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Review

Consensus statement on the care of the hyperglycaemic/diabetic patient during and in the immediate follow-up of acute coronary syndrome

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Abstract

The Diabetes and Cardiovascular Disease study group of the *Société francophone du diabète* (SFD, French Society of Diabetes) in collaboration with the *Société française de cardiologie* (SFC, French Society of Cardiology) have devised a consensus statement on the care of the hyperglycaemic/diabetic patient during and in the immediate follow-up of acute coronary syndrome (ACS); in particular, it includes the different phases of ACS [the intensive care unit (ICU) period, the post-ICU period and the short-term follow-up period after discharge, including cardiac rehabilitation] and also embraces all of the various diagnostic and therapeutic issues with a view to optimalizing the collaboration between cardiologists and diabetologists. As regards diagnosis, subjects with HbA_{1c} greater or equal to 6.5% on admission may be considered diabetic while, in those with no known diabetes and HbA_{1c} less than 6.5%, it is recommended that an OGTT be performed 7 to 28 days after ACS. During hospitalization in the ICU, continuous insulin treatment should be initiated in all patients when admission blood glucose levels are greater or equal to 180 mg/dL (10.0 mmol/L) and, in those with previously known diabetes, when preprandial glucose levels are greater or equal to 140 mg/dL (7.77 mmol/L) during follow-up. The recommended blood glucose target is 140–180 mg/dL (7.7–10 mmol/L) for most patients. Following the ICU period, insulin treatment is not mandatory for every patient, and other antidiabetic treatments may be considered, with the choice of optimal treatment depending on the metabolic profile of the patient. Patients should be referred to a diabetologist before discharge from hospital in cases of unknown diabetes diagnosed during ACS hospitalization, of HbA_{1c} greater or equal to 8% at the time of admission, or newly introduced insulin therapy or severe/repeated hypoglycaemia. Referral to a diabetologist after hospital discharge is recommended if diabetes is diagnosed by the OGTT, or during cardiac rehabilitation in cases of uncontrolled diabetes ($HbA_{1c} \geq 8\%$) or severe/repeated hypoglycaemia.

Keywords: Diabetes; Acute coronary syndrome; Myocardial infarction; Consensus; Cardiology; Hyperglycaemia; Review

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Résumé

Consensus sur la prise en charge du patient hyperglycémique et/ou diabétique au cours et au décours immédiat d'un syndrome coronaire aigu.

Le groupe d'étude Cœur et Diabète de la Société francophone du diabète (SFD), en collaboration avec la Société française de cardiologie (SFC), a rédigé un consensus sur la « prise en charge du patient diabétique/hyperglycémique au cours et au décours immédiat d'un syndrome coronaire aigu (SCA) » en intégrant les différentes périodes du SCA (soins intensifs, hospitalisation post-soins intensifs et le suivi immédiat incluant la réadaptation cardiaque), en considérant aussi bien les problèmes diagnostiques que thérapeutiques et dans le souhait d'optimiser la collaboration entre cardiologues et diabétologues. En ce qui concerne le diagnostic, les patients qui ont une HbA_{1c} lors de l'admission supérieure ou égale à 6,5 % peuvent être considérés comme diabétiques. Chez les patients non diabétiques dont l'HbA_{1c} est inférieure à 6,5 %, il est recommandé de pratiquer un test de charge en glucose sept à 28 jours après le SCA. Au cours de l'hospitalisation en soins intensifs, un traitement par insuline devra être initié, chez tous les patients, en cas de glycémie à l'admission supérieure ou égale à 1,80 g/L (10,0 mmol/L) et, chez les patients diabétiques connus avant le SCA, en cas de glycémie pré-prandiale supérieure ou égale à 1,40 g/L (7,77 mmol/L). L'objectif glycémique pour la majorité des patients doit se situer entre 1,40 et 1,80 g/L (7,7–10 mmol/L). Après l'hospitalisation en soins intensifs, le traitement insulinique n'est pas obligatoire chez tous les patients et il sera possible d'utiliser d'autres traitements antidiabétiques dont le choix sera dicté par le profil métabolique du patient diabétique. Le patient devra être adressé à un diabétologue, avant sa sortie de l'hôpital, dans les situations suivantes : diabète diagnostiqué lors du SCA, HbA_{1c} à l'admission supérieure ou égale à 8 %, instauration d'un traitement par insuline et/ou hypoglycémies répétées ou sévères. Au décours de l'hospitalisation, une consultation diabétologique sera demandée en cas de diabète diagnostiqué lors du test de charge en glucose et, au cours de la réadaptation cardiaque, en cas de diabète mal contrôlé ($HbA_{1c} \geq 8$ %) et/ou d'hypoglycémies répétées ou sévères.

Mots clés : Diabète ; Syndrome coronaire aigu ; Infarctus du myocarde ; Consensus ; Cardiologie ; Hyperglycémie ; Revue générale

1. Introduction

Type 2 diabetes is a major risk factor of cardiovascular morbidity and mortality [1,2]. An increased cardiovascular risk is already present in those with mildly elevated levels of blood glucose that are still below the threshold for diabetes [3–5], while the prevalence of diabetes or abnormal glucose metabolism is very high in patients presenting with acute coronary syndrome (ACS). Indeed, among patients hospitalized for ACS, 30–40% have diabetes, 25–36% show impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) and only 30–40% have normal glucose tolerance [6–9]. In addition, the prognosis after ACS is impaired in diabetic patients [9]. Thus, diabetes care during and in the immediate follow-up of ACS is an important issue. So far, recommendations for diabetes treatment during ACS are limited, with no specific guidelines for glucose management in ACS patients, and no consensus on the use of non-insulin treatments during and in the immediate follow-up of ACS. Furthermore, cardiologists have no clear recommendations as to when to refer a patient to a diabetologist during and following ACS. Moreover, in patients presenting with ACS and hyperglycaemia, but with no previously known diabetes, there is a need for a clear diagnostic pathway for the diagnosis and management of abnormal glucose metabolism (IFG/IGT) and diabetes.

For these reasons, the Diabetes and Cardiovascular Disease study group of the *Société Francophone du Diabète* (SFD, French Society of Diabetes) in collaboration with the *Société Française de Cardiologie* (SFC, French Society of Cardiology) have put together a consensus statement on the care of the hyperglycaemic/diabetic patient during and in the immediate follow-up of ACS. The objective was to devise a consensus statement to cover the hyperglycaemic/diabetic patient during each phase of ACS [intensive care unit (ICU) period, post-ICU period and short-term follow-up period after discharge, including cardiac rehabilitation] while embracing all of the various diagnostic and therapeutic issues to optimize the collaboration between cardiologists and diabetologists (Fig. 1). The consensus uses the recommendation grades of the French Haute Autorité de santé (HAS, National Health Authority): Level A = established scientific proof (based on high-quality randomized comparative trials or meta-analysis of randomized control trials); level B = scientific hypothesis (based on low-quality randomized comparative trials, well-designed non-randomized comparative studies or cohort studies); and level C = low level of proof (based on case–control studies) [10].

2. Screening for glucose metabolism disorders in patients with ACS

2.1. Stress hyperglycaemia

Epidemiological data show that the prevalence of known diabetes in patients referred for ACS is greater or equal to 30%. Stress can also facilitate the development of abnormal glucose metabolism. Therefore, stress hyperglycaemia is commonly found in patients with ACS, and is a powerful predictor of in-hospital survival and in-hospital complications in patients with and without established diabetes [11,12]. It has also been suggested that tight control of glycaemia during the acute phase might improve survival, thereby justifying the routine measurement of glucose levels on admission. However, admission levels of glucose are not a recognized diagnostic criterion of intermediate hyperglycaemia or diabetes, and do not predict the classification of glucose tolerance after ACS [13–15]. Admission glucose levels should therefore not be used to classify glucose tolerance, but rather to initiate early insulin treatment.

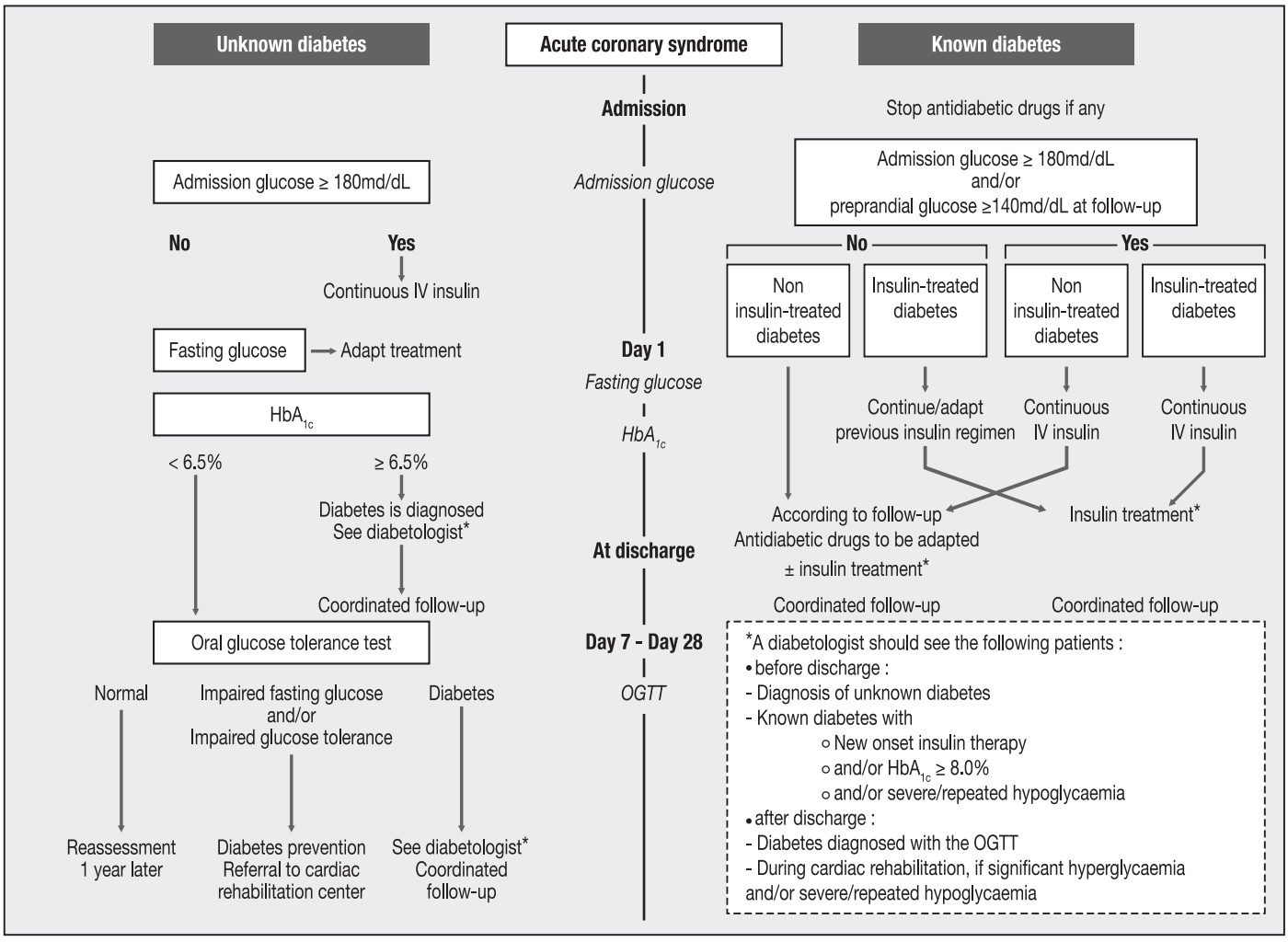

Fig. 1. Summary of the consensus statement on care of the hyperglycaemic/diabetic patient during and in the immediate follow-up of an ACS.

2.2. *Definition and classification of intermediate hyperglycaemia and diabetes*

The criteria currently used in France [14] are those established by the World Health Organization (WHO) based on the level of fasting plasma glucose (FPG) and/or glucose level 2 h (2hPG) after an oral glucose tolerance test (OGTT) performed in the morning after a 12-h fast (with a 75-g glucose load) [13]. Diabetes is defined as FPG greater or equal to 7.0 mmol/L (126 mg/dL) or 2hPG greater or equal to 11.1 mmol/L (200 mg/dL). IFG is defined as FPG greater or equal to 6.1 mmol/L (110 mg/dL) and less than 7.0 mmol/L, and IGT is defined as a 2hPG greater or equal to 7.8 mmol/L (140 mg/dL) and less than 11.1 mmol/L [13]. The American Diabetes Association (ADA) has recommended decreasing the FPG threshold from 6.1 to 5.6 mmol/L (100 mg/dL) to define IFG, thereby replacing the OGTT with the new FPG criterion [16]. The current French diagnostic criteria that define prediabetic states (IFG, IGT) and diabetes are summarized below.

A recent proposal has been to use the HbA_{1c} as a diagnostic criterion for diabetes ($HbA_{1c} \geq 6.5\%$) and to identify subjects at risk of future diabetes, using a threshold of greater or equal to 6.0% [17], lowered to greater or equal to 5.7% by the ADA [16]. At present, the use of the HbA_{1c} as a diagnostic criterion for intermediate hyperglycaemia or diabetes is not recommended in France.

2.3. *Screening for undiagnosed glucose metabolism disorders*

2.3.1. *Which diagnostic test?*

European epidemiological studies show that the prevalence of abnormal glucose metabolism at the time of hospital discharge [6], and at 2 [18], 3 [6] and 12 months thereafter [19], is extremely high not only in ACS patients with known diabetes, but also in those with no known diabetes; indeed, about a third of these patients has diabetes and another third has intermediate hyperglycaemia. Also, these prevalences have been reported to be almost twice as high in patients with ACS as in their matched controls [20]. However, the OGTT is necessary for the appropriate classification of glucose tolerance in patients with ACS [5,21], as FPG measurement alone leads to the underdiagnosis of dysglycaemic states in two-thirds of ACS patients [6,15,20].

This is also true when 5.6 rather than 6.1 mmol/L is used as the FPG threshold [22]. In fact, a European expert committee has recently recommended the OGTT for all patients following ACS [23].

In addition, there are few data on the use of HbA_{1c} as a diagnostic criterion for diabetes or intermediate hyperglycaemia after ACS. In theory, the HbA_{1c} is of interest as it reflects exposure to hyperglycaemia during the previous 2–3 months and, therefore, is not influenced by the stress caused by ACS. However, studies of series of patients without acute disease show that strategies using either OGTT or HbA_{1c} do not diagnose the same patients: there is increasing evidence of discrepancies between the two screening methods for the classification for dysglycaemia [24–26]. It has been reported that admission HbA_{1c} levels correlate with the presence of diabetes after ACS [6] and with an abnormal OGTT 3 months after ACS, with an adjusted odds ratio (OR) of 3.8 (1.8–7.8) for HbA_{1c} levels greater than 5.7% [27]. However, admission HbA_{1c} values in patients with or without diabetes 3 months thereafter largely overlap [6,27]. Nonetheless, following ACS, HbA_{1c} levels greater or equal to 6.5% have been shown to have a positive predictive value of 100% for a 2hPG value greater or equal to 11.1 mmol/L and could, therefore, be used instead of the OGTT to diagnose diabetes after ACS [15].

2.3.2. When to test?

The admission glucose level and an OGTT performed early after myocardial infarction (MI) do not provide reliable information on the long-term glucometabolic state [15,27]. When OGTT results at the time of hospital discharge in patients with ACS were compared with those 3 months later [28], among the patients with a normal OGTT, 48% had IGT and 4% had diabetes after 3 months. Of those with diabetes according to the OGTT at discharge, 53% still had diabetes, 32% had IGT and 15% had a normal OGTT 3 months thereafter. The results of OGTTs performed in ACS patients at hospital discharge also provide reliable information on the glucometabolic state at 12 months. For example, of 42 patients with diabetes at discharge, the OGTT was still abnormal in almost all cases 12 months after ACS: 12 patients had IGT and 27 still had diabetes [19].

Should the OGTT be reassessed later after ACS, when patients are in a stable condition? Wallander et al. [19] reported that a repeat OGTT at 12 months could further identify 42% of subjects with abnormalities.

2.3.3. Who to screen?

As the usual clinical and biological factors associated with abnormal glucose metabolism overlap considerably, they are not clinically relevant as a screening strategy [6,22,27,28]. Indeed, a model built from FPG, high-density lipoprotein (HDL) cholesterol, age and log-HbA_{1c} to classify patients into normal glucose tolerance, IGT and diabetes misclassified 44% of the patients, of whom 18% were overdiagnosed and 26% were underdiagnosed [22]. Furthermore, a low HbA_{1c} does not predict a normal OGTT [15].

Consensus statement (Screening for glucose metabolism disorders)

1. *Admission glucose* (Level A) as fasting plasma glucose (Level A) and HbA_{1c} (professional agreement) on the first day after ACS should be measured in all patients.
2. *Admission glucose* diagnoses stress hyperglycaemia and leads to the initiation of early insulin treatment if admission glucose is greater or equal to 180 mg/dL (10.0 mmol/L; Level A). However, the admission glucose level cannot predict glucose metabolism disorders in stable conditions after ACS (Level B).
3. *Fasting plasma glucose* should be used to manage treatment (Level A).
4. Subjects with HbA_{1c} greater or equal to 6.5% may be considered diabetic (professional agreement).
5. In patients with no known diabetes and HbA_{1c} less than 6.5%, glucose metabolism disorders after ACS should be assessed using the OGTT (Level A), as measuring only FPG leads to the underdiagnosis of dysglycaemic states in two-thirds of patients (Level A). The OGTT should be performed 7 to 28 days after ACS in stable conditions (Level B), often after discharge as the mean duration of hospitalization after ACS is less than 7 days. The diagnostic criteria are similar as those used in subjects with no cardiovascular history (Table 1).

3. Diabetes care in cardiology intensive care units

Poor glycaemic control in diabetic patients and stress hyperglycaemia in non-diabetic subjects are both associated with poorer outcomes after acute MI [9]. However, it is not yet clear whether strict glycaemic control during acute MI hospitalizations improves outcomes.

3.1. Does intensive antidiabetic treatment in a cardiology ICU provide any benefit?

Some studies have shown that intensive insulin treatment is beneficial. The Diabetes Mellitus Insulin–Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial, involving 620 diabetic patients with acute MI and glycaemia greater than 11 mmol/L (198 mg/dL), showed that an insulin–glucose infusion for 24 h, followed by subcutaneous insulin four times daily for greater or equal to 3 months, compared with standard treatment (insulin therapy only if clinically indicated) induced not only a significant reduction in HbA_{1c}, but also a significant drop in mortality at 1 year (19% *vs* 26%, respectively) and at 3.4 years (33% *vs* 44%, respectively) [29]. As the DIGAMI study

Table 1
Criteria for the diagnosis of disorders of glucose metabolism.

Fasting plasma glucose in mg/dL (mmol/L)	2 h after oral glucose load (75 g) in mg/dL (mmol/L)		
	< 140 (7.8)	140–199 (7.8–11.0)	≥ 200 (11.1)
< 110 (6.1)	Normal	IGT	Diabetes
110–125 (6.1–6.9)	IFG	IFG and IGT	Diabetes
≥ 126 (7.0)	Diabetes	Diabetes	Diabetes

IGT: impaired glucose tolerance; IFG: impaired fasting glucose; NB: the OGTT should be performed 7 to 28 days after ACS in stable conditions.

also included outpatient insulin therapy, the isolated effect of in-hospital glycaemic control could not be easily assessed. However, an observational study conducted in 50,205 patients hospitalized for ACS showed that insulin treatment was beneficial in patients with no history of diabetes, but an admission glycaemia greater or equal to 200 mg/dL (11.1 mmol/L) [30]. In that study, patients who were not treated with insulin had, after adjusting for confounding factors, significantly increased relative risks of death—specifically, 56% at 7 days and 51% at 30 days.

Nevertheless, the benefit of intensive insulin treatment has not been observed in other studies. In the DIGAMI-2 trial, patients with type 2 diabetes and acute MI were randomly assigned to receive one of three glucose-management strategies: group 1, inpatient insulin infusion/outpatient intensive subcutaneous insulin therapy; group 2, inpatient insulin infusion/outpatient standard treatment; and group 3, inpatient/outpatient standard glucose management [31]. Although it was anticipated that mortality rates would be lowest for group 1, in fact, the rates were similar across all three groups. However, the study had several problems, including similar glycaemic control in all three groups, low event rates and a lack of statistical power due to poor recruitment. In the Hyperglycemia: Intensive Insulin Infusion in Infarction (HI-5) study of 240 patients with acute MI and diabetes or admission glycaemia greater or equal to 140 mg/dL (7.8 mmol/L), mortality in hospital at 3 and 6 months did not differ between treatment with insulin/dextrose infusion for at least 24 h and conventional therapy [32]. However, the HI-5 study was seriously flawed by a too-small number of patients, lack of blinding, maintenance of glycaemic control for only 24 h, and failure to attain a significant difference in mean 24-h blood glucose between the intensive therapy and control groups [32]. Subset analyses found that in-hospital mortality rates (0% *vs* 7%), and at 3 and 6 months (2% *vs* 11%), were considerably lower in patients with mean blood glucose levels less or equal to 144 mg/dL (8.0 mmol/L) during the first 24 h.

A meta-analysis of 15 randomized trials (10,140 patients) comparing the effect of tight glucose control [glycaemic target less or equal to 150 mg/dL (8.3 mmol/L)] with less stringent glycaemic control in ICU patients showed that mortality in patients with tight glucose control was similar to that of patients with less stringent glycaemic control [26.7% *vs* 25.6%, respectively; not significant (NS)] [33].

3.2. Risk of hypoglycaemia

Intensive insulin treatment has been associated with an increased risk of hypoglycaemia in up to 19% of patients when defined as glycaemia less than 40 mg/dL (2.2 mmol/L), and in up to 32% of patients when defined as glycaemia less than 60 mg/dL (3.3 mmol/L) [34]. Hypoglycaemia can lead to seizures, brain damage, depression, cardiac arrhythmias and death [35]. The risk of hypoglycaemia was also evaluated in the large multicentre Normoglycemia in Intensive Care Evaluation–Survival using Glucose Algorithm Regulation (NICE–SUGAR) trial, which randomly assigned 6104 ICU patients to either intensive insulin treatment [glycaemic target of 81–108 mg/dL (4.5–6 mmol/L)] or conventional glucose control [glycaemic target of < 180 mg/dL (< 10 mmol/L)] [36]. Intensive insulin treatment compared with conventional glucose control led to significantly lower time-weighted glycaemia [115 *vs* 144 mg/dL (6.2 *vs* 7.9 mmol/L)], and significant increases in severe hypoglycaemia (6.8% *vs* 0.5%) and 90-day mortality (27.5% *vs* 24.9%, OR: 1.14, 95% CI: 1.02–1.28) [36]. The Efficacy of Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial, comparing intensive insulin treatment [glycaemic target of 80–110 mg/dL (4.4–6.1 mmol/L)] with conventional glucose control [glycaemic target of 180–200 mg/dL (10–11.1 mmol/L)] in ICU patients with severe sepsis, was stopped early because the intensive insulin treatment significantly increased rates of hypoglycaemia (12.1% *vs* 2.1%) and serious adverse events (10.9% *vs* 5.2%) [37]. The multicentre Glucontrol trial, involving 1101 critically ill patients, showed that intensive insulin treatment versus conventional treatment induced a higher rate of hypoglycaemia (8.7% *vs* 2.7%), and a non-significant trend towards higher 28-day mortality and in-hospital mortality [38]. A retrospective study of 7820 patients hospitalized for acute MI reported that hypoglycaemia was associated with increased mortality in patients not treated with insulin, but not in patients treated with insulin [39].

Thus, so far, the data in the literature show that, in populations of critically ill patients, intensive insulin treatment [glycaemic target of 80–110 mg/dL (4.4–6.1 mmol/L)] increases the incidence of severe hypoglycaemia and may increase mortality compared with the more permissive blood glucose ranges of 140–180 mg/dL (7.8–10 mmol/L).

3.3. Which insulin infusion protocol?

Intravenous infusion of insulin is usually recommended with a concomitant infusion of glucose. However, a wide variability in the insulin infusion protocols used in critical care has been reported, with differences in initial insulin dose, titration of insulin, use of insulin bolus, glycaemic targets and

methods for adjusting insulin protocols [40]. This reflects the lack of consensus in the delivery of intravenous insulin in critical care.

Consensus statement (Diabetes care in intensive care unit)

1. In cases of *unknown diabetes*, continuous insulin treatment has to be initiated when admission blood glucose level is greater or equal to 180 mg/dL (10.0 mmol/L; Level A).
2. In cases of *previously known diabetes*:
   - continuous insulin treatment has to be initiated when the admission blood glucose is greater or equal to 180 mg/dL (10.0 mmol/L) and/or preprandial glucose is greater or equal to 140 mg/dL (7.77 mmol/L) during follow-up in an intensive care unit (Level A);
   - all other antidiabetic treatments should be stopped during hospitalization in a cardiology intensive care unit (professional agreement);
   - if the patient had known diabetes treated with insulin and admission blood glucose less than 180 mg/dL (10.0 mmol/L) and/or preprandial glucose less than 140 mg/dL (7.7 mmol/L) during follow-up in an intensive care unit, the insulin regimen used prior to hospitalization can be continued (professional agreement).
3. A blood glucose target of 140 to 180 mg/dL (7.7 to 10 mmol/L) is recommended for most patients, rather than the more stringent target of 110 to 140 mg/dL (6.1 to 7.7 mmol/L; Level A).
4. A blood glucose target less than 110 mg/dL (6.1 mmol/L) is not recommended (Level A).
5. The recommended insulin treatment is continuous IV insulin infusion with a preprandial bolus (see proposed protocol below). Insulin dosage is to be adapted according to capillary glucose measurements (Level A).
6. In patients on continuous IV insulin infusion, blood (capillary) glucose is to be monitored 1 h after initiation, then every 2 h (Level A).
7. In hyperglycaemic/diabetic patients not on continuous IV insulin infusion, blood (capillary) glucose is to be monitored before each meal, 2 h after meals and at bedtime (professional agreement).
8. In cardiology intensive care units, the treatment of diabetes that requires insulin needs to be performed by an experienced team including a diabetologist (professional agreement).

A protocol for insulin administration in a cardiology intensive care unit and a protocol for transition from intravenous to subcutaneous insulin are given in the Addendum.

4. Diabetes care during hospitalization in a post-intensive care unit

Following the period in the ICU, insulin treatment is not mandatory for every patient with diabetes, and other antidiabetic treatments may be considered. The choice of optimal treatment, however, depends on the metabolic profile of the patient. In cases of uncontrolled diabetes ($HbA_{1c} \geq 8\%$), referral to a diabetologist is recommended.

4.1. Metformin

In the United Kingdom Prospective Diabetes Study (UKPDS), monotherapy with metformin in diabetic patients with a body mass index (BMI) greater or equal to 25 kg/m^2 was associated with significant decreases in overall mortality (−36%) and MI (−39%), and a non-significant decrease in stroke (−41%), compared with treatment with sulphonylurea or insulin [41]. However, the participants in the UKPDS were newly diagnosed type 2 diabetes patients mostly in primary prevention. Little data on metformin after MI are available, whereas many case–control studies have shown reductions in cardiovascular morbidity and mortality with metformin (*vs* sulphonylurea) [42]. One meta-analysis showed that metformin treatment was associated with a significant decrease in cardiovascular mortality (OR: 0.74; 95% CI: 0.62–0.89) compared with other antidiabetic treatments [43]. In the 19,699 patients with type 2 diabetes and a history of cardiovascular disease in the Reduction of Atherothrombosis for Continued Health (REACH) registry, a significant reduction in 2-year mortality was observed with metformin (adjusted HR: 0.76; $P < 0.001$) [44]. This benefit was also observed in patients with renal failure or a history of congestive heart failure, usually considered contraindications for metformin [44]. In the DIGAMI-2 study, metformin was associated with a significant 37% reduction in non-fatal cardiovascular events at 2 years ($P = 0.03$) [45], and significant decreases in all-cause mortality ($P = 0.01$) and cancer mortality ($P = 0.02$) at 4 years [46]. Although no prospective studies with metformin have been performed in patients with type 2 diabetes after ACS, data from case–control studies and the DIGAMI-2 trial suggest that the use of metformin in such situations may be recommended. In a Danish study of 10,920 patients hospitalized for heart failure, treatment with metformin was associated with a low risk of mortality compared with treatment with sulphonylurea or insulin [47]. However, its use is not recommended in cases of uncontrolled cardiac or renal failure.

4.2. Sulphonylureas

Results from the University Group Diabetes Program (UGDP) trial showed a potential increase in cardiovascular risk in patients treated with first-generation sulphonylureas [48]. Controversial experimental studies have suggested that,

as sulphonylurea binds to K+ channels, it could impair myocardial preconditioning, a natural cardioprotective mechanism. In experimental models of ischaemia, coronary artery vasodilation was impaired in animals given sulphonylurea treatment [49].

However, several observational studies failed to establish an association between sulphonylurea treatment and the occurrence of ACS, although a recent observational study suggested a greater incidence of cardiovascular death and congestive heart failure in patients taking sulphonylurea compared with those taking metformin [50]. In the UKPDS and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial, no increase in cardiovascular risk was found when treatment was intensified by sulphonylurea [51,52] and, in an earlier study, no association was reported between the size of MI and previous treatment with glibenclamide [53]. On the other hand, observational studies in patients who had undergone coronary angioplasty after MI have shown an increase in cardiovascular mortality in those using sulphonylurea that was attributed to deterioration of preconditioning [54]. One case–control study reported a 30% increase in cardiovascular death following MI in patients treated with first-generation sulphonylureas and with glibenclamide [55], although several recent pharmacoepidemiological studies failed to find any increase in cardiovascular risk with second-generation sulphonylureas after ACS [56–58]. Nevertheless, in the Danish registry, cardiovascular risk was higher in patients treated with sulphonylureas, with the exception of gliclazide, than with metformin [59]. Data from the sulphamide-treated patients in the French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) have shown that in-hospital mortality was significantly lower in patients receiving pancreatic cell-specific sulphonylurea (gliclazide or glimepiride; 2.7%) compared with glibenclamide (7.5%; $P = 0.019$), indicating potential differences among the various sulphonylurea drugs [57].

4.3. Glinides

Only limited and/or indirect data are available on glinides and cardiovascular risk. In the Danish registry, no firm conclusions could be drawn due to a lack of statistical power, although there was a trend towards greater cardiovascular risk with glinides than with metformin [OR: 1.29 (0.86–1.94)] [59]. In the Nateglinide and Valsartan Impaired Glucose Tolerance Outcomes Research (NAVIGATOR), no increases in cardiovascular morbidity and/or cardiovascular mortality were found with nateglinide compared with a placebo [60].

4.4. Acarbose

In experimental models of ischaemia reperfusion, a decrease in the size of necrotic lesions was reported with acarbose [61], and type 2 diabetes patients treated with acarbose showed greater improvements in endothelial function in the postprandial phase than those treated with nateglinide [62]. A lower risk of cardiovascular events was also observed in glucose-intolerant patients treated with acarbose *vs* placebo in the STOP-NIDDM trial [63]. In addition, treatment with acarbose was associated with a lower risk of MI in a meta-analysis of seven clinical trials involving patients with type 2 diabetes (HR: 0.36, 95% CI: 0.16–0.80; $P = 0.012$) [64].

4.5. Pioglitazone

Pioglitazone is a peroxisome proliferator-activated receptor-gamma (PPAR-γ) agonist receptor that improves insulin sensitivity and glucose control, decreases plasma triglycerides and increases HDL cholesterol. Several studies have shown a reduction in inflammatory markers, such as C-reactive protein (CRP), and improvement in endothelial dysfunction in patients taking pioglitazone. In the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) of patients with type 2 diabetes and cardiovascular disease, pioglitazone (*vs* placebo) induced a non-significant reduction in the primary endpoint, including leg amputation and leg revascularization, but also led to a significant reduction in major cardiovascular events (−16%) [65] and a significant 28% reduction in recurrent MI in patients with a history of MI [66]. A meta-analysis confirmed the benefits of pioglitazone for ischaemic cardiovascular events, but also showed an increase in heart failure [67]. Another meta-analysis of controlled studies of diabetic patients with heart failure showed that the glitazones were associated with an increased risk of hospital admission for heart failure, but also with reduced all-cause mortality [68]. In the PROactive, the incidence of heart failure was increased with pioglitazone *vs* placebo (7.5% *vs* 5.2%, respectively), but with no increase in heart-failure-induced mortality (1.4% *vs* 0.9%, respectively) [65].

All the available data confirm the global cardiovascular benefit of pioglitazone in patients with type 2 diabetes and a history of MI, with a significant reduction in the risk of a recurrent event. One complementary analysis suggested that the cardiovascular benefit of pioglitazone in the PROactive may have partly been due to the increase in plasma HDL cholesterol [69]. However, the use of pioglitazone in France has recently been suspended due to concerns over bladder-cancer risks, although pioglitazone is still available in most countries worldwide, and has the approval of European (European Medicines Agency, EMEA) and American (Food and Drug Administration, FDA) drugs agencies.

4.6. Glucagon-like peptide (GLP)-1 agonists

GLP-1 agonists reduce hyperglycaemia by enhancing glucose-induced insulin secretion and inhibiting glucagon production. Experimental and clinical studies have suggested that GLP-1 can protect the heart against ischaemia/reperfusion injury, and improve left-ventricle contractility and endothelial function [70–72].

A recent analysis of data from health-insurance agencies suggests, after adjusting for potential confounding factors, cardiovascular benefit with exenatide [adjusted HR: 0.81 (0.68–0.95); $P = 0.01$] [73], although patients with a recent cardiovascular event were excluded from the study. In a meta-analysis of 12 controlled randomized studies with exenatide,

including diabetes patients with a history of cardiovascular disease, a non-significant decrease in the prespecified endpoint [cardiovascular death, MI, ischaemic stroke, revascularization; OR: 0.70 (0.38–1.31); $P > 0.05$] was observed [74]. Analysis of the pooled data from clinical trials with liraglutide showed no significant effect of liraglutide on cardiovascular events [75]. A study comparing exenatide (10 μg BID) with liraglutide (1.8 mg once daily) showed greater reductions with liraglutide in HbA_{1c} (−1.12% *vs* −0.79%; $P < 0.0001$) and in triglycerides, although no differences between the two drugs were noted in body weight, blood pressure, low-density lipoprotein (LDL) or HDL cholesterol, or incidence of cardiovascular events [76]. When data from clinical trials of both exenatide and liraglutide were combined, a significant reduction in the risk of major cardiovascular events was observed versus placebo [OR: 0.46 (0.26–0.83); $P = 0.009$], but not versus active antidiabetic treatment [77].

4.7. Dipeptidyl peptidase (DPP)-4 inhibitors

DPP-4 inhibitors reduce GLP-1 enzymatic degradation, thus leading to moderate increases in its plasma concentration. Pooled analysis of the data from 19 clinical trials with sitagliptin *vs* a placebo or other active antidiabetic treatments showed non-significant differences in the incidence of major cardiovascular events [78]. In an analysis of the pooled data from 25 clinical trials with vildagliptin, the relative risk of major cardiovascular events (cardiovascular death, MI, stroke) compared with controls (a placebo or active antidiabetic treatment) was 0.88 (0.37–2.11), and 0.78 (0.51–1.19) in the subgroup of patients in secondary prevention [79]. In an analysis of pooled data from trials of saxagliptin, but with a limited number of patients, saxagliptin was shown to be associated with a lower risk of cardiovascular events [OR: 0.43 (0.23–0.80)] [80]. A meta-analysis showed a non-significant decrease of the risk of cardiovascular events and all-cause death with DPP inhibitors [81].

Consensus statement (Diabetes care in a post intensive care unit)

1. Metformin is not contraindicated after ACS in the absence of renal failure (professional agreement).
2. Following ACS, due to the increase in cardiovascular risk reported in observational studies, it is recommended to not use a first-generation sulphonylurea or glibenclamide (Level C).
3. Glinides are not contraindicated following ACS (professional agreement).
4. Acarbose may be used following ACS when needed, according to the metabolic phenotype of the patient (predominant postprandial hyperglycaemia) (professional agreement).
5. Pioglitazone, when available, is not contraindicated following ACS. It must not be used in cases of congestive heart failure or when LVEF is less than 45% (professional agreement).
6. GLP-1 agonists are not contraindicated following ACS (professional agreement).
7. DPP-4 inhibitors are not contraindicated following ACS (professional agreement).

5. Diabetes care during cardiac rehabilitation

A comprehensive cardiac rehabilitation programme should include supervised physical activity after cardiac assessment, education on all cardiovascular risk factors (including diabetes), promotion of physical activity as a therapeutic intervention, psychological support, nutritional counselling and planning of long-term regular physical activity following cardiac rehabilitation. Cardiac rehabilitation decreases all-cause and cardiovascular morbidity and mortality in patients after ACS [82]. Peak exercise capacity, measured in metabolic equivalents (MET), is known to be an important prognostic factor. Each 1-MET increase in exercise capacity conferred a 12% improvement in survival in several subgroups, including type 2 diabetes patients [83]. However, it has also been shown that hyperglycaemia during cardiac rehabilitation is associated with a smaller improvement in exercise capacity [84].

Nevertheless, cardiac rehabilitation also improves psychological well-being [85], patients' adherence to pharmacological advice and lifestyle modifications, and patients' motivation for future long-term physical activity. In addition, it is a cost-effective intervention after an acute coronary event [86].

Many studies have shown the benefit of physical activity for glycaemic control, for reductions in weight and visceral adipose tissue, and for insulin sensitivity [87]. Also, regular physical activity in patients with IGT can prevent or delay the onset of type 2 diabetes [88,89].

Cardiac rehabilitation reduces depression in diabetic patients and increases patients' motivation for lifestyle modifications [85]. It should be started soon after clinical stabilization and the patient's assessment by a submaximum exercise stress test. The exercise component of the programme, prescribed by a cardiologist, is a combination of endurance and light resistance training sessions associated with, for example, flexibility training, chest physiotherapy and hydrotherapy. It should be individualized for each patient.

During cardiac rehabilitation, blood glucose levels need to be controlled regularly because of the effect of physical activity on glucose metabolism. It has been shown that blood glucose reduction correlates with the duration of the aerobic physical-training session and lasts up to 30 h following exercise [90,91]. Self-monitoring of blood glucose (SMBG) provides a potential

tool for controlling blood glucose, and preventing significant hypoglycaemia during and after physical activity, particularly in patients treated with insulin and/or insulin-secreting agents [92]. Furthermore, SMBG can be helpful for adjusting antidiabetic treatments, if necessary, and for educational purposes [93].

Indeed, cardiac rehabilitation represents a unique opportunity to refer a patient for education covering not only the usual information on diabetes, but also the benefits of physical activity to diabetes and the management of diabetes during physical activity (with the help of SMBG). Such education reinforces patients' empowerment [94]. Patients with and without diabetes should also be given nutritional counselling to prevent cardiovascular disease. In patients with diabetes, additional information should be given on weight reduction, and the prevention and treatment of hypoglycaemic episodes [95]. Cardiac rehabilitation provides an opportunity to optimize the treatment of diabetes, and referral to a diabetologist/diabetology team can also be useful (see below) [96].

So far, no data are available for cardiac rehabilitation in patients with diabetic complications (peripheral neuropathy, retinopathy and nephropathy).

Consensus statement (During cardiac rehabilitation)

1. Cardiac rehabilitation decreases total and cardiovascular morbidity and mortality in patients after ACS (Level A). Although no outcome trials specifically for the diabetic population are available, we may expect that cardiac rehabilitation is likely to induce similar benefits in patients with diabetes.
2. Cardiac rehabilitation is an opportunity to show patients the benefits of regular physical activity not only for cardiovascular prevention, but also for improving glycaemic control and preventing diabetes (Level A).
3. Blood glucose should be checked before exercise in every patient with diabetes. In addition, blood glucose testing should also be performed at the end, and 4–6 h after, each physical-activity session in patients treated with insulin or insulin secretagogues (sulphonylureas or glinides) to reduce the risk of hypoglycaemic episodes (professional agreement).
4. When blood glucose before exercise is greater than 250 mg/dL (13.9 mmol/L), ketonuria needs to be checked. If the patient is without ketosis, feeling well and properly hydrated, then physical activity can be performed with caution, with regular capillary blood testing recommended at least hourly during the training session (professional agreement).
5. During cardiac rehabilitation, the patient should be referred to a diabetologist/diabetology team in the following cases: uncontrolled diabetes with significant hyperglycaemia ($HbA_{1c} > 8\%$); and/or severe/repeated hypoglycaemia (professional agreement).

6. Nutrition/Diet

Nutrition plays an important role in the treatment of diabetes. It is important for optimal glycaemic control, and also plays an important role in the primary and secondary prevention of cardiovascular disease [97]. Nutritional treatment needs to be discussed with the diabetic patient, with cultural and ethnical specificities taken into account. The dietary programme should be adapted to each patient. It has also been confirmed that nutritional education provided by care providers who are familiar with diabetes and nutritional cardiovascular prevention, and trained in patients' education, leads to beneficial results in the control of glycaemia and cardiovascular risk factors [98–100].

A balance between ingested carbohydrates and insulin (endogenous or therapeutically administered) is critical for postprandial blood glucose control. Thus, the proportion of carbohydrates in the diet is crucial for glycaemic control in patients with diabetes, and the quantity of carbohydrate in a meal is the major determinant of postprandial glycaemia [101,102]. In patients with diabetes treated with diet only and/or oral antidiabetic agents and/or fixed insulin doses, it is usually recommended to have, for each meal (breakfast, lunch, dinner), a reproducible carbohydrate ratio from day to day. In patients treated with rapid insulin before each meal, the quantity of carbohydrate in the meal can be modified, but the dose of insulin for the meal should then be adjusted accordingly. To do this, the patient needs to be educated by a trained diabetology team.

For the prevention of coronary artery disease, it is recommended to reduce saturated fats, trans fatty acids and sodium, and to adopt a Mediterranean-style diet (rich in monounsaturated fats, omega-3 fatty acids, fruits and vegetables). All these nutritional recommendations have been shown to reduce cardiovascular risk factors (mostly lipids and high blood pressure) in patients with diabetes [103–105].

In patients with type 2 diabetes, hypertriglyceridaemia is frequently seen. In situations of frank hypertriglyceridaemia (> 400 mg/dL), fructose (which promotes hepatic triglyceride production) should be restricted and the consumption of fruits limited. After ACS, consultation with a dietitian is mandatory in patients with overt hypertriglyceridaemia. As a matter of fact, consultation with a dietitian may be of value for all patients with diabetes after ACS to obtain dietary recommendations specifically for diabetes, prevention of atherosclerosis and, if necessary, weight reduction. The nutritional recommendations presented

here are limited to the ACS period, and do not embrace all of the dietary recommendations for patients with diabetes.

Consensus statement (Nutrition/Diet)

During hospitalization:

1. There is no specific recommended carbohydrate level for patients with diabetes. The proportion of carbohydrate in the diet does not need to be different from that for non-diabetics. A minimum carbohydrate amount of 150 g/day is recommended (Level A).
2. In the absence of a diabetology team working in the cardiology ICU, it is recommended to use a fixed carbohydrate dose for each meal (professional agreement).
3. Patients with diabetes are recommended to have three meals a day (in the absence of a concomitant procedure; Level A).
4. Unnecessary fasting should be avoided (professional agreement).
5. Low glycaemic-index (GI) foods should be preferred over high GI foods (Level B).
6. In general, sucrose should be avoided (professional agreement).
7. Sucrose is not recommended between meals with the exception of hypoglycaemia (professional agreement).
8. For patients who wish to have sucrose, it should be included in a meal and replace an equivalent dose of carbohydrate (Level A).

At discharge, specific recommendations for coronary artery disease prevention:

1. Saturated fat should be limited to less than 10% of total energy intake and, if possible, be less than 7% (Level A).
2. Trans fatty acids should be avoided (Level A).
3. A Mediterranean-style diet rich in fruits, vegetables and monounsaturated fatty acids is recommended (Level A).
4. In cases of overt hypertriglyceridaemia, the patient should be referred to a dietitian (professional agreement).
5. Consultation with a dietitian is recommended in diabetes patients after ACS.

7. When should a patient with diabetes be referred to a diabetologist?

Several consensus statements have emphasized the benefits of referring a patient to a diabetologist during hospitalization for conditions other than diabetes [106–108]. Referral to a diabetologist during hospitalization for ACS is likely to confer substantial benefits to patients with diabetes. Hospitalization for ACS provides a unique opportunity to optimize the treatment of diabetes and to educate patients in diabetes self-management [109].

It is advisable, before discharge from hospital, to set up a strategy for optimal outpatient glucose control in patients with established diabetes or newly diagnosed diabetes. It is generally advisable to refer a patient with diabetes to a diabetologist before discharge or within 1 month of discharge [108].

The importance of patients' education is emphasized in the ADA and American Association of Clinical Endocrinologists (AACE) consensus statement [107]. Because the length of hospital stay for ACS is usually short, during hospitalization, it is recommended to limit diabetes-related education to an inventory of basic 'survival skills' (level of understanding related to the diagnosis of diabetes, SMBG and explanation of home glycaemic goals; definition, recognition, treatment and prevention of hyperglycaemia and hypoglycaemia; information on diet; when and how to take glucose-lowering medications, including the administration of insulin; sick-day management; and identification of a healthcare provider responsible for diabetes care after discharge). Several studies have shown that medication errors and adverse drug events are linked to poor communication of instructions to the patient at the time of discharge [110,111]. Thus, clear instructions at discharge and during outpatient care are necessary to provide a reference for patients and their outpatient providers. It has also been shown that an insulin-specific discharge instruction form can provide greater clarity and more consistent instructions for insulin dosing and SMBG in comparison to a generic hospital discharge form [112]. Several studies have shown that an educational programme on diabetes during hospitalization leads to better outcomes, such as improved glycaemic control [113,114], fewer hospitalizations [113,114], fewer episodes of ketoacidosis [114] and reduced length of hospital stays [115]. Moreover, in patients hospitalized in medical and surgical cardiac care units, an interventional programme on diabetes, including clear self-care instructions before discharge, significantly decreased the frequency of prolonged and severe hyperglycaemia, and the frequency of nosocomial infections [116]. Thus, a clear educational programme covering the basic points of diabetes is highly recommended before discharge, whether performed by a diabetologist and/or a diabetes educator.

In fact, diabetes care delivered by an endocrinologist/diabetologist during hospitalization has been shown to result in better outcomes, such as improved glycaemic control [117], fewer readmissions for diabetes [117,118], reduced length of hospital stays [118] and reduced costs [118]. In diabetic patients hospitalized for conditions other than diabetes, referral to an endocrinologist/diabetologist has been shown to significantly reduce the mean hospital length of stay from 8.2 to 5.5 days [119].

Consensus statement (Referral to a diabetologist)

1. In the *cardiology ICU*, the treatment of diabetes or stress hyperglycaemia that requires insulin needs to be delivered by an experienced team that includes a diabetologist (professional agreement).
2. *Referral to a diabetologist before hospital discharge*: the patient should be referred to a diabetologist ***before discharge*** from hospital in the following situation:
   - unknown diabetes, diagnosed during ACS hospitalization ($HbA_{1c} \geq 6.5\%$);
   - and/or known diabetes with admission HbA_{1c} greater or equal to 8%;
   - and/or newly introduced insulin therapy;
   - and/or severe/repeated hypoglycaemia (Level B).

   If a diabetologist is not available, the cardiologist should contact a diabetology department to organize hospitalization following hospitalization in the cardiology department (professional agreement).
3. *Referral to a diabetologist **after** hospital discharge*:
   - In patients without diabetes at discharge (no known diabetes at admission and admission $HbA_{1c} < 6.5\%$), it is recommended to perform an OGTT between days 7 and 28. If diabetes is diagnosed by the OGTT, the patient should be referred to a diabetologist for education, initiation of antidiabetic therapy and planning of the future follow-up of the patient in coordination with the primary-care physician (professional agreement).
   - Follow-up of the patient with diabetes should be coordinated with the primary-care physician (professional agreement).
   - After discharge, the patients with diabetes may be referred to centres specializing in diabetes education if available (professional agreement).
4. *Referral to a diabetologist during **cardiac rehabilitation**:* the patient should be referred to a diabetologist in the following situation:
   - uncontrolled diabetes with significant hyperglycaemia
   - and/or severe/repeated hypoglycaemia (professional agreement).

Disclosure of interest

Authors declare, during the three previous years, occasional involvements: advisory services and/or clinical trials as investigator and/or medical formation, and/or invitation at congress with the following companies: Abbott (BC, EC, PV), AstraZeneca/BMS (AML, BC, BV, EC, FB, PV), Bayer (BV, EC, PV), Boehringer Ingelheim (BV, PV), GSK (EC, PM, PV), Lifescan (BC, RR), Lilly (BC, BV, EC, PM, PV, RR), Medtronic (AML, RR), Menarini (RR), Merck-Sereno (BC, EC, PV), MSD (BC, BV, EC, PM, PV, RR), Novartis (BV, EC, PV), Novo-Nordisk (BV, EC, FB, PM, PV, RR), Roche (AML, RR), Sanofi (BC, BV, EC, FB, RR), Servier (BV, EC, RR), Takeda (EC, FB).

Addendum.

Proposed insulin protocol for cardiology intensive care unit:

- Use rapid-acting insulin analogs (50 units diluted in 50 ml Glucose 5%).
- A parallel infusion of Glucose 5% is also set up.
- A total amount of 150 g of carbohydrates a day has to be given (including both Glucose 5% infusion and oral food).

Initial dose: the initial dose of insulin depends on the admission blood glucose (BG).

Admission BG	Insulin dose
180–300 mg/dL (10–16.6 mmol/L)	2 U/h
300–400 mg/dL (16.6–22.2 mmol/L)	3 U/h
> 400 mg/dL (22.2 mmol/L)	4 U/h

Then, insulin dosage will be adapted to BG level (monitored 1 hr after initiation, then every 2 hours).

BG level	Insulin dose
< 80 mg/dL (4.4 mmol/L)	Stop insulin
80–140 mg/dL (4.4–7.8 mmol/L)	↘ by 0.5 U/h
140–180 mg/dL (7.8–10 mmol/L)	→ unchanged
180–300 mg/dL (10–16.6 mmol/L)	↗ by 1 U/h
> 300 mg/dL (16.6 mmol/L)	↗ by 1.5 U/h

In patients older than 75 years old, insulin dosage could be adapted to BG as follows.

BG level	Insulin dose
< 80 mg/dL (4.4 mmol/L)	Stop insulin
80–140 mg/dL (4.4–7.8 mmol/L)	Stop insulin
140–180 mg/dL (7.8–10 mmol/L)	→ unchanged
180–300 mg/dL (10–16.6 mmol/L)	↗ by 0.5 U/h
> 300 mg/dL (16.6 mmol/L)	↗ by 1 U/h

- If the patient eats, a bolus of insulin will be given with an initial bolus dose of 4 units. Thereafter, the bolus dose will be adapted according to the postprandial BG levels.

- In cases of mild hypoglycaemia (BG < 80 mg/dL [4.4 mmol/L]), insulin infusion is stopped and 15 g oral sugar is given to the patient. BG testing is performed every 30 minutes and insulin infusion is re-started when BG > 140 mg/dL (7.8 mmol/L) with half of the previous insulin infusion rate.
- In cases of severe hypoglycaemia (BG < 40 mg/dL [2.2 mmol/L]), Glucose 30% is injected into the patient.

Proposed protocol for transition from intravenous to subcutaneous insulin [120]:

1. Calculate the average insulin intravenous infusion rate in the last 12 hours to obtain the mean hourly rate and multiply by 24 to get the total daily insulin requirement.
2. Halve this 24-h insulin dose to obtain the long-acting insulin analog dose and total daily rapid-acting insulin analog dose.
3. Give the long-acting insulin analog subcutaneous monodose 2 hours before the first meal and the discontinuation of intravenous glucose infusion.
4. Split the total daily rapid-acting insulin analog dose into 20% at breakfast, 40% at lunch and 40% at dinner, according to a similar distribution of carbohydrates in the typical Mediterranean diet.

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