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Guidelines

Management of diabetes in patients hospitalized for acute cardiac events: Joint position paper from the French Society of Cardiology and the French-speaking Diabetes Society☆

Patrick Henry[a,*], Sophie Jacqueminet[b,n,o], Gilles Lemesle[c,p,q,r], Gaetan Prevost[d,s,t], Boccara[e,u,o], Emmanuel Cosson[f,v], Etienne Puymirat[g], Denis Angoulvant[h,w], François Roubille[i], Serge Kownator[j], Paul Valensi[k,x], Victor Aboyans[l,y], Bruno Vergès[m,z]

[a] *Department of Cardiology, Lariboisière Hospital, AP–HP, INSERM U942, Université Paris Cité, 75010 Paris, France*
[b] *Diabetology Department, La Pitié Salpêtrière-Charles Foix University Hospitals, 75013 Paris, France*
[c] *Heart and Lung Institute, CHU de Lille, 59000 Lille, France*
[d] *INSERM U1239, University of Rouen Normandy, 76821 Mont-Saint-Aignan, France*
[e] *Department of Cardiology, Hôpital Saint-Antoine, AP–HP, 75012 Paris, France*
[f] *Department of Endocrinology, Diabetology and Nutrition, Avicenne Hospital, AP–HP, Université Paris 13, Sorbonne-Paris-Cité, CRNH-IdF, CINFO, 93000 Bobigny, France*
[g] *Department of Cardiology, Hôpital Européen Georges-Pompidou, AP–HP, 75015 Paris, France*
[h] *Department of Cardiology, Hôpital Trousseau, CHRU de Tours, 37170 Chambray-lès-Tours, France*
[i] *PhyMedExp, Cardiology Department, CHU de Montpellier, University of Montpellier, INSERM, CNRS, INI-CRCT, 34295 Montpellier, France*
[j] *Centre Cardiologique et Vasculaire "Coeur de Lorraine", 57100 Thionville, France*
[k] *Polyclinique d'Aubervilliers, 93300 Aubervilliers, France*
[l] *Department of Cardiology, CHU de Limoges, 87000 Limoges, France*
[m] *Department of Endocrinology and Diabetology, CHU de Dijon, 21000 Dijon, France*
[n] *Sorbonne Université, 75005 Paris, France*
[o] *Institute of Cardiometabolism and Nutrition (ICAN), 75013 Paris, France*
[p] *Lille University, 59000 Lille, France*
[q] *INSERM U1011-EGID, Institut Pasteur de Lille, 59000 Lille, France*
[r] *FACT (French Alliance for Cardiovascular Trials), 75000 Paris, France*
[s] *Department of Endocrinology, Diabetes and Metabolic Diseases, CHU de Rouen, 76000 Rouen, France*
[t] *INSERM CIC-CRB 1404, 76000 Rouen, France*
[u] *GRC no 2, C2MV (Complications Cardiovasculaires et Métaboliques chez les patients vivant avec le Virus de l'immunodéficience humaine), INSERM UMR_S 938, Centre de Recherche Saint-Antoine, Sorbonne Université, 75012 Paris, France*
[v] *Nutritional Epidemiology Research Team (EREN), Centre of Research in Epidemiology and StatisticS (CRESS), Université Sorbonne Paris Nord and Université Paris Cité, INSERM, INRAE, CNAM, 93017 Bobigny, France*
[w] *INSERM UMR 1327 (ISCHEMIA "Membrane Signalling and Inflammation in Reperfusion Injuries"), Université de Tours, 37032 Tours, France*
[x] *Université Paris 13, Sorbonne Paris Cité, 93000 Bobigny, France*
[y] *EpiMaCT, INSERM 1094/IRD 270, Limoges University, 87025 Limoges, France*
[z] *INSERM UMR 1231, 21000 Dijon, France*

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ABSTRACT

Patients with type 2 diabetes, but also older patients with type 1 diabetes, are at major risk of cardiovascular morbidity and death. After an acute cardiac event, the prognosis of patients with diabetes is impaired, with clear increases in in-hospital and long-term morbidity and deaths. Both hyper- and hypoglycaemia are deleterious after an acute cardiac event, and the decision to start intravenous insulin is often challenging. Moreover, some antidiabetic treatments have cardioprotective effects, and the onset of an acute cardiac event provides an opportunity to shift to these treatments. The objective of this position statement is to offer practical tools to cardiologists seeking to improve the care of patients with diabetes hospitalized for an acute cardiac event, and to optimize collaboration between cardiologists and diabetologists. After a summary of the evidence for antidiabetic treatments in patients with acute cardiac

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CAD, coronary artery disease; CI, confidence interval; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP1-RA, glucagon-like peptide-1 receptor antagonists; HbA1c, glycated haemoglobin; HF, heart failure; ICCU, intensive cardiac care unit; MACE, major adverse cardiac events; MI, myocardial infarction; SGLT2, sodium-glucose cotransporter 2; T1D, type 1 diabetes; T2D, type 2 diabetes.

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* Corresponding author. Department of Cardiology, Lariboisière Hospital, AP–HP, 2, rue Ambroise-Paré, 75010 Paris, France.
E-mail address: Patrick.henry@aphp.fr (P. Henry).

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events, we propose an algorithm to start and adapt intravenous insulin in the most severe patients, and conclude with standard insulin protocols or oral treatments at discharge. We also discuss appropriate antidiabetic treatment of these patients at discharge, based on the main cardiological diagnosis, kidney function and antidiabetic strategies. Finally, situations in which the diabetologist must be consulted are discussed.

1. Background

Patients with type 2 diabetes (T2D), but also older patients with type 1 diabetes (T1D), are at major risk of cardiovascular morbidity and death. This increased cardiovascular risk is already present at mildly elevated concentrations of blood glucose below the threshold for diabetes [1,2]. The prevalence of diabetes or abnormal glucose metabolism is very high in patients presenting with an acute coronary syndrome (ACS) [3]. Indeed, among patients hospitalized for an ACS, 30–40% have diabetes, 25–36% show impaired fasting glucose or impaired glucose tolerance and only 30–40% have normal glucose tolerance. Moreover, the prognosis after an ACS-related event is worse in patients with diabetes [3,4]. Hyperglycaemia and hypoglycaemia could be deleterious in unstable patients hospitalized in an intensive cardiac care unit (ICCU) [5]. Heart failure (HF) is also much more frequent; men show a 2-fold increased risk of HF, and women a 4-fold increased risk [6]. Approximately 24% of patients with HF overall and 40% of hospitalized patients with HF have diabetes [7]. Diabetes is associated with a high risk of HF, mainly with preserved ejection fraction or linked to coronary artery disease (CAD) [8]. Thus, diabetes management during and in the days following an acute cardiac disease event is an important task. In 2012, the Société Francophone du Diabète (SFD; French-speaking Diabetes Society) and the Société Française de Cardiologie (SFC; French Society of Cardiology) published a consensus statement on the "Care of the hyperglycaemic/diabetic patient during and in the immediate follow-up of an ACS" [9]. However, over the past 10 years, new glucose-lowering treatments have become available, including agents that show specific cardiovascular benefits, such as glucagon-like peptide-1 receptor antagonists (GLP1-RAs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors. This consensus statement takes into account the data obtained in cardiovascular outcome trials testing novel glucose-lowering drugs. The aim of this new consensus is to give very practical tools to cardiologists caring for patients with diabetes hospitalized for an acute cardiac event, and to optimize the collaboration between cardiologists and diabetologists.

2. Literature review

2.1. Diabetes and acute cardiac diseases

2.1.1. Prevalence of diabetes and prediabetes in acute cardiac diseases

In parallel to the current epidemic of diabetes and metabolic syndrome, the proportion of patients with diabetes in ICCUs has increased. Over a time span of 20 years (1995–2015), the FAST-MI programme recorded an increasing prevalence of diabetes in patients with non-ST-segment elevation myocardial infarction (MI) (from 20% to 27%; $P < 0.001$), whereas this prevalence remained quite stable in patients with ST-segment elevation MI (16% and 16.5%, respectively) [3]. Similarly, in Italy, between 2001 and 2010, the prevalence of diabetes increased from 25% to 36% in patients with non-ST-segment elevation MI [10]. Merging data from EUROASPIRE IV and V, the proportion of known diabetes in patients with MI was higher in women than in men (39.2% vs 28.4%; $P < 0.0001$). Oral glucose tolerance testing detected unknown diabetes in 13.4% and 14.6% of women and men, respectively, and these figures almost doubled when glucose intolerance was also considered [1]. Diabetes is also frequent in patients with other causes of hospitalization in the ICCU; 25–50% of patients admitted for decompensated HF have diabetes [11,12].

2.1.2. Risks associated with diabetes

Diabetes is associated with both a higher risk of cardiovascular diseases and a poorer outcome in patients with documented cardiovascular disease. Diabetes is associated with coagulation abnormalities and a higher risk of atherothrombotic events (especially coronary events), and, after an acute event, short- and long-term prognoses are poorer [13]. As an illustration, in a large meta-regression, diabetes was and remained steadily associated with a 65–85% increased risk of death after an acute MI, despite improvements in management over time [8].

Patients with diabetes are at increased risk of HF and recurrent hospitalization [8], and diabetes is associated with a 2-fold increased risk of HF occurrence in patients with chronic CAD or after acute MI. Additionally, patients with HF and diabetes have poorer outcomes than their counterparts without diabetes [14]. In a European cohort of patients with acute HF, the presence of diabetes was independently associated with an increased risk of in-hospital death, 1-year death and rehospitalization for HF, underscoring the need for more effective and personalized treatments of diabetes in this particularly high-risk population [15]. It is important to notice that individuals with T1D have a higher risk of death after their first-ever MI; in particular, poor kidney function is associated with a high risk of death and an excessive risk of secondary cardiovascular events [16].

2.1.3. Impact of various glucose disorders and glycated haemoglobin

In several studies of patients with ACS, impaired glucose tolerance or newly detected diabetes was associated with a higher long-term incidence of major adverse cardiac events (MACE) [2,17] or reinfarction [4]. In a large prospective registry study of patients with ACS, 1-year MACE and death rates and long-term (> 3 years) death rates were higher in those with known or newly detected diabetes or with impaired glucose tolerance [5].

Glycated haemoglobin (HbA1c) has a prognostic value in patients with acute MI and newly detected glucose abnormalities (impaired glucose tolerance or diabetes according to an oral glucose tolerance test performed before discharge); elevated HbA1c concentration appears to be one of the strongest independent risk factors for death, and HbA1c concentrations > 5.9% in patients with impaired glucose tolerance and > 7% in patients with new diabetes are associated with reduced posthospital survival [5]. In a systematic review including data from 25 studies involving 304,253 patients with ACS, higher HbA1c concentration was a significant predictor of in-hospital death and short-term (< 1 year) death in patients without known or newly detected diabetes [18].

2.2. Impact of hyperglycaemia, hypoglycaemia and glycaemic variability on the prognosis of patients with diabetes and acute cardiac disease

2.2.1. Stress hyperglycaemia

Stress hyperglycaemia is defined as a transient increase in blood glucose during acute stress, and is restricted to patients without previous evidence of diabetes [19,20]. As a consequence, stress hyperglycaemia is correlated with a higher death rate in ICCUs in patients with cardiogenic shock [21] and acute MI [22]. Hyperglycaemia at admission has been shown to be independently associated with 30-day and 1-year risk of death, independent of diabetic state [20].

Many mechanisms are involved: the release of major stress hormones (cortisol, catecholamines) and glucagon overload. All of these mechanisms induce insulin resistance, with increased hepatic glucose output and glycogen break-down [20], leading to glucotoxicity with mitochondrial impairment. Hyperglycaemia also promotes inflammation and endothelial dysfunction, and is associated with a prothrombotic state [23]. High blood glucose is associated with increased reactive oxygen species, which inhibit myocardial cell replication and differentiation, favouring the development of cardiac myopathy. Tight glycaemic control has been shown to reduce inflammation, decrease the production of reactive oxygen species and increase cardiomyocyte replication and differentiation [23].

Lowering glucose concentrations in critically ill patients appears logical, and has been shown to be efficient in improving the clinical outcomes of patients in the surgical context [24], taking into account that too-tight control can lead to death [25]. It is important to remember that definitions and thresholds of stress hyperglycaemia vary in the literature.

2.2.2. Hyperglycaemia

Many studies have shown that admission blood glucose concentration is an independent factor for death and in-hospital complications in patients with diabetes [3]. In a meta-analysis by Capes et al., the in-hospital death rate was increased by 70% in patients with diabetes with an admission blood glucose concentration > 180 mg/dL (10.0 mmol/L) [26]. Persistent hyperglycaemia during hospitalization for ACS also has a negative impact on prognosis. A prospective study by Svensson et al. showed that the 2-year death rate in patients with diabetes whose lowest blood glucose value during a hospital stay for ACS was > 120 mg/dL (6.6 mmol/L) was 48% higher compared with patients whose lowest blood glucose values were between 56 mg/dL (3.1 mmol/L) and 119 mg/dL (6.5 mmol/L), after adjustment for confounding factors, including admission glycaemia [27]. In patients at high cardiovascular risk admitted to an ICCU, both hyperglycaemia at admission (> 162 mg/dL or 9.0 mmol/L) and sustained hyperglycaemia (average glucose concentration > 144 mg/dL or 8.0 mmol/L) were independently associated with all-cause death [28]. The potential benefit of optimal glycaemic control during an ACS event in patients with diabetes has been demonstrated by several studies. The DIGAMI 1 trial showed that for patients with diabetes hospitalized for ACS, an insulin-glucose infusion for 24 h followed by subcutaneous insulin 4 times daily for ≥ 3 months, compared with a standard treatment (insulin therapy only if clinically indicated), induced a significant reduction in HbA1c concentrations and a significant drop in the death rate at 1 year (19% vs 26%) and at 3.4 years (33% vs 44%) [29]. The DIGAMI 2 trial confirmed the overall benefit in terms of deaths of hyperglycaemia reduction in patients with diabetes with ACS, but independent of the treatment used (insulin infusion during hospitalization followed by intensive subcutaneous insulin therapy; insulin infusion during hospitalization followed by standard glucose-lowering treatment, including oral antidiabetic agents; or standard antidiabetic treatment including oral glucose-lowering agents during and after hospitalization). All these data suggest that blood glucose is a significant and independent predictor of death in patients with diabetes, thus indicating the central role of glucose control.

2.2.3. Hypoglycaemia

In the ACCORD study, intensive glucose-lowering treatment associated with hypoglycaemia was associated with increased death rates, mainly in patients with previous cardiovascular disease events [30]. In acute cardiac diseases, hypoglycaemia also seems to influence the outcomes of patients with diabetes hospitalized for ACS. In a study by Svensson et al., a single blood glucose measurement < 54 mg/dL (3 mmol/L) during hospitalization was associated with a 93% increase in the relative risk of long-term death [27]. In the CLARITY-TIMI-28 study, the 30-day death rate was greater in patients at the upper (> 199 mg/dL/11.0 mmol/L) and lower (< 81 mg/dL/4.5 mmol/L) extremes of blood glucose measured at admission to hospitals, showing a U-shaped curve [31]. In a Japanese study, a blood glucose concentration of < 127 mg/dL (7 mmol/L) and a blood glucose concentration of > 198 mg/dL (11.0 mmol/L) were both independent predictors of death in patients with diabetes with acute MI [32].

2.2.4. Glycaemic variability

Glycaemic variability is also likely to influence the prognosis of patients hospitalized for ACS. In patients with diabetes hospitalized for acute MI, the mean amplitude of blood glucose excursion, an indicator of within-day glycaemic variability, was independently associated with the severity of coronary disease assessed by the SYNTAX score [33]. In patients hospitalized for an acute MI, the mean amplitude of blood glucose excursion has been to shown to be an independent predictor of the occurrence of a major cardiovascular event 12 months combine [34] or 39 months [35] after the MI. In a recent French prospective study, a blood glucose glycaemic variability of > 47 mg/dL (2.70 mmol/L) during hospitalization was the most important independent predictor of MACE after ACS (odds ratio, 2.21; 95% confidence interval [CI] 1.64–2.98; $P < 0.001$) [36]. The pathophysiological effects of glycaemic variability on the cardiovascular system may combine the effects of hypo/hyperglycaemia along with effects on the parasympathetic system.

2.3. Antidiabetic treatment in unstable cardiac patients: What is the evidence?

2.3.1. Insulin

Insulin therapy during ACS has been studied for over 50 years [37]. In all, more than 25,000 patients have been included in clinical studies with different insulin therapy protocols; however, the results are conflicting, and a number of issues remain outstanding. In the 1960s, the concept of glucose-insulin-potassium arose. The provision of insulin, high-dose glucose and potassium was thought to improve myocardial energy metabolism and prevent ventricular arrhythmia in the context of ischaemic injury. Although the concept and the first results were very promising, the benefit of this protocol in terms of major cardiovascular outcomes has not been clearly demonstrated with regard to the results of 10 published clinical studies; seven studies including a total of 25,496 patients did not find any difference between treated and control groups [38].

Besides glucose-insulin-potassium protocols, insulin therapy has been studied as a cornerstone for tight blood glucose control during ACS [37]. As observational studies have demonstrated that hyperglycaemia is associated with more adverse outcomes in patients with ACS, improving glycaemic control as soon as possible is attractive. Intensive insulin therapy was the logical choice

to achieve this objective in the context of critically ill patients. In the DIGAMI study [39], 620 patients with ACS and blood glucose > 198 mg/dL (11 mmol/L) were randomized to receive either intensive insulin therapy for 24 h followed by multidose subcutaneous insulin for at least 3 months or conventional therapies for hyperglycaemia. After 1 year, a significant 29% reduction in the relative risk of all-cause death was observed [39]. However, it is important to note that at least three other randomized controlled trials [40,41] with either different insulin protocols or more strict blood glucose targets did not confirm any benefit from intensive insulin therapy. Several reasons were given to explain these conflicting data. First, a major issue is the frequency of hypoglycaemia in the intensive insulin therapy arms. Second, it was postulated that the benefit of insulin should also be linked to its vasodilator property [37]. In conclusion, despite these conflicting data, insulin therapy is widely considered to be effective, with quick action and few contraindications, and so is recommended to reach blood glucose targets in the ICCU, but with the necessity of avoiding hypoglycaemia.

No randomized clinical trials comparing intervention glucose strategies with intensive insulin treatment have been conducted in patients with acute HF in the ICCU. Although insulin is known to promote peripheral oedema via an antinatriuretic effect, the ORIGIN study did not find any difference in MACE or HF hospitalizations in the treated arm in over 12,500 patients with high cardiovascular risk and glucose dysregulation [42]. Therefore, insulin treatment, again for its quick and flexible effects, is probably the easiest to use to reach the blood glucose target in patients with acute HF [43].

2.3.2. Sulfonylureas

Since the UGDP study [44], which was discontinued prematurely because of excess death in the tolbutamide-treated group, the potentially deleterious effect of sulfonylureas has received considerable attention. By binding subunits of potassium channels present in β cells, but also in cardiomyocytes, these molecules can impair myocardial preconditioning and worsen ischaemic injury. Conflicting data exist between observational studies and randomized controlled trials [45]. In summary, some observational studies suggested a higher adverse cardiovascular outcome incidence with sulfonylureas, whereas randomized clinical trials did not demonstrate any difference. Regarding observational studies, there is a high degree of heterogeneity in the duration of follow-up and molecule exposure, cardiovascular outcomes and/or sample size. Moreover, pharmacological properties may vary depending on the molecules; for example, gliclazide and glipizide could be more selective for pancreatic sulfonylurea receptors and so less implicated in myocardial preconditioning impairment (animal experimental data). Therefore, sulfonylureas should probably not be considered as a homogeneous class with regard to cardiovascular safety. Two large randomized controlled trials were expected to provide complementary highlights. First, in the TOSCA.it study [46], 3028 patients with T2D were included: 1335 were assigned to pioglitazone and 1493 to sulfonylureas (glibenclamide $n = 24$ [2%], glimepiride $n = 723$ [48%] or gliclazide $n = 745$ [50%]) as add-on treatments to metformin. After a median follow-up of 57 months, the incidence of cardiovascular events was similar for sulfonylureas compared with pioglitazone, whereas the frequency of hypoglycaemia, as expected, was significantly higher in the sulfonylurea-treated group. In the CAROLINA study [47], more than 6000 patients with T2D (40% with previous cardiovascular disease) were randomized to receive either linagliptin (a dipeptidyl peptidase-4 [DPP-4] inhibitor) or glimepiride (1–4 mg) as an add-on to usual treatment. After a median follow-up of 6.3 years, there was no significant difference in the occurrence of the primary endpoint (time to first occurrence of cardiovascular death, non-fatal MI or non-fatal stroke) between the two arms. These two recent randomized controlled trials suggest that, despite a higher risk of hypoglycaemic events compared with other drugs, the new generation sulfonylureas might be not deleterious to cardiovascular safety.

Considering HF, sulfonylureas have not been associated with oedema or sodium retention. In the UKPDS [48] and, more recently, in the CAROLINA study [47], incidences of adverse cardiovascular events were not higher in the sulfonylurea-treated group compared with those using other agents, despite more frequent hypoglycaemic events.

2.3.3. Metformin

At the cellular level, the effect of metformin is largely mediated by the activation of adenosine monophosphate-activated protein kinase, a key molecule orchestrating many biochemical processes, including glucose uptake, glycolysis, oxidation of free fatty acids and mitochondrial biogenesis [49]. At the systemic level, this drug improves endothelial function and protects against oxidative stress, inflammation and the negative effects of angiotensin II. On the myocardium, metformin attenuates ischaemia-reperfusion injury and prevents adverse remodelling, even if inconstant [50]. The effects of metformin on myocardial cell metabolism and contractile function could be significant during transient ischaemia, during an acute increase in workload and in the early stages of diabetic/hypertensive disease. A decrease in the low-reflow phenomenon was suggested, but was not confirmed, by a study testing ejection fraction after acute MI [51]. In a post-hoc analysis of the DIGAMI 2 study, the choice of glucose-lowering drugs appeared to be of prognostic importance for patients after acute MI; insulin may be associated with an increased risk of non-fatal cardiac events, whereas metformin seems to be protective against risk of death [40].

In a study including 379 patients with ST-segment elevation MI without diabetes undergoing primary percutaneous coronary intervention, patients were randomized to 4 months of treatment with metformin (500 mg twice daily; $n = 191$) or placebo ($n = 188$). At 4 months, left ventricular ejection fraction and N-terminal prohormone of brain natriuretic peptide concentration were similar in the two groups, and MACEs were observed in six patients (3.1%) and two patients (1.1%), respectively ($P = 0.16$). No cases of lactic acidosis were observed. After a 2-year follow-up, multivariable adjustment demonstrated that the incidence of MACE was similar in the two groups (hazard ratio 1.02, 95% CI 0.10–10.78; $P = 0.99$) [52,53].

In a retrospective cohort study of 24,953 Medicare beneficiaries with diabetes discharged after hospitalization for acute MI, the independent association between a discharge prescription for metformin, thiazolidinediones or both agents and outcomes at 1 year was assessed. Insulin-sensitizing drugs (metformin, thiazolidinediones) were not associated with a significantly different risk of death in older patients with diabetes within 1 year following an acute MI compared with other antihyperglycaemic agents, except for thiazolidinediones, which were associated with a higher risk of readmission for HF after MI [54].

Metformin is associated with decreased deaths and morbidity in stable patients with HF with T2D [55]. Few decompensated HF data sets have been published. A total of 7620 patients with diabetes and incident HF in a USA national insurance claims database were analysed, 3799 (50%) of whom were exposed to metformin. At 1.7 years of follow-up, conventional models suggested potential acute benefits in reducing HF exacerbation with metformin use (adjusted hazard ratio 0.76, 95% CI 0.60–0.97), whereas other models, which provided a better fit for the data, suggested a lack of systematic effect (adjusted hazard ratio 0.91, 95% CI 0.69–1.20) [56]. Finally, in the REACH registry, no increase in HF was observed with metformin [57].

Metformin-associated lactic acidosis is a rare but life-threatening adverse drug reaction to take into consideration in the setting of acute or decompensated patients, who often exhibit decreased kidney function. During acute decompensated HF, timely treatment may prevent the decrease in kidney function to the threshold associated with an increased risk of metformin-associated lactic acidosis. Metformin should not be withheld from patients with diabetes with stable HF who do not have other risk factors for acute decompensated HF or lactic acidosis [55].

Recent guidelines for antidiabetic medications advocate metformin as a first-line therapy for all patients with T2D. However, metformin may be associated with increased risk of acute kidney injury, acute dialysis and lactate acidosis in some patients. In a retrospective nationwide cohort study, 168,443 drug-naïve patients with T2D aged $\geq$ 50 years who were starting treatment with either metformin or sulfonylurea in Denmark between 2000 and 2012 were included (70.7% initiated treatment with metformin). One-year risks of acute dialysis were 92.4 per 100,000 (95% CI 67.1–121.3) and 142.7 per 100,000 (95% CI 118.3–168.0) for sulfonylureas and metformin, respectively. Metformin-associated 1-year risk of acute dialysis was increased by 50.3 per 100,000 (95% CI 7.9–88.6), corresponding to an odds ratio of 1.53 (95% CI 1.06–2.23), thus providing evidence of potential harm pertaining to the use of metformin [58].

In conclusion, metformin cannot be systematically prescribed to patients with T2D because of the presence of numerous contraindications corresponding to situations that may increase the risk of lactic acidosis. However, recent data suggest that patients with T2D who are considered "at risk" because of the presence of cardiac disease would probably benefit from metformin therapy.

2.3.4. Dipeptidyl peptidase-4 inhibitors

DPP-4 inhibitors are oral antidiabetic agents that reduce GLP1 enzymatic degradation, thus leading to moderate increases in its plasma concentration. They are well tolerated, with very few side effects. Prospective cardiovascular outcome trials (namely SAVOR-TIMI with saxagliptin in patients with T2D and history of MI or at very high cardiovascular risk, TECOS with sitagliptin in patients with T2D and established cardiovascular disease and EXAMINE with alogliptin in patients with T2D and a recent MI or unstable angina) did not show any increase or decrease in the rate of ischaemic events [59–61]. The "neutral" effect of DPP-4 inhibitors on ischaemic cardiovascular events was confirmed in a large meta-analysis including 55,141 patients [62]. In the SAVOR trial, an increase in hospitalization for HF with saxagliptin was observed [60], whereas this was not observed with alogliptin in EXAMINE or with sitagliptin in TECOS.

No specific data on the use of DPP-4 inhibitors during an acute cardiac event are available. The "neutral" effect of DPP-4 inhibitors on ischaemic events was also observed in the EXAMINE trial, where treatment with alogliptin was introduced early (15–90 days) after an ACS, indicating that DPP-4 inhibition appears to be safe in the high-risk period following an ACS [63]. The absence of any cardiovascular beneficial effect of DPP-4 inhibitors during an ACS is suggested by a study that did not show any improvement in endothelial dysfunction with sitagliptin in patients with ACS with glucose intolerance or T2D [64].

2.3.5. Glucagon-like peptide-1 agonists

GLP1-RAs are modified glucagon-like peptide-1 proteins that are resistant to DPP-4 enzymatic degradation, and are administered by subcutaneous daily or weekly injection. Their administration induces supraphysiological plasma concentrations of GLP1-RA, which increases insulin secretion in a glucose-dependent manner and decreases glucagon secretion, but also significantly reduces body weight and insulin resistance [65]. GLP1-RAs are not directly responsible for hypoglycaemic events, but may be responsible for hypoglycaemia in association with insulin or insulin-secreting agents (sulfonylureas, glinides). Prospective cardiovascular outcome studies have shown that liraglutide, semaglutide and dulaglutide significantly reduce MACE in patients with T2D with a history of coronary disease or at high cardiovascular risk. In the LEADER trial, liraglutide reduced MACE by 13% ($P = 0.01$) and cardiovascular deaths by 22% ($P = 0.007$) [66]. In SUSTAIN-6, semaglutide reduced MACE by 26% ($P = 0.02$) and non-fatal stroke by 49% ($P = 0.04$) [67]. In REWIND, dulaglutide reduced MACE by 12% ($P = 0.026$) and non-fatal stroke by 24% ($P = 0.017$) [68].

Although the benefit of GLP1-RAs for ACS is not entirely clear, several trials indicate a positive effect of GLP1-RAs during ACS. In an experimental study performed with 20 patients with normal left ventricular function and single-vessel coronary disease, administration of GLP1-RAs reduced ischaemic left ventricular dysfunction after ischaemia during balloon occlusion [69]. In a study including patients with ST-segment elevation MI undergoing percutaneous coronary intervention, administration of the GLP1-RA exenatide at the time of reperfusion significantly increased the myocardial salvage index [70]. In two prospective randomized studies, administration of exenatide at time of reperfusion in patients with ST-segment elevation MI undergoing percutaneous coronary intervention did not reduce infarct size [71,72]. Two meta-analyses reported improved left ventricular ejection fraction and reduced infarct size with GLP1-RAs in patients undergoing percutaneous coronary intervention or coronary artery bypass grafting [73,74]. So far, clear evidence of a cardiovascular benefit for GLP1-RAs during ACS is lacking, and we need high-quality, well-designed trials to evaluate their precise effect in ACS situations.

The use of GLP1-RAs, with proven cardiovascular benefit, is recommended in association with metformin for patients with T2D with a history of cardiovascular disease. Evidence of cardiovascular benefit following GLP1-RA administration during ACS is lacking. A meta-analysis of cardiovascular outcome trials comparing GLP1-RAs and placebo showed a significant 9% reduction in hospitalization for HF ($P = 0.013$) [75]. In the double-blind, placebo-controlled, randomized FIGHT trial, time to death and rehospitalization for HF were not significantly modified by treatment with liraglutide [76]. In the LIUVE trial, treatment with liraglutide for patients with reduced left ventricular ejection fraction was associated with the occurrence of more serious cardiac events (cardiac death, ventricular tachycardia, atrial fibrillation, ACS or worsening of HF) [77]. In a recent study, it has been shown that the combination of GLP1-RAs and SGLT2 inhibitors is associated with a lower risk of MACE and serious renal events compared with either drug class alone [78].

2.3.6. Sodium-glucose cotransporter-2 inhibitors

SGLT2 inhibitors are oral glucose-lowering drugs that act by inhibiting the sodium cotransporter in the renal proximal tubule, leading to diminished renal glucose reabsorption, which reduces plasma glucose, and to increased glucose urinary excretion and then body weight reduction. SGLT2 inhibitors are not directly responsible for hypoglycaemic events, but may be responsible for hypoglycaemia in association with insulin or insulin-secreting agents (sulfonylureas, glinides).

Prospective cardiovascular outcome studies performed with patients with T2D showed that SGLT2 inhibitors significantly reduced MACE, and that this effect was mostly driven by a dramatic reduction in hospitalization for HF (−35% with empagliflozin in EMPAREG-OUTCOME; −33% with canagliflozin in CANVAS; −27% with dapagliflozin in DECLARE-TIMI) [79–81]. In patients with HF with reduced or preserved ejection fraction, SGLT2 inhibitors reduced cardiovascular death and hospitalization for HF, and the same benefit was shown in patients without diabetes with HF, indi-

Table 1
Summary of the cardiovascular effects of antidiabetic treatments [92].

	Chronic CAD	Chronic HF	Acute CAD	Acute HF	Risk of Hypoglycemia	Remarks
Metformin	+	+	0	0	0	Risk of lactic acidosis Warning in case of severe heart or renal failure
Sulfonylureas/glinides	–	0	?	?	++	All Sulfonylureas are not similar
DPP4is	0	≈0	0	≈0	0	Saxagliptin has shown an increased risk of heart failure No association with GLP1-RAs
iSGLT2	++	+++	≈0	+++	0*	Renal protection
GLP1-RAs	+++	–	≈0	–	0*	Weight loss Gastrointestinal side effects needing dose escalation
Insulin	0	–	+	–	+++	

+: positive effect; –: negative effect; 0: no effect; ≈0: probably no effect; ?: unknown; *: can increase the risk of hypoglycaemia when associated with hypoglycaemic agents; CAD: coronary artery disease; DPP-4: dipeptidyl peptidase-4; GLP-RAs: glucagon-like peptide-1 receptor antagonists; HF: heart failure; SGLT2: sodium-glucose cotransporter 2.

cating a cardioprotective effect, independent of glucose changes [82]. No study has evaluated the use of SGLT2 inhibitors during the ACS period. Thus, there is no clear-cut agreement regarding their use during and immediately after ACS. In the EMPULSE study, initiation of empagliflozin in patients hospitalized for acute HF was well tolerated, and induced significant clinical benefits concerning symptoms in the 90 days after starting treatment [83]. In patients with diabetes and recent worsening HF, sotagliflozin therapy, initiated before or shortly after discharge, resulted in significantly lower total numbers of hospitalizations and deaths from cardiovascular causes [84]. In the randomized, placebo-controlled EMPA-RESPONSE-AHF trial, empagliflozin reduced the combined endpoint of in-hospital worsening HF, rehospitalization for HF or death at 60 days compared with placebo [85]. This suggests that SGLT2 inhibitors should be initiated early. Thus, it is now advised, for patients with HF, to adopt a rapid sequencing strategy, with early use of SGLT2 inhibitors in combination with other drugs dedicated to HF, with rapid uptitration, as recommended by the European Society of Cardiology [84,86,87].

The systematic introduction of SGLT2 inhibitors in the days following acute MI has been studied in 4017 patients with acute MI, but no diabetes or chronic HF, who were randomly assigned to 10 mg of dapagliflozin or placebo. The primary outcome was a composite of death, hospitalization for HF and five cardiometabolic outcomes analysed using the win ratio method. There were significantly more wins for dapagliflozin than for placebo (win ratio 1.34, 95% CI 1.20–1.50), which was driven by the cardiometabolic outcomes. The composite of time to cardiovascular death/hospitalization for HF did not differ between the two groups [88]. Among 3260 patients at increased risk of HF after acute MI, treatment with empagliflozin also did not lead to a significantly lower risk of a first hospitalization for HF or death from any cause than placebo [89]. In the EMMY trial, in patients with a recent myocardial infarction, empagliflozin was associated with a significantly greater reduction in N-terminal prohormone of brain natriuretic peptide concentration, accompanied by a significant improvement in echocardiographic functional and structural variables [90].

Table 1 summarizes the main cardiovascular effects of antidiabetic treatments and the risk of hypoglycaemia.

3. Algorithms

All of the treatments proposed in these algorithms should be considered as suggestions, and must be adapted to each patient's profile. It is important to call a diabetologist in case of doubt or in cases of intolerance, unexpected events or difficulty in achieving targeted glucose control. In case of allergy or previous poor tolerance to a glucose-lowering drug or a combination of drugs, the choice of treatment must be discussed with a diabetologist. Intravenous insulin treatment must be proposed only when medical and paramedical staff are experienced, can perform repeated glucose and ketone measurements and are trained to immediately manage hypoglycaemia. Staff must pay close attention to the blood glucose units used (mg/dL or mmol/L). In the figures and tables, the units are mg/dL; Table 2 gives the equivalences. Measurement of blood capillary ketones is preferable to urinary strip testing because of time lapse. Blood ketones > 1.5 mmol/L are significant, and blood ketones > 3.0 mmol/L require immediate diabetological advice.

Table 2
Converting glucose concentration (mg/dL ↔ mmol/L).

Converting glucose level mg/dL - mmol/L								
mg/dL	40	80	140	200	250	300	350	400
mmol/L	2.2	4.4	7.8	11.1	13.9	16.7	19.4	22.2

The higher threshold suggests to start with oral treatment to correct hypoglycaemia and the lower with IV treatment – however, it must be adapted to each patient case (see Table 3 to manage).

3.1. Arrival of the patient at the ICCU

Fig. 1 shows the initial algorithm following admission to the ICCU. We propose accepting a large range of glucose concentrations to avoid an overly complex adaptation of the glucose-lowering treatment in a cardiological unit where hypoglycaemic events following bolus of insulin can be deleterious.

There are two reasons to propose insulin treatment for a patients with diabetes hospitalized for an acute cardiac event: cardiac instability and significant hyperglycaemia.

3.1.1. Cardiac instability

The first step is to detect patients with cardiac instability, i.e. at high risk of in-hospital cardiovascular morbidity and death. These patients need glucose concentration stability, although several glucose-lowering drugs may interact with their cardiac disease. Of course, identification of these high-risk patients is at the discretion of the clinician, and other conditions can be involved, such as severe pulmonary embolism, severe endocarditis or aortic dissection... In patients with cardiac instability without previous insulin treatment, all oral glucose-lowering drugs and GLP1-RAs must be

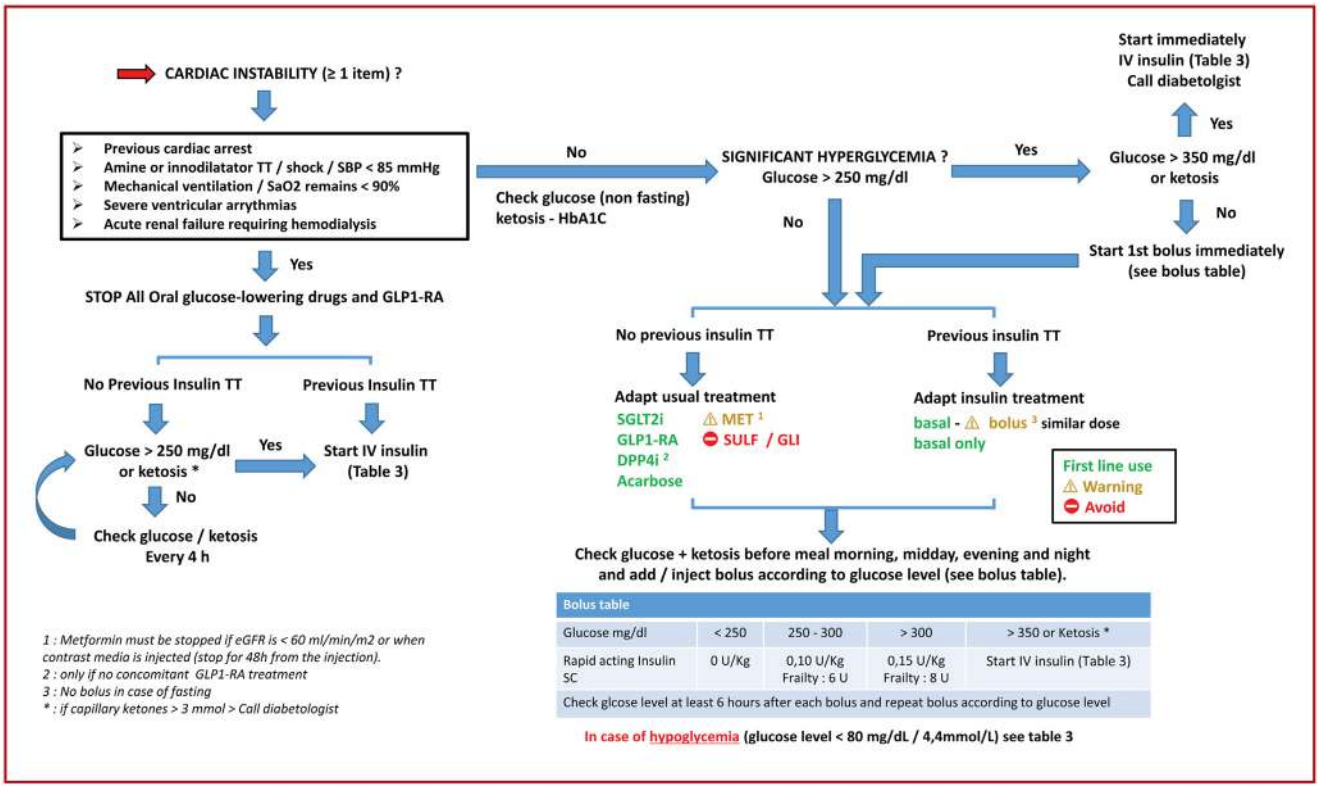


Fig. 1. Initial algorithm following admission to intensive cardiac care unit. conc.: concentration; DPP-4i: dipeptidyl peptidase-4 inhibitor; GLI: glinides; GLP1-RA: glucagon-like peptide-1 receptor antagonist; HbA1c: glycated haemoglobin; IV: intravenous; MET: metformin; SaO_2: oxygen saturation; SBP: systolic blood pressure; SC: subcutaneous; SGLT2i: sodium-glucose cotransporter 2 inhibitor; SULF: sulfamides; TT: treatment. [a] Metformin must be stopped if estimated glomerular filtration rate is < 60 mL/min/m^2 or when contrast media is injected (stop for 48 h from the injection); [b] Only if no concomitant GLP1-RA treatment; [c] No bolus in case of fasting; [d] If capillary ketones > 3 mmol, call diabetologist.

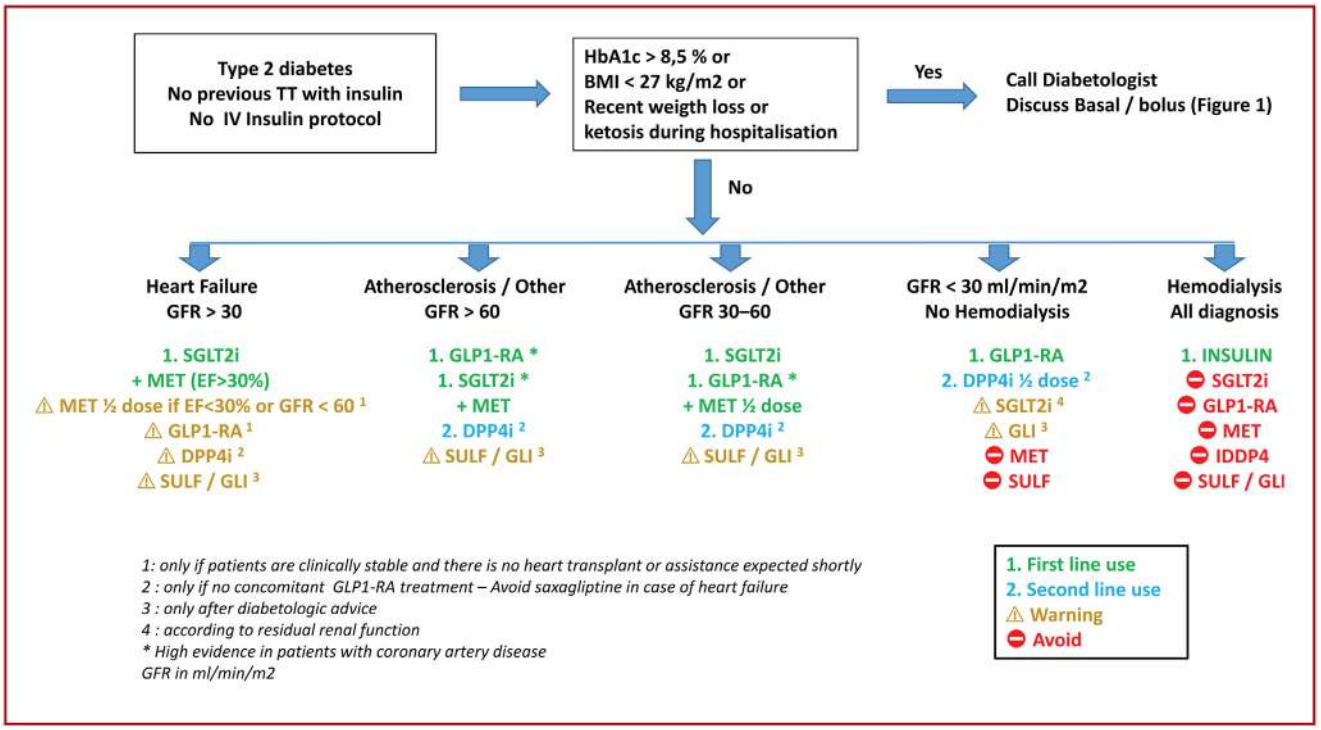


Fig. 2. Algorithm for discharge of patients with type 2 diabetes not previously treated with insulin from the intensive cardiac care unit. BMI: body mass index; DPP-4i: dipeptidyl peptidase-4 inhibitor; EF: ejection fraction; eGFR: estimated glomerular filtration rate; GLI: glinides; GLP1-RA: glucagon-like peptide-1 receptor antagonist: HbA1c: glycated haemoglobin; IV: intravenous; MET: metformin; SGLT2i: sodium-glucose cotransporter 2 inhibitor; SULF: sulfamides; TT: treatment. [a] Only if patients are clinically stable and there is no heart transplant or assistance expected shortly. [b] Only if no concomitant GLP1-RA treatment; avoid saxagliptin in case of heart failure. [c] Only after diabetological advice. [d] High evidence in patients with coronary artery disease. [e] According to residual renal function.

Table 3
Main interactions reported between antidiabetic agents and cardiac drugs.

	Insulin	GLP1-RA	SGLT2i	DPP4i	Sulfamides	Metformin
Beta blockers (mainly non selective)	Mask and prolong hypoglycemia				May enhance hypoglycemia risk and mask hypoglycemia	
Aspirin					increase sulfonylurea levels	May enhance glucose-lowering effects
Diuretics	May induce hyperglycemia	Deshydration	Deshydration hypotension		May reduce sulfonylurea effectiveness by causing hyperglycemia	Can increase metformin levels
ACE inibitors	May enhance insulin sensitivity		hypotension	angioedema		
Ca channel inhibitors						May reduce metformin efficacy

Artificial intelligence has enabled a more exhaustive refinement of the data. ACE: angiotensin-converting enzyme; DPP-4: dipeptidyl peptidase-4; GLP-RAs: glucagon-like peptide-1 receptor antagonists; SGLT2: sodium-glucose cotransporter 2.

stopped, and glucose concentration and ketosis must be monitored at least every 4 h. When the glucose concentration is > 250 mg/L (14 mmol/L) or blood capillary ketones are ≥ 1.5 mmol/L, intravenous insulin must be started, and the glucose concentration must be monitored as proposed in Fig. 2. If patients were previously treated with insulin, intravenous insulin should also be started in case of cardiac instability if the blood glucose concentration is > 250 mg/L (14 mmol/L), and subcutaneous injections of insulin must be stopped.

3.1.2. *Significant hyperglycaemia*

Significant hyperglycaemia is defined as a glucose concentration > 250 mg/dL (14 mmol/L). Such a situation requires insulin treatment to be started. In patients without cardiac instability, intravenous insulin treatment is required if the glucose concentration is > 350 mg/dL (20 mmol/L) or if blood capillary ketones are ≥ 1.5 mmol/L. In this latter case, the diabetologist must be called in order to anticipate future de-escalation of the treatment and to discuss the need for chronic insulin treatment if not previously applied. The glucose concentration must be monitored as proposed in Fig. 1. In patients without cardiac instability, insulin treatment in the form of administration/addition of a bolus injection of rapid-acting insulin may be proposed if the glucose concentration is between 250 and 350 mg/dL (14 and 20 mmol/L) and capillary ketones are < 1.5 mmol/L.

3.1.3. *No cardiac instability or significant hyperglycaemia*

If the patient has no severe cardiac instability or significant hyperglycaemia, the previous glucose-lowering treatment can be maintained. When patients are treated with oral glucose-lowering treatments or GLP1-RAs, the first-line glucose-lowering treatments to prefer are marked as "1". Metformin must be stopped if the estimated glomerular filtration rate (eGFR) is < 60 mL/min, because of the risk of severe renal failure that is frequently associated with several acute cardiac diseases, and when contrast media is injected (stop for 48 h from injection time). Sulfonylureas and glinides must be stopped because of the risk of hypoglycaemia and their potential harmful cardiometabolic effect. Maintenance of previous glucose-lowering treatment, as proposed above, is also possible in a patient with a glucose concentration between 250 and 350 mg/dL (14 and 20 mmol/L) and capillary ketones < 1.5 mmol/L, in whom bolus insulin treatment has been started. Glucose must be checked at least four times/day (before each meal and near 11 pm) and ketones at least once every day and if glucose concentration > 250 mg/dL (14 mmol/L). In case of previous insulin treatment, the basal dose must be maintained every day, but bolus (rapid insulin) doses must be skipped in case of fasting. The glycaemic target is between 140 mg/dL (7.7 mmol/L) and 250 mg/L (14 mmol/L). When the dose of basal (long-acting) insulin used by the patient is unknown, it is possible to start with 0.2 U/kg/day when the body mass index (BMI) is 20–30 kg/m^2, 0.3 U/kg/day when the BMI is > 30 kg/m^2 and 0.15 U/kg/day if aged > 75 years, the BMI is < 20 kg/m^2 or the eGFR is < 30 mL/min/m^2. If the glucose concentration is > 250 mg/L during monitoring of the patient, bolus injections of rapid-acting insulin must be given. If a bolus is injected, the glucose concentration must be checked 6 h later, and another bolus can be injected according to the "bolus table", including through the night. In case of hypoglycaemia (glucose concentration < 80 mg/dL/4.4 mmol/L), see Fig. 1.

Table 3 presents a summary of the main interactions between antidiabetic agents and cardiac drugs.

3.2. *Intravenous insulin management in the ICCU*

Table 4 shows the management of intravenous insulin treatment in the ICCU. Intravenous insulin is started in case of cardiac instability if the fasting glucose concentration is > 250 mg/dL (14 mmol/L), or if there is significant hyperglycaemia (when the fasting glucose concentration is > 350 mg/dL/20 mmol/L) in all patients. All glucose-lowering treatments (including subcutaneous insulin and GLP1-RAs) must be stopped. As a result of the decrease in potassium concentration associated with intravenous insulin treatment, potassium concentration must be checked 4 h and 12 h after the start of intravenous insulin treatment, and more frequently when the concentration is < 4 mmol/L. Potassium supplementation must be given to the patient when the potassium concentration is decreasing (< 4 mmol/L). In patients with renal failure, potassium

Table 4
Intravenous insulin protocol.

- ✓ **STOP all antidiabetic treatments** including sub-cutaneous insulin and GLP1-RA
- ✓ **Prepare 50 U of rapid Insulin diluted in 50 ml Glucose 5%** (electric syringe : 1 ml = 1 U insulin) + Perfusion of Glucose 5% in parallel
- ✓ **Start IV insulin when blood glucose (BG) > 250 mg/dl following the table**
- ✓ **Blood potassium check** 4 hours and 12 hours after beginning of IV insulin and then at least every day
- ✓ **Capillary blood glucose must be checked at least every 2 hours** unless mentioned otherwise in the table

Glucose - mg/dL	< 54	< 80	80 - 140	140 - 200	200 - 250	250 - 300	300 - 350	≥ 350	≥ 400
INITIAL perfusion speed (ml/h)	-	-	-	-	-	2	2,5	3	4
ADAPTATION of perfusion speed (ml/h)	STOP	STOP	- 1	No change	+ 1	+ 1	+ 1.5	+ 2	+ 2
Insulin bolus for MEAL	0	0	2	4	4	4	4	4	4
CHECK blood glucose every	15 mn	15 mn	2 h	2 h	2 h	2 h	1 h	1 h	1 h

Hypoglycemia
- If blood glucose < 54 mg/dL : glucose 30% IV 10 to 20 ml
- If blood glucose < 80 mg/dL : give oral sugar 15 g if symptoms
- Restart IV insulin with half speed when blood glucose > 140 mg/dl

Hyperglycemia
- Check Ketosis
- If capillary ketones > 3 mmol or insulin speed > 5 ml/h → Call diabetologist

concentration must be checked more frequently than when potassium is given as a supplement.

Intravenous insulin infusion is prepared by diluting 50 U of rapid insulin in 50 mL of a 5% glucose solution in an electric syringe. Electric syringe perfusion should be placed as close as possible to the vein. A perfusion with 5% glucose must be added in parallel to prevent or correct a hypoglycaemic trend (be careful not to flush this perfusion). The initial speed of the electric syringe (mL/h) is indicated in Table 4 in the line "initial perfusion speed". The glucose concentration must be checked every hour at the beginning of intravenous infusion. According to the glucose concentration, the dose of insulin delivered is adapted by increasing or decreasing the speed of the electric syringe according to the line "adaptation of perfusion speed" in Table 4. When the glucose concentration is < 80 mg/dL (4.4 mmol/L), intravenous insulin must be stopped and glucose concentration checked every 15 minutes until the blood glucose is > 140 mg/dL (7.7 mmol/L). When the glucose concentration is < 70 mg/dL (3.5 mmol/L) or between 70 mg/dL (3.5 mmol/L) and 80 mg/dL (4.4 mmol/L) with symptoms of hypoglycaemia, 15 g of oral sugar must be given to the patient. When the glucose concentration is < 54 mg/dL (3.0 mmol/L) or when a patient with blood glucose values between 54 mg/dL (3.0 mmol/L) and 70 mg/dL (3.5 mmol/L) experiences symptoms of hypoglycaemia, intravenous insulin must be stopped immediately, and intravenous glucose (10–20 mL of glucose 30%) must be administered immediately. In case of hypoglycaemia, the glucose concentration must be checked every 15 minutes until the blood glucose concentration is > 140 mg/dL (7.7 mmol/L); then, intravenous insulin infusion can be restarted at half the speed used before the hypoglycaemic event. When a meal is given to the patient, a bolus of intravenous insulin must be added according to the glucose concentration, as indicated in the "insulin bolus for meal" line (able 3). Note that only a half bolus must be administered when a light meal is provided to the patient. The blood glucose check must be performed every 2 h, including throughout the night, according to the line "check blood glucose every" (Table 4). Close follow-up of glucose concentrations and adequate monitoring of insulin will also be helpful to reduce glycaemic variability.

Table 5 shows how to do the relay of intravenous insulin. Intravenous insulin can be stopped when all items can be checked:

- after > 24 h of intravenous insulin;
- when the patient is cardiologically stable (see Fig. 1);
- when the insulin speed is < 5 mL/h (if the intravenous insulin speed is > 5 mL/h, ask the diabetologist for advice before stopping);
- when the mean glucose concentration before meals is < 250 mg/dL (14 mmol/L).

Relay must be performed with basal and bolus insulin, except if the intravenous insulin speed is < 1 mL/h in patients with T2D without previous insulin treatment. In this last case, a relay with oral antidiabetic treatment or GLP1-RAs without insulin can be discussed with the diabetologist. Intravenous insulin is stopped when the first insulin basal/bolus dose is injected. The basal dose is half the amount of the total intravenous insulin infusion over the past 24 h. The bolus dose is half the amount of intravenous insulin infusion over the past 24 h divided over three meals. For example, if the last speed for a patient is 2 mL/h over the past 24 h, the volume infused per day is 2 mL × 24 = 48 mL. As the electric syringe contains 1 U of insulin/mL, this corresponds to 48 U of insulin per day. The basal (long-acting) dose to inject is a half dose, i.e. 24 U/day. The bolus dose to inject is a half dose (24 U/day) divided over three meals, i.e. 8 U before each meal, unless the patient is fasting.

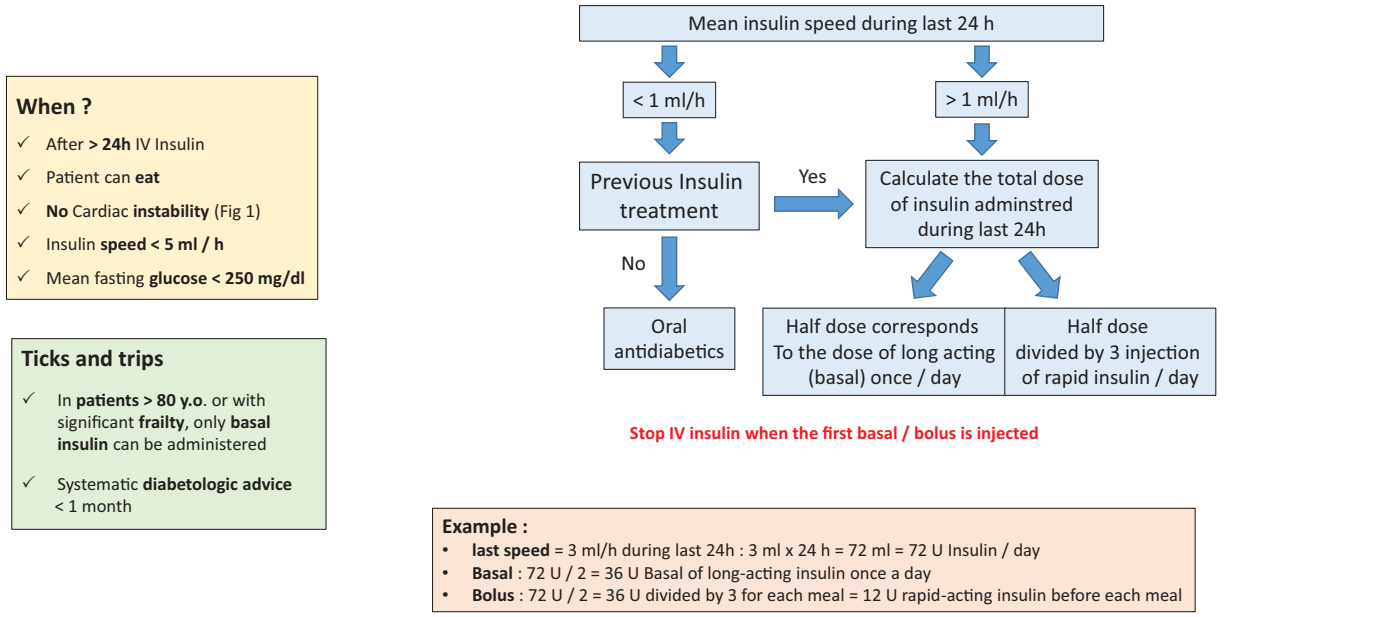
In patients with T1D, the previous insulin treatment (basal/bolus insulin regimen or insulin pump) must be started immediately after the interruption of intravenous insulin treatment, and ketones must be checked if glucose concentration is > 250 mg/dL.

In patients aged > 80 years or with significant frailty, only basal insulin can be administered while waiting for diabetological advice.

When an oral treatment is started, intravenous insulin must be stopped 2 h after the first oral glucose-lowering drug administration.

Note that, in case of doubt, the diabetologist must be called to validate the scheme according to the patient's profile, and a consultation must be planned in the first month following discharge.

Table 5
Relay of IV insulin protocol.



3.3. Treatment at discharge for patients with T2D not previously treated with insulin

Fig. 2 proposes an algorithm to determine the best glucose-lowering treatment for ICCU discharge in patients with T2D without previous insulin treatment. The algorithm includes patients in whom diabetes has been discovered during hospitalization or who were not previously treated. It is important to remember that diabetological advice has to be provided to these patients within the first month following discharge, to adapt glucose-lowering therapeutic schemes.

Note that if a patient previously treated with oral glucose-lowering drugs or GLP1-RAs has an HbA1c of > 8.5%, a BMI < 27 kg/m^2, recent weight loss or ketosis during hospitalization, a switch to insulin treatment has to be considered. The diabetologist must be called in order to confirm and discuss the insulin treatment regimen. When diabetological advice is difficult to obtain, the patient can be discharged with only basal insulin treatment following the doses used for intravenous insulin treatment (Table 5) or adapted for age, BMI and eGFR; it is possible to start with 0.2 U/kg/day when the BMI is 20–30 kg/m^2, 0.3 U/kg/day when the BMI is > 30 kg/m^2 or 0.15 U/kg/day when aged > 75 years or the BMI is < 20 kg/m^2 or the eGFR is < 30 mL/min/m^2. In this case, diabetological advice/hospitalization must be proposed in less than 15 days following discharge.

First-line treatments that have shown positive cardiac effects are marked with "1" and second-line treatments with "2", to add when glycaemic control remains suboptimal with the first-line treatment. Indeed, SGLT2 inhibitors and GLP1-RAs have shown strong and consistent benefits for the prognosis of patients with diabetes and an established cardiac disease. It is important to remember that the absence of hypoglycaemia induced by first-line treatments allows their association straight away in accordance with cardiological or renal indications, regardless of HbA1c and mean glucose concentration (when they are prescribed without any other antidiabetic treatment except metformin). SGLT2 inhibitors and GLP-RAs can favour hypoglycaemia only if they are added to other treatments that can induce hypoglycaemia (sulfonylureas, glinides and insulin).

The glycaemic goal depends on the patient's age and profile, and must be determined with the diabetologist. In most patients, the target is to obtain an HbA1c of < 7% without hypoglycaemic events [91].

Four main situations are presented below: patients with HF (primary or associated with another cardiac disease); patients hospitalized for atherosclerotic disease or another cardiological diagnosis; patients with eGFR < 30 mL/min/m^2, who are considered separately, whatever their main diagnosis, because several antidiabetic treatments are avoided or must be adapted; and patients treated with haemodialysis.

Patients with HF are separated according to eGFR (> 60 vs 30–60 mL/min/m^2). Patients with HF and eGFR > 60 mL/min/m^2 must be treated preferentially with SGLT2 inhibitors if the ejection fraction is > 30%. If the ejection fraction is < 30%, a half dose of metformin can be administered only if the patient is clinically stable and no heart transplant or assistance is expected shortly. GLP1-RAs can be administered if patients are stable. DPP-4 inhibitors, except saxagliptin, can be administered, but only if other glucose-lowering treatments are already administered, in the absence of concomitant GLP1-RA treatment and if insulin treatment is not required. Sulfonylureas or glinides may be prescribed only after diabetological advice. Similar recommendations can be made for patients hospitalized with acute HF and eGFR between 30 and 60 mL/min/m^2, except for metformin, which has to be used systematically at half dose in this last case.

In patients with atherosclerotic or other cardiac disease with eGFR > 30 mL/min/m^2, a similar distinction must be made according to eGFR (> 60 vs 30–60 mL/min/m^2). In patients with eGFR > 60 mL/min/m^2, a GLP1-RA with metformin is the first-line treatment for patients with CAD. SGLT2 inhibitors can be added as first-line treatment in patients with a history of CAD, according to the design of initial studies with SGLT2 inhibitors. DPP-4 inhibitors can be used in the absence of concomitant GLP1-RA treatment. Sulfonylureas or glinides may be prescribed only after diabetological advice, but must be positioned after the other classes because of the risk of hypoglycaemic events and their potential cardiometabolic risk. In patients hospitalized for atherosclerotic heart disease or another cardiological diagnosis, when eGFR is between 30 and

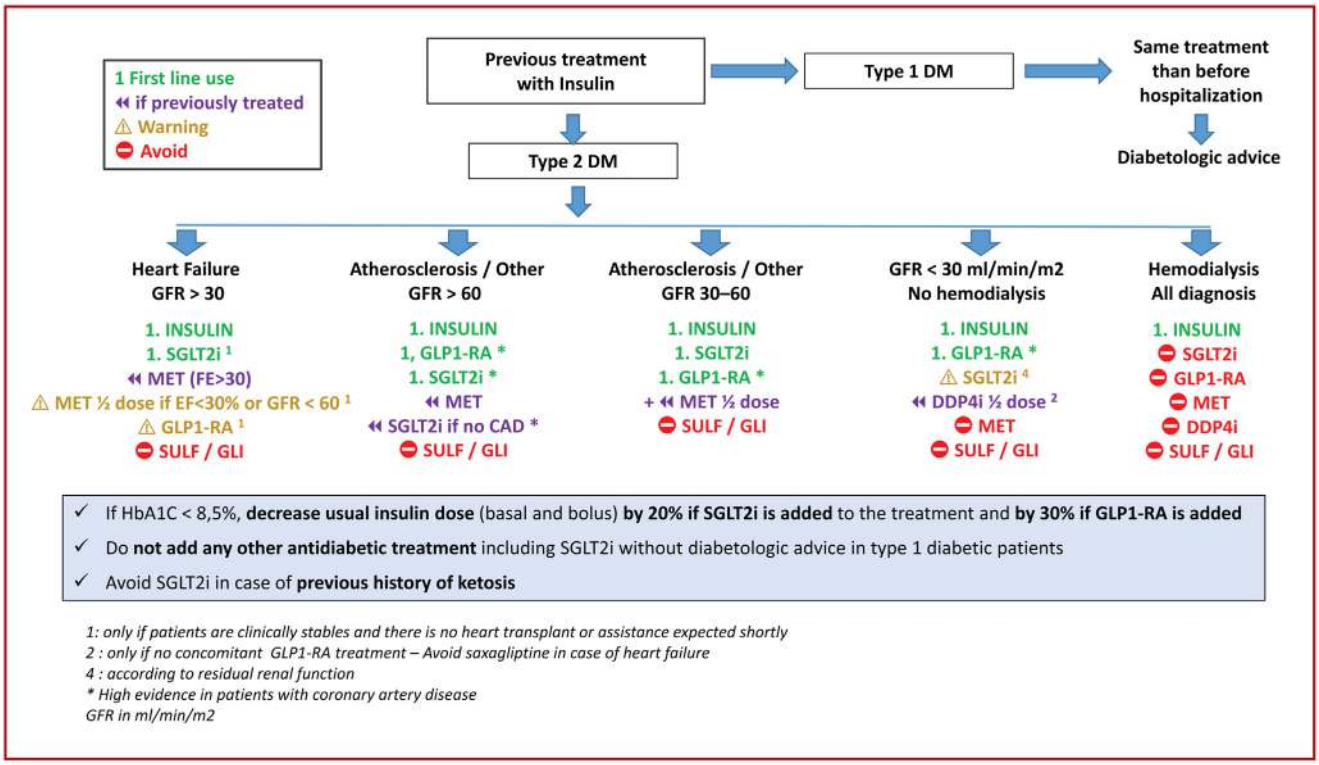


Fig. 3. Algorithm for discharge of patients with type 2 diabetes previously treated with insulin from the intensive cardiac care unit. CAD: coronary artery disease; DPP-4i: dipeptidyl peptidase-4 inhibitor; EF: ejection fraction; eGFR: estimated glomerular filtration rate; GLI: glinides; GLP1-RA: glucagon-like peptide-1 receptor antagonist: HbA1c: glycated haemoglobin; MET: metformin; SGLT2i: sodium-glucose cotransporter 2 inhibitor; SULF: sulfamides. [a] Only if patients are clinically stable and there is no heart transplant or assistance expected shortly. [b] High evidence in patients with CAD. [c] Only if no concomitant GLP1-RA treatment; avoid saxagliptin in case of heart failure. [d] According to residual renal function.

60 mL/min/m^2, SGLT2 inhibitors must be proposed systematically as a first-line treatment, in association with GLP1-RAs for patients with CAD, and metformin has to be used at half dose.

In patients with eGFR < 30 mL/min/m^2, whatever the initial diagnosis, several warnings must be taken into consideration. GLP1-RAs must be proposed as first-line treatment. For patients with HF, SGLT2 inhibitors can be proposed in patients with enough residual renal function. DPP-4 inhibitors may also be used in the absence of concomitant GLP1-RA treatment. Glinides may be used, but only after diabetological advice, because of their risk of hypoglycaemia. Metformin and sulfonylureas are contraindicated. In this profile of patients, insulin has to be discussed more rapidly than in other groups because of a restricted panel of allowed glucose-lowering treatments. It is therefore important to check glycaemic control carefully in very insulin-resistant and elderly patients.

Finally, in patients treated with haemodialysis, insulin is the only treatment allowed.

3.4. Treatment at discharge for patients with diabetes previously treated with insulin

Fig. 3 presents the algorithm for the ICCU discharge of patients with T2D treated with insulin before hospitalization. Specialized diabetological advice has to be provided within the first month after discharge in order to adapt the insulin regimen. First-line treatments are marked with "1," and the symbol "⏮⏮" describes treatment that can be maintained if the patient was receiving treatment before the acute cardiac event.

If the patient has T1D, the treatment must be similar to the prehospitalization regimen. However, it is important to call the diabetologist in order to check whether another insulin regimen is not better suited. Other glucose-lowering treatments, such as GLP1-RAs and SGLT2 inhibitors, can be added only after diabetological advice in this population. However, we have to remember that SGLT2 inhibitors are contraindicated in patients with T1D.

In patients with T2D previously treated with insulin, for those with HbA1c > 8.5%, BMI < 27 kg/m^2 or detection of ketosis during hospitalization, the diabetologist must be called in order to discuss the insulin regimen.

Apart from insulin treatment, it is important to remember that SGLT2 inhibitors and GLP1-RAs have shown a strong and consistent benefit in the prognosis of patients with T2D with cardiac disease, including those already treated with insulin. Moreover, metformin treatment is associated with a decrease in insulin resistance, which allows lowering of the insulin dose. It is therefore mandatory to add these treatments for patients with T2D with cardiac disease already treated with insulin. Note that if a patient was previously treated with basal insulin alone, a similar regimen can be proposed. The diabetologist must be called in order to discuss the insulin regimen.

Three main cases are presented: patients with HF (primary or associated with another cardiac disease); patients hospitalized for atherosclerotic disease or with another diagnosis; and patients with eGFR < 30 mL/min/m^2, who are considered separately, whatever their main diagnosis.

Patients with HF are separated according to eGFR (> 60 vs 30–60 mL/min/m^2). Patients with HF and eGFR > 60 mL/min/m^2 must be treated with insulin and SGLT2 inhibitors. Metformin can be added if it was already used before hospitalization and if the ejection fraction is > 30%. If not, the diabetologist will add metformin during the following consultation, if needed. If the ejection fraction is < 30%, metformin can be administered only if previously administered and the patient is clinically stable and there is no heart transplant or assistance expected shortly (we suggest that a half dose should be considered in this latter case). GLP1-RAs may be

Table 6
When is calling for a diabetologist's advice mandatory?

- **Immediately**
  - If capillary ketones > 3 mmol
  - Insulin speed > 5 U ml/h after 24h of IV insulin treatment
  - Glucose > 350 mg/dl for more than 24h
- **Before discharge**
  - HbA1c > 8,5 % at entry
  - BMI < 27 kg/m2 or recent weigth loss
  - Type 1 diabetes when you expect to add other antidabetic treatment including iSGLT2
  - Patients have more than 3 antidiabetic treatments
- **After discharge**
  - Appointement < 1 month if insulin has been added to the treatment
  - Appointement > 3 months for all other patients

BMI: body mass index; HbA1c: glycated haemoglobin; SGLT2: sodium-glucose cotransporter 2; IV: intravenous; T1D: type 1 diabetes.

administered if the patient is stable and there is no heart transplant or assistance expected shortly. Sulfonylureas and glinides must be avoided.

In patients with atherosclerotic or other cardiac disease, a similar distinction must be made according to eGFR (> 60 vs 30–60 mL/min/m^2). In patients with eGFR > 60 mL/min/m^2, GLP1-RAs are the first-line treatment added to insulin for patients with CAD. SGLT2 inhibitors can be added as a first-line treatment in patients with CAD according to the design of initial studies with SGLT2 inhibitors. In patients without CAD, SGLT2 inhibitors can be prescribed if the patient was already treated before hospitalization. Metformin may be added if it was already used before hospitalization. If not, the diabetologist will add metformin later if needed. DPP-4 inhibitors can be used in the absence of concomitant GLP1-RA treatment. Sulfonylureas and glinides must be avoided. When eGFR is between 30 and 60 mL/min/m^2, SGLT2 inhibitors must be proposed systematically as a first-line treatment, with secondary prescription of GLP1-RAs in patients with CAD, and metformin at half dose.

In patients with eGFR < 30 mL/min/m^2, whatever the initial diagnosis, GLP1-RAs can be proposed as first-line treatment in combination with insulin in patients with CAD. SGLT2 inhibitors can be added according to residual renal function. Metformin, sulfonylureas and glinides are contraindicated.

For patients treated with haemodialysis, insulin is the only treatment allowed.

Finally, for patients with T2D treated with insulin, whatever the patient's profile, if SGLT2 inhibitors are added to the previous insulin treatment, a decrease in insulin dose (both basal and bolus) of approximately 20% is recommended to avoid hypoglycaemia. When GLP1-RAs are added to the treatment, a decrease of 30% of insulin dose (both basal and bolus) is recommended.

3.5. When is calling for a diabetologist's advice mandatory?

As shown in Table 6, calling for a diabetologist's advice is mandatory during hospitalization in the ICCU if there is severe ketosis (ketones ≥ 3 mmol/L) if there is an elevated speed of insulin infusion (≥ 5 mL/h) after 24 h of intravenous insulin treatment or if blood glucose is elevated (≥ 350 mg/dL or 19 mmol/L) for more than 24 h.

A diabetologist's advice is also mandatory before discharge if HbA1c was > 8.5% at admission, if the BMI is < 27 kg/m^2 or there has been recent weight loss (situation suggesting potential deficit of insulin secretion and possible indication for insulin treatment), if the patient is receiving three or more antidiabetic treatments and in case of a patient with T1D for whom initiation of treatment with SGLT2 inhibitors or GLP1-RAs is discussed for cardiological reasons. We have to remember that SGLT2 inhibitors are contraindicated in patients with T1D because of a high risk of ketoacidosis, and that the cardiovascular benefit of GLP1-RAs has not been shown in T1D.

Finally a diabetologist's advice is mandatory shortly after hospitalization in cardiology if there is a diagnosis of diabetes during hospitalization in cardiology or initiation of a new diabetic treatment during hospitalization in cardiology.

4. Conclusions

Taking account of the increased risk of death and morbidity in patients with diabetes with cardiac disease, and the impressive benefits of new antidiabetic treatments, it appears mandatory to seek to optimize antidiabetic treatment during hospitalization for an acute cardiac problem. This consensus paper can help cardiologists working in ICCUs to optimize the antidiabetic treatment of their patients, and can inform cardiologists about situations in which calling the diabetologist is mandatory.

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The authors declare that they have no competing interest.

References

[1] Ferrannini G, De Bacquer D, Vynckier P, De Backer G, Gyberg V, Kotseva K, et al. Gender differences in screening for glucose perturbations, cardiovascular risk factor management and prognosis in patients with dysglycaemia and coronary artery disease: results from the ESC-EORP EUROASPIRE surveys. Cardiovasc Diabetol 2021;20:38.
[2] Tamita K, Katayama M, Takagi T, Yamamuro A, Kaji S, Yoshikawa J, et al. Newly diagnosed glucose intolerance and prognosis after acute myocardial infarction: comparison of post-challenge versus fasting glucose concentrations. Heart 2012;98:848–54.
[3] Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P, et al. Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. Circulation 2017;136:1908–19.
[4] Kuhl J, Jorneskog G, Wemminger M, Bengtsson M, Lundman P, Kalani M. Long-term clinical outcome in patients with acute coronary syndrome and dysglycaemia. Cardiovasc Diabetol 2015;14:120.

[5] Mazurek M, Kowalczyk J, Lenarczyk R, Zielinska T, Sedkowska A, Pruszkowska-Skrzep P, et al. The prognostic value of different glucose abnormalities in patients with acute myocardial infarction treated invasively. Cardiovasc Diabetol 2012;11:78.
[6] Dunlay SM, Givertz MM, Aguilar D, Allen LA, Chan M, Desai AS, et al. Type 2 diabetes mellitus and heart failure: a scientific statement from the American Heart Association and the Heart Failure Society of America: this statement does not represent an update of the 2017 ACC/AHA/HFSA heart failure guideline update. Circulation 2019;140:e294–324.
[7] Dei Cas A, Khan SS, Butler J, Mentz RJ, Bonow RO, Avogaro A, et al. Impact of diabetes on epidemiology, treatment, and outcomes of patients with heart failure. JACC Heart Fail 2015;3:136–45.
[8] Bauters C, Lamblin N, Mc Fadden EP, Van Belle E, Millaire A, de Groote P. Influence of diabetes mellitus on heart failure risk and outcome. Cardiovasc Diabetol 2003;2:1.
[9] Verges B, Avignon A, Bonnet F, Catargi B, Cattan S, Cosson E, et al. Consensus statement on the care of the hyperglycaemic/diabetic patient during and in the immediate follow-up of acute coronary syndrome. Arch Cardiovasc Dis 2012;105:239–53.
[10] De Luca L, Olivari Z, Bolognese L, Lucci D, Gonzini L, Di Chiara A, et al. A decade of changes in clinical characteristics and management of elderly patients with non-ST elevation myocardial infarction admitted in Italian cardiac care units. Open Heart 2014;1:e000148.
[11] Fairman E, Delfino F, Mauro V, Charask A, Castillo Costa Y, Rafaelli A, et al. Diabetes as a predictor of in-hospital and one-year outcomes after decompensated heart failure. Curr Probl Cardiol 2021;46:100579.
[12] Kong MG, Jang SY, Jang J, Cho HJ, Lee S, Lee SE, et al. Impact of diabetes mellitus on mortality in patients with acute heart failure: a prospective cohort study. Cardiovasc Diabetol 2020;19:49.
[13] Dillinger JG, Saeed A, Spagnoli V, Sollier CB, Sideris G, Silberman SM, et al. High platelet reactivity on aspirin in patients with acute ST elevation myocardial infarction. Thromb Res 2016;144:56–61.
[14] De Groote P, Lamblin N, Mouquet F, Plichon D, McFadden E, Van Belle E, et al. Impact of diabetes mellitus on long-term survival in patients with congestive heart failure. Eur Heart J 2004;25:656–62.
[15] Targher G, Dauriz M, Laroche C, Temporelli PL, Hassanein M, Seferovic PM, et al. In-hospital and 1-year mortality associated with diabetes in patients with acute heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. Eur J Heart Fail 2017;19:54–65.
[16] Smidtslund P, Jansson Sigfrids F, Ylinen A, Elonen N, Harjutsalo V, Groop PH, et al. Prognosis after first-ever myocardial infarction in type 1 diabetes is strongly affected by chronic kidney disease. Diabetes Care 2023;46:197–205.
[17] Ritsinger V, Tanoglidi E, Malmberg K, Nasman P, Ryden L, Tenerz A, et al. Sustained prognostic implications of newly detected glucose abnormalities in patients with acute myocardial infarction: long-term follow-up of the glucose tolerance in patients with acute myocardial infarction cohort. Diab Vasc Dis Res 2015;12:23–32.
[18] Pan W, Lu H, Lian B, Liao P, Guo L, Zhang M. Prognostic value of HbA1c for in-hospital and short-term mortality in patients with acute coronary syndrome: a systematic review and meta-analysis. Cardiovasc Diabetol 2019;18:169.
[19] Dungan KM, Braithwaite SS, Preiser JC. Stress hyperglycaemia. Lancet 2009;373:1798–807.
[20] Scheen M, Giraud R, Bendjelid K. Stress hyperglycemia, cardiac glucotoxicity, and critically ill patient outcomes current clinical and pathophysiological evidence. Physiol Rep 2021;9:e14713.
[21] Abdin A, Poss J, Fuernau G, Ouarrak T, Desch S, Eitel I, et al. Prognostic impact of baseline glucose levels in acute myocardial infarction complicated by cardiogenic shock-a substudy of the IABP-SHOCK II-trial [corrected]. Clin Res Cardiol 2018;107:517–23.
[22] Timmer JR, Hoekstra M, Nijsten MW, van der Horst IC, Ottervanger JP, Slingerland RJ, et al. Prognostic value of admission glycosylated hemoglobin and glucose in nondiabetic patients with ST-segment-elevation myocardial infarction treated with percutaneous coronary intervention. Circulation 2011;124:704–11.
[23] Gallo G, Savoia C. New insights into endothelial dysfunction in cardiometabolic diseases: potential mechanisms and clinical implications. Int J Mol Sci 2024;25:1–14.
[24] van den Berghe G, Wouters P, Weekers F, Verwaest C, Bruyninckx F, Schetz M, et al. Intensive insulin therapy in critically ill patients. N Engl J Med 2001;345:1359–67.
[25] 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.
[26] Capes SE, Hunt D, Malmberg K, Gerstein HC. Stress hyperglycaemia and increased risk of death after myocardial infarction in patients with and without diabetes: a systematic overview. Lancet 2000;355:773–8.
[27] Svensson AM, McGuire DK, Abrahamsson P, Dellborg M. Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. Eur Heart J 2005;26:1255–61.
[28] Lipton JA, Barendse RJ, Van Domburg RT, Schinkel AF, Boersma H, Simoons MI, et al. Hyperglycemia at admission and during hospital stay are independent risk factors for mortality in high risk cardiac patients admitted to an intensive cardiac care unit. Eur Heart J Acute Cardiovasc Care 2013;2:306–13.
[29] Malmberg K. Prospective randomised study of intensive insulin treatment on long term survival after acute myocardial infarction in patients with diabetes mellitus. DIGAMI (Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction) Study Group. BMJ 1997;314:1512–5.
[30] Gerstein HC, Miller ME, Byington RP, Goff Jr DC, Bigger JT, Buse JB, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–59.
[31] Pinto DS, Kirtane AJ, Pride YB, Murphy SA, Sabatine MS, Cannon CP, et al. Association of blood glucose with angiographic and clinical outcomes among patients with ST-segment elevation myocardial infarction (from the CLARITY-TIMI-28 study). Am J Cardiol 2008;101:303–7.
[32] Ishihara M, Kojima S, Sakamoto T, Kimura K, Kosuge M, Asada Y, et al. Comparison of blood glucose values on admission for acute myocardial infarction in patients with versus without diabetes mellitus. Am J Cardiol 2009;104:769–74.
[33] Benalia M, Zeller M, Mouhat B, Guenancia C, Yameogo V, Greco C, et al. Glycaemic variability is associated with severity of coronary artery disease in patients with poorly controlled type 2 diabetes and acute myocardial infarction. Diabetes Metab 2019;45:446–52.
[34] Su G, Mi SH, Tao H, Li Z, Yang HX, Zheng H, et al. Impact of admission glycemic variability, glucose, and glycosylated hemoglobin on major adverse cardiac events after acute myocardial infarction. Diabetes Care 2013;36:1026–32.
[35] Takahashi H, Iwahashi N, Kirigaya J, Kataoka S, Minamimoto Y, Gohbara M, et al. Glycemic variability determined with a continuous glucose monitoring system can predict prognosis after acute coronary syndrome. Cardiovasc Diabetol 2018;17:116.
[36] Gerbaud E, Darier R, Montaudon M, Beauvieux MC, Coffin-Boutreux C, Coste P, et al. Glycemic variability is a powerful independent predictive factor of midterm major adverse cardiac events in patients with diabetes with acute coronary syndrome. Diabetes Care 2019;42:674–81.
[37] Nam MC, Byrne CD, Kaski JC, Greaves K. Insulin in acute coronary syndrome: a narrative review with contemporary perspectives. Cardiovasc Drugs Ther 2016;30:493–504.
[38] Janiger JL, Cheng JW. Glucose-insulin-potassium solution for acute myocardial infarction. Ann Pharmacother 2002;36:1080–4.
[39] Malmberg K, Ryden L, Efendic S, Herlitz J, Nicol P, Waldenstrom A, et al. Randomized trial of insulin-glucose infusion followed by subcutaneous insulin treatment in diabetic patients with acute myocardial infarction (DIGAMI study): effects on mortality at 1 year. J Am Coll Cardiol 1995;26:57–65.
[40] Mellbin LG, Malmberg K, Norhammar A, Wedel H, Ryden L, Investigators D. The impact of glucose lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial. Eur Heart J 2008;29:166–76.
[41] Nerenberg KA, Goyal A, Xavier D, Sigamani A, Ng J, Mehta SR, et al. Piloting a novel algorithm for glucose control in the coronary care unit: the RECREATE (REsearching Coronary REduction by Appropriately Targeting Euglycemia) trial. Diabetes Care 2012;35:19–24.
[42] Gerstein HC, Jung H, Ryden L, Diaz R, Gilbert RE, Yusuf S, et al. Effect of basal insulin glargine on first and recurrent episodes of heart failure hospitalization: the ORIGIN Trial (Outcome Reduction With Initial Glargine Intervention). Circulation 2018;137:88–90.
[43] Nassif ME, Kosiborod M. A review of cardiovascular outcomes trials of glucose-lowering therapies and their effects on heart failure outcomes. Am J Cardiol 2019;124(Suppl 1):S12–9.
[44] Meinert CL, Knatterud GL, Prout TE, Klimt CR. A study of the effects of hypoglycemic agents on vascular complications in patients with adult-onset diabetes. II. Mortality results. Diabetes 1970;19(Suppl.):789–830.
[45] Abdelmoneim AS, Eurich DT, Light PE, Senior PA, Seubert JM, Makowsky MJ, et al. Cardiovascular safety of sulphonylureas: over 40 years of continuous controversy without an answer. Diabetes Obes Metab 2015;17:523–32.
[46] Vaccaro O, Masulli M, Nicolucci A, Bonora E, Del Prato S, Maggioni AP, et al. Effects on the incidence of cardiovascular events of the addition of pioglitazone versus sulfonylureas in patients with type 2 diabetes inadequately controlled with metformin (TOSCA.IT): a randomised, multicentre trial. Lancet Diabetes Endocrinol 2017;5:887–97.
[47] Rosenstock J, Kahn SE, Johansen OE, Zinman B, Espeland MA, Woerle HJ, et al. Effect of linagliptin vs glimepiride on major adverse cardiovascular outcomes in patients with type 2 diabetes: the CAROLINA randomized clinical trial. JAMA 2019;322:1155–66.
[48] UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998;352:837–53.
[49] Scheen AJ, Paquot N. [Use of metformin in diabetic patients with cardiac disease: benefit-risk balance]. Rev Med Suisse 2013;9:1527–33.
[50] Lexis CP, van der Horst IC, Lipsic E, Wieringa WG, de Boer RA, van den Heuvel AF, et al. Effect of metformin on left ventricular function after acute myocardial infarction in patients without diabetes: the GIPS-III randomized clinical trial. JAMA 2014;311:1526–35.
[51] Techiryan G, Weil BR, Palka BA, Canty Jr JM. Effect of intracoronary metformin on myocardial infarct size in swine. Circ Res 2018;123:986–95.
[52] Bromage DI, Godec TR, Pujades-Rodriguez M, Gonzalez-Izquierdo A, Denaxas S, Hemingway H, et al. Metformin use and cardiovascular outcomes after acute myocardial infarction in patients with type 2 diabetes: a cohort study. Cardiovasc Diabetol 2019;18:168.
[53] Hartman MHT, Prins JKB, Schurer RAJ, Lipsic E, Lexis CPH, van der Horst-Schrivers ANA, et al. Two-year follow-up of 4 months metformin treatment vs placebo in ST-elevation myocardial infarction: data from the GIPS-III RCT. Clin Res Cardiol 2017;106:939–46.

[54] Inzucchi SE, Masoudi FA, Wang Y, Kosiborod M, Foody JM, Setaro JF, et al. Insulin-sensitizing antihyperglycemic drugs and mortality after acute myocardial infarction: insights from the National Heart Care Project. Diabetes Care 2005;28:1680–9.
[55] Boyd A, Nawarskas J. Metformin use in decompensated heart failure. Cardiol Rev 2008;16:269–72.
[56] Weir DL, Abrahamowicz M, Beauchamp ME, Eurich DT. Acute vs cumulative benefits of metformin use in patients with type 2 diabetes and heart failure. Diabetes Obes Metab 2018;20:2653–60.
[57] Roussel R, Travert F, Pasquet B, Wilson PW, Smith Jr SC, Goto S, et al. Metformin use and mortality among patients with diabetes and atherothrombosis. Arch Intern Med 2010;170:1892–9.
[58] Carlson N, Hommel K, Olesen JB, Gerds TA, Soja AM, Vilsboll T, et al. Metformin-associated risk of acute dialysis in patients with type 2 diabetes: a nationwide cohort study. Diabetes Obes Metab 2016;18:1283–7.
[59] Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med 2015;373:232–42.
[60] Scirica BM, Braunwald E, Raz I, Cavender MA, Morrow DA, Jarolim P, et al. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579–88.
[61] White WB, Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, et al. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med 2013;369:1327–35.
[62] Wu S, Hopper I, Skiba M, Krum H. Dipeptidyl peptidase-4 inhibitors and cardiovascular outcomes: meta-analysis of randomized clinical trials with 55,141 participants. Cardiovasc Ther 2014;32:147–58.
[63] Sharma A, Cannon CP, White WB, Liu Y, Bakris GL, Cushman WC, et al. Early and chronic dipeptidyl-peptidase-iv inhibition and cardiovascular events in patients with type 2 diabetes mellitus after an acute coronary syndrome: a landmark analysis of the EXAMINE trial. J Am Heart Assoc 2018;7.
[64] Hage C, Brismar K, Lundman P, Norhammar A, Ryden L, Mellbin L. The DPP-4 inhibitor sitagliptin and endothelial function in patients with acute coronary syndromes and newly detected glucose perturbations: a report from the BEGAMI study. Diab Vasc Dis Res 2014;11:290–3.
[65] Aroda VR. A review of GLP-1 receptor agonists: evolution and advancement, through the lens of randomised controlled trials. Diabetes Obes Metab 2018;20(Suppl. 1):22–33.
[66] Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JF, Nauck MA, et al. Liraglutide and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2016;375:311–22.
[67] Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jodar E, Leiter LA, et al. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med 2016;375:1834–44.
[68] Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. Lancet 2019;394:121–30.
[69] Read PA, Hoole SP, White PA, Khan FZ, O'Sullivan M, West NE, et al. A pilot study to assess whether glucagon-like peptide-1 protects the heart from ischemic dysfunction and attenuates stunning after coronary balloon occlusion in humans. Circ Cardiovasc Interv 2011;4:266–72.
[70] Lonborg J, Vejlstrup N, Kelbaek H, Botker HE, Kim WY, Mathiasen AB, et al. Exenatide reduces reperfusion injury in patients with ST-segment elevation myocardial infarction. Eur Heart J 2012;33:1491–9.
[71] Garcia Del Blanco B, Otaegui I, Rodriguez-Palomares JF, Bayes-Genis A, Fernandez-Nofrerias E, Vilalta Del Olmo V, et al. Effect of COMBinAtion therapy with remote ischemic conditioning and exenatide on the Myocardial Infarct size: a two-by-two factorial randomized trial (COMBAT-MI). Basic Res Cardiol 2021;116:4.
[72] Roos ST, Timmers L, Biesbroek PS, Nijveldt R, Kamp O, van Rossum AC, et al. No benefit of additional treatment with exenatide in patients with an acute myocardial infarction. Int J Cardiol 2016;220:809–14.
[73] Huang M, Wei R, Wang Y, Su T, Li Q, Yang X, et al. Protective effect of glucagon-like peptide-1 agents on reperfusion injury for acute myocardial infarction: a meta-analysis of randomized controlled trials. Ann Med 2017;49:552–61.
[74] Ogbu IR, Ngwudike C, Lal K, Danielian A, Daoud SN. Role of glucagon-like peptide-1 agonist in patients undergoing percutaneous coronary intervention or coronary artery bypass grafting: a meta-analysis. Am Heart J Plus 2021;11:100063.
[75] Giugliano D, Maiorino MI, Bellastella G, Longo M, Chiodini P, Esposito K. GLP-1 receptor agonists for prevention of cardiorenal outcomes in type 2 diabetes: an updated meta-analysis including the REWIND and PIONEER 6 trials. Diabetes Obes Metab 2019;21:2576–80.
[76] Margulies KB, Hernandez AF, Redfield MM, Givertz MM, Oliveira GH, Cole R, et al. Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction: a randomized clinical trial. JAMA 2016;316:500–8.
[77] Jorsal A, Kistorp C, Holmager P, Tougaard RS, Nielsen R, Hanselmann A, et al. Effect of liraglutide, a glucagon-like peptide-1 analogue, on left ventricular function in stable chronic heart failure patients with and without diabetes (LIVE)-a multicentre, double-blind, randomised, placebo-controlled trial. Eur J Heart Fail 2017;19:69–77.
[78] Simms-Williams N, Treves N, Yin H, Lu S, Yu O, Pradhan R, et al. Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population based cohort study. BMJ 2024;385:e078242.
[79] Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med 2017;377:644–57.
[80] Wiviott SD, Raz I, Bonaca MP, Mosenzon O, Kato ET, Cahn A, et al. Dapagliflozin and cardiovascular outcomes in type 2 diabetes. N Engl J Med 2019;380:347–57.
[81] Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373:2117–28.
[82] McMurray JJV, Solomon SD, Inzucchi SE, Kober L, Kosiborod MN, Martinez FA, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. N Engl J Med 2019;381:1995–2008.
[83] Voors AA, Angermann CE, Teerlink JR, Collins SP, Kosiborod M, Biegus J, et al. The SGLT2 inhibitor empagliflozin in patients hospitalized for acute heart failure: a multinational randomized trial. Nat Med 2022;28:568–74.
[84] Bhatt DL, Szarek M, Steg PG, Cannon CP, Leiter LA, McGuire DK, et al. Sotagliflozin in patients with diabetes and recent worsening heart failure. N Engl J Med 2021;384:117–28.
[85] Damman K, Beusekamp JC, Boorsma EM, Swart HP, Smilde TDJ, Elvan A, et al. Randomized, double-blind, placebo-controlled, multicentre pilot study on the effects of empagliflozin on clinical outcomes in patients with acute decompensated heart failure (EMPA-RESPONSE-AHF). Eur J Heart Fail 2020;22:713–22.
[86] Mebazaa A, Davison B, Chioncel O, Cohen-Solal A, Diaz R, Filippatos G, et al. Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): a multinational, open-label, randomised, trial. Lancet 2022;400:1938–52.
[87] Packer M, McMurray JJV. Rapid evidence-based sequencing of foundational drugs for heart failure and a reduced ejection fraction. Eur J Heart Fail 2021;23:882–94.
[88] James S, Erlinge D, Storey RF, McGuire DK, de Belder M, Eriksson N, et al. Dapagliflozin in myocardial infarction without diabetes or heart failure. NEJM Evid 2024;3. EVIDoa2300286.
[89] Butler J, Jones WS, Udell JA, Anker SD, Petrie MC, Harrington J, et al. Empagliflozin after acute myocardial infarction. N Engl J Med 2024;390:1455–66.
[90] von Lewinski D, Kolesnik E, Tripolt NJ, Pferschy PN, Benedikt M, Wallner M, et al. Empagliflozin in acute myocardial infarction: the EMMY trial. Eur Heart J 2022;43:4421–32.
[91] Darmon P, Bauduceau B, Bordier L, Detournay B, Gautier J-F, Gourdy P, et al. Prise de position de la Société Francophone du Diabète (SFD) sur les stratégies d'utilisation des traitements anti-hyperglycémiants dans le diabète de type 2-2023. Med Mal Metab 2023;17:664–93.
[92] Marx N, Federici M, Schutt K, Muller-Wieland D, Ajjan RA, Antunes MJ, et al. 2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes. Eur Heart J 2023;44:4043–140.