011. Acesso em 28/05/2018. Disponível em: https://www.ncbi.nlm.nih.gov/books/NBK209539/
14. Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE Jr, et al. ACC/AHA 2007 guidelines for the management of patients with unstable angina/non Stelevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non–ST-Elevation Myocardial Infarction). Circulation. 2007;116:e148 –304.
15. FRagmin and Fast Revascularisation during InStability in Coronary artery disease Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. Lancet. 1999;354:708 –15.
16. Kastrati A, Mehilli J, Neumann F-J, Dotzer F, ten Berg J, Bollwein H, et al, for the Intracoronary *Stent*ing, Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 2 Trial I. Abciximab in patients with acute coronary syndromes undergoing percutaneous coronary intervention after clopidogrel pretreatment: the ISAR-REACT 2 Randomized Trial. JAMA 2006;295:1531–1538.
17. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. FRISC II Investigators. Fast Revascularisation during Instability in Coronary artery disease. Lancet 2000;356:9–16.
18. Cannon CP, Weintraub WS, Demopoulos LA, Vicari R, Frey MJ, Lakkis N, et al. Comparison of early invasive and conservative strategies in patients with unstable coronary syndromes treated

with the glycoprotein IIb/IIIa inhibitor tirofiban. N Engl J Med. 2001;344:1879–87.

19. Hasin T, Hochadel M, Gitt AK, Behar S, Bueno H, Hasin Y. Comparison of treatment and outcome of acute coronary syndrome in patients with versus patients without diabetes *mellitus*. Am J Cardiol. 2009;103:772–8.
20. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. Circulation. 1999;100:1602–8.
21. Norhammar A, Malmberg K, Diderholm E, Lagerqvist B, Lindahl B, Rydén L, et al. Diabetes *mellitus*: the major risk factor in unstable coronary artery disease even after consideration of the extent of coronary artery disease and benefits of revascularization. J Am Coll Cardiol. 2004;43:585–91.
22. Wiviott SD, Braunwald E, Angiolillo DJ, Meisel S, Dalby AJ, Verheugt FW, et al. Greater clinical benefit of more intensive oral antiplatelet therapy with prasugrel in patients with diabetes *mellitus* in the trial to assess improvement in therapeutic outcomes by optimizing platelet inhibition with prasugrel-Thrombolysis in Myocardial Infarction 38. Circulation. 2008;118:1626–36.
23. James S, Angiolillo DJ, Cornel JH, Erlinge D, Husted S, Kontny F, et al. Ticagrelor vs. clopidogrel in patients with acute coronary syndromes and diabetes: a substudy from the PLATelet inhibition and patient Outcomes (PLATO) trial. Eur Heart J. 2010;31:3006–16.
24. Roffi M, Angiolillo DJ, Kappetein AP. Current concepts on coronary revascularization in diabetic patients. Eur Heart J. 2011;32:2748–57.
25. Dalby AJ, Gottlieb S, Cyr DD, Magnus Ohman E, McGuire DK, Ruzyllo W, et al. Dual antiplatelet therapy in patients with diabetes and acute coronary syndromes managed without revascularization. Am Heart J. 2017;188:156-66.
26. Valgimigli M, Bueno H, Byrne RA, Collet JP, Costa F, Jeppsson A, et al. 2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS: The Task Force for dual antiplatelet therapy in coronary artery disease of the European Society of Cardiology (ESC) and of the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 201814;39(3):213-60.
27. Amsterdam EA, Wenger NK, Brindis RG, Casey DE Jr, Ganiats TG, Holmes DR Jr, et al. 2014 ACC/AHA guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/ American Heart Association Task Force on Practice Guidelines. Circulation. 2014;130:e344–e426.
28. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet. 2001;358:527–33.
29. Sabatine MS, Cannon CP, Gibson CM, López-Sendón JL, Montalescot G, Theroux P, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med. 2005;352:1179–89.
30. Sabatine MS, Cannon CP, Gibson CM, et al.: Effect of clopidogrel pretreatment before percutaneous coronary intervention in patients with ST-elevation myocardial infarction treated with fibrinolytics:the PCI-CLARITY study. JAMA. 2005, 294:1224-32.
31. Ho PM, Peterson ED, Wang L, Magid DJ, Fihn SD, Larsen GC, et al. Incidence of death and acute myocardial infarction associated with stopping clopidogrel after acute coronary syndrome. JAMA. 2008, 299:532–9.
32. Angiolillo DJ, Fernandez-Ortiz A, Bernardo E, Ramírez C, Sabaté M, Jimenez-Quevedo P, et al. Clopidogrel withdrawal is associated with proinflammatory and prothrombotic effects in patients with diabetes and coronary artery disease. Diabetes. 2006, 55:780–4.
33. Roffi M, Chew DP, Mukherjee D, Bhatt DL, White JA, Heeschen C, et al. Platelet glycoprotein IIb/IIIa inhibitors reduce mortality in diabetic patients with non-ST-segment-elevation acute coronary syndromes. Circulation. 2001;104:2767–71.
34. Giugliano RP, White JA, Bode C, Armstrong PW, Montalescot G, Lewis BS, et al. the EARLY ACS Investigators. Early versus delayed, provisional eptifibatide in acute coronary syndromes. N Engl J Med. 2009;360:2176–90.
35. Mehilli J, Kastrati A, Schuhlen H, Dibra A, Dotzer F, von Beckerath N, et al. Randomized clinical trial of abciximab in diabetic patients undergoing elective percutaneous coronary interventions after treatment with a high loading dose of clopidogrel. Circulation. 2004;110:3627–35.
36. Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the management of ST segment elevation acute myocardial infarction of the European Society of Cardiology (ESC). Eur Heart J. 2012;33:2569–619.
37. Mahaffey KW, Cohen M, Garg J, Antman E, Kleiman NS, Goodman SG, et al. High-risk patients with acute coronary syndromes treated with low-molecular-weight or unfractionated heparin: outcomes at 6 months and 1 year in the SYNERGY trial. JAMA. 2005;294:2594–600.
38. Blazing MA, de Lemos JA, White HD, Fox KA, Verheugt FW, Ardissino D, et al. Safety and efficacy of enoxaparin vs unfractionated heparin in patients with non-Stsegment elevation acute coronary syndromes who receive tirofiban and aspirin: a randomized controlled trial. JAMA. 2004;292:55–64.
39. Gustafsson I, Hvelplund A, Hansen KW, Galatius S, Madsen M, Jensen JS, et al. Underuse of an invasive strategy for patients with diabetes with acute coronary syndrome: a nationwide study. Open Heart. 2015 Feb 6;2(1):e000165.
40. O'Donoghue ML, Vaidya A, Afsal R, Alfredsson J, Boden WE, Braunwald E, et al. An invasive or conservative strategy in patients with diabetes *mellitus* and non-ST-segment elevation acute coronary syndromes: a collaborative meta-analysis of randomized trials. J Am Coll Cardiol. 2012;60(2):106-11.
41. Januzzi JL, Cannon CP, DiBattiste PM, Murphy S, Weintraub W, Braunwald E, et al.Effects of renal insufficiency on early invasive management in patients with acute coronary syndromes (the TACTICS-TIMI 18 Trial). Am J Cardiol. 2002;90:1246–9.
42. Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group [no authors listed]. Lancet. 1994; 343:311–22.
43. Grines C, Patel A, Zijlstra F, Weaver WD, Granger C, Simes RJ; et al. Primary coronary angioplasty compared with intravenous thrombolytic therapy for acute myocardial infarction: six-month follow up and analysis of individual patient data from randomized trials. Am Heart J. 2003;145:47–57.
44. Hlatky MA, Boothroyd DB, Bravata DM, Boersma E, Booth J, Brooks MM, et al. Coronary artery bypass surgery compared with percutaneous coronary interventions for multivessel disease: a collaborative analysis of individual patient data from ten randomised trials. Lancet. 2009;373:1190–7.
45. Ramanathan K, Abel JG, Park JE, Fung A, Mathew V, Taylor CM, et al. Surgical Versus Percutaneous Coronary Revascularization in Patients With Diabetes and Acute Coronary Syndromes. J Am Coll Cardiol. 2017;70(24):2995-3006.
46. Chaitman BR, Hardison RM, Adler D, Gebhart S, Grogan M, Ocampo S, et al. The Bypass Angioplasty Revascularization Investigation 2 Diabetes randomized trial of different treatment strategies in type 2 diabetes *mellitus* with stable ischemic heart disease: impact of treatment strategy on cardiac mortality and myocardial infarction. Circulation. 2009;120:2529–40.
47. Frye RL, August P, Brooks MM, Hardison RM, Kelsey SF, MacGregor JM, et al. A randomized trial of therapies for type 2 diabetes and coronary artery disease. N Engl J Med. 2009;360:2503–15.
48. Banning AP, Westaby S, Morice MC, Kappetein AP, Mohr FW, Berti S, et al. Diabetic and nondiabetic patients with left main and/or 3-vessel coronary artery disease: comparison of outcomes with

cardiac surgery and paclitaxel-eluting *stent*s. J Am Coll Cardiol. 2010;55:1067–75.

49. Farkouh ME, Domanski M, Sleeper LA, Siami FS, Dangas G, Mack M, et al. Strategies for multivessel revascularization in patients with diabetes. N Engl J Med. 2012;367:2375-84.
50. Morrison DA, Sethi G, Sacks J, Henderson W, Grover F, Sedlis S, et al. Percutaneous coronary intervention versus coronary artery bypass graft surgery for patients with medically refractory myocardial ischemia and risk factors for adverse outcomes with bypass: a multicenter, randomized trial. J Am Coll Cardiol. 2001;38:143–9.
51. Stettler C, Allemann S, Wandel S, Kastrati A, Morice MC, Schomig A, et al. Drug eluting and bare metal *stent*s in people with and without diabetes: collaborative network meta-analysis. BMJ. 2008;337:a1331.
52. Brar SS, Leon MB, Stone GW, Mehran R, Moses JW, Brar SK, et al. Use of drug-eluting *stent*s in acute myocardial infarction: a systematic review and metaanalysis. J Am Coll Cardiol. 2009;53:1677–89.
53. Stone GW, Lansky AJ, Pocock SJ, Gersh BJ, Dangas G, Wong SC, et al. Paclitaxel-eluting *stent*s versus bare-metal *stent*s in acute myocardial infarction. N Engl J Med. 2009;360:1946–59.
54. Fuster V, Farkouh ME. Acute Coronary Syndromes and Diabetes *Mellitus*: A Winning Ticket for Prasugrel. Circulation. 2008;118:1607-8.
55. De Caterina R, Madonna R, Sourij H, Wascher T. Glycaemic control in acute coronary syndromes: prognostic value and therapeutic options. Eur Heart J. 2010;31:1557–64.
56. Finfer S, Chittock DR, Su SY, Blair D, Foster D, Dhingra V, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med. 2009;360:1283–97.
57. Kosiborod M, Inzucchi SE, Goyal A, Krumholz HM, Masoudi FA, Xiao L, et al. Relationship between spontaneous and iatrogenic hypoglycemia and mortality in patients hospitalized with acute myocardial infarction. JAMA. 2009;301:1556–64.
58. Malmberg K, Norhammar A, Wedel H, Rydén L. Glycometabolic state at admission: important risk marker of mortality in conventionally treated patients with diabetes *mellitus* and acute myocardial infarction: long-term results from the Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction (DIGAMI) study. Circulation. 1999;99:2626–32.
59. Van den Berghe G, Wilmer A, Hermans G, Meersseman W, Wouters PJ, Milants I, et al. Intensive insulin therapy in the medical ICU. N Engl J Med. 2006;3 54:449–61.
60. Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients with Acute Myocardial Infarction). Circulation. 2004;110;e82–293.
61. Kushner FG, Hand M, Smith SC Jr, King SB 3rd, Anderson JL, Antman EM, et al. 2009 Focused updates: ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction (updating the 2004 guideline and 2007 focused update) and ACC/AHA/SCAI guidelines on percutaneous coronary intervention (updating the 2005 guideline and 2007 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009;120:2271–306.
62. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA. 2008;300:933-44.
63. Hochholzer W, Trenk D, Frundi D, Blanke P, Fischer B, Andris K, et al. Time dependence of platelet inhibition after a 600-mg loading dose of clopidogrel in a large, unselected cohort of candidates for percutaneous coronary intervention. Circulation.2005;111:2560–4.
64. Moghissi ES, Korytkowski MT, DiNardo M, Einhorn D, Hellman R, Hirsch IB, et al. American Association of Clinical Endocrinologists and American Diabetes Association consensus statement on inpatient glycemic control. Diabetes Care. 2009;32:1119–31.
65. Timóteo AT, Papoila AL, Rio P, Miranda F, Ferreira ML, Ferreira RC, et al. Prognostic impact of admission blood glucose for all-cause mortality in patients with acute coronary syndromes: added value on top of GRACE risk score. Eur Heart J Acute Cardiovasc Care. 2014 Sep;3(3):257-63.
66. Diaz R, Goyal A, Mehta SR, Afzal R, Xavier D, Pais P, et al. Glucose–insulin–potassium therapy in patients with ST-segment elevation myocardial infarction. JAMA. 2007;298:2399–405.
67. Kuliczkowski W, Gąsior M, Pres D, Kaczmarski J, Greif M, Łaszewska A, et al. Effect of glycemic control on response to antiplatelet therapy in patients with diabetes *mellitus* and ST-segment elevation myocardial infarction. Am J Cardiol. 2012;110(3):331-6.
68. Kosiborod M. Hyperglycemia in Acute Coronary Syndromes: From Mechanisms to Prognostic Implications. Endocrinol Metab Clin North Am. 2018;47(1):185-202.
69. Piccolo R, Franzone A, Koskinas KC, Räber L, Pilgrim T, Valgimigli M, et al. Effect of Diabetes *Mellitus* on Frequency of Adverse Events in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention. Am J Cardiol. 2016;118(3):345-52.
70. White WB, Kupfer S, Zannad F, Mehta CR, Wilson CA, Lei L, et al. Cardiovascular Mortality in Patients With Type 2 Diabetes and Recent Acute Coronary Syndromes From the EXAMINE Trial. Diabetes Care. 2016;39(7):1267-73.
71. Jiménez-Navarro MF, López-Jiménez F, Barsness G, Lennon RJ, Sandhu GS, Prasad A. Long-term prognosis of complete percutaneous coronary revascularisation in patients with diabetes with multivessel disease. Heart. 2015;101(15):1233-9.
72. Elbarouni B, Ismaeil N, Yan RT, Fox KA, Connelly KA, Baer C, et al. Temporal changes in the management and outcome of Canadian diabetic patients hospitalized for non-ST-elevation acute coronary syndromes. Am Heart J. 2011 Aug;162(2):347-55.e1.
73. Colwell JA, Nesto RW. The platelet in diabetes. Diabetes Care. 2003;26:2181–8.
74. Gale CP, Metcalfe E, West RM, Das R, Kilcullen N, Morrell C, et al. An assessment of the concentration-related prognostic value of cardiac troponin I following acute coronary syndrome. Am J Cardiol. 2011;108(9):1259-65.