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

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Introduction

Type 2 diabetes is a major risk for cardiovascular morbidity and mortality (1,2). The increased risk for coronary artery disease is already present at mildly elevated levels of blood glucose still below the threshold for diabetes (3-5). The prevalence of diabetes or abnormal glucose metabolism is very high in patients presenting with an acute coronary syndrome (ACS). Indeed, among patients hospitalized for an ACS, 30% to 40% have diabetes, 25% to 36% show impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) and only 30% to 40% have normal glucose tolerance (6-9). In addition, the prognosis after an ACS is impaired in diabetic patients (9). Thus diabetes care during and in the immediate follow-up of an ACS is an important issue. So far, recommendations on diabetes treatment during an ACS are limited. There is clearly a lack of specific guidelines with regard to glucose management in ACS patients. There is no consensus statement on the use of non-insulin treatments during and in the immediate follow-up of an ACS. Furthermore, cardiologists have no clear recommendations on when to refer a patient to a diabetologist/diabetology team during and following an ACS. In addition, in patients presenting with an ACS, without previously known diabetes but with hyperglycaemia, there is a need for a clear diagnostic pathway for the diagnosis and the management of abnormal glucose metabolism (IFG/IGT) and diabetes.

For these reasons the Diabetes and Cardiovascular Disease study group of the SFD (Société Francophone du Diabète), in collaboration with the SFC (Société Française de Cardiologie), has decided to set up a consensus statement on the "Care of the hyperglycaemic /diabetic patient during and in the immediate follow-up of an acute coronary syndrome". The aim was to write a consensus statement with regard to the hyperglycaemic/diabetic patient at different times of an ACS (the Intensive Care Unit [ICU] period, the post-ICU period and the short-term follow-up after discharge including cardiac rehabilitation), embracing all of the different diagnostic and therapeutic issues and optimizing the collaboration between

cardiologists and diabetologists. We have used for this consensus, the recommendation grades according to the French HAS; 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-run non randomized comparative studies or cohort studies) and level C: low level of proof (based on case-control studies) (10).

I) Screening for glucose metabolism disorders in patients with an acute coronary syndrome

Stress hyperglycaemia

Patients with known diabetes have a greater risk of ACS than their non-diabetic counterparts. Epidemiologic data show that the prevalence of known diabetes in patients referred for ACS is 30% or more. Known diabetes is also associated with a poor prognosis of ACS (11-13). Stress can also facilitate the development of abnormal glucose metabolism. Therefore, stress hyperglycaemia is common in patients with ACS and is a powerful predictor of in-hospital survival (14). It is also associated with an increased risk of in-hospital complications in patients both with and without established diabetes mellitus (15). Thus, elevated blood glucose can be considered as a marker of in-hospital complication. It has also been suggested that tight control of glucose values during the acute phase could improve survival, which justifies the routine measurement of glucose levels at admission. However, the admission level of glucose is not recognized as a diagnostic criterion for intermediate hyperglycaemia or diabetes (16,17). Furthermore, it cannot predict the classification of glucose tolerance after the ACS (18). Admission glucose levels should therefore not be used to classify glucose tolerance, but rather to initiate early insulin treatment. The glucose metabolism status in patients with ACS should therefore be based on classical diagnostic criteria.

Definition and classification of intermediate hyperglycaemia and diabetes:

The criteria currently used in France (17) are those established by the World Health Organization and based on the level of fasting plasma glucose (FPG) and/or the glucose level 2 hours (2hPG) after an oral 75g glucose load (16). The oral glucose tolerance test (OGTT) should be performed in the morning, after a 12-hour fast (FPG) and includes PG measurements before and 120 minutes (2hPG) after a 75g glucose load given in 200 ml of water ingested within 5 minutes. If possible, patients should be given 250 g of jam in the afternoon before the OGTT to compensate for any previous restriction of carbohydrate (19,20). The OGTT may be performed outside hospital. Diabetes is defined as FPG $\geq$7.0 mmol/L (126 mg/dl) or 2hPG $\geq$11.1 mmol/L (200 mg/dL). IFG is defined as FPG $\geq$6.1 mmol/L (110 mg/dL) and <7 mmol/L and IGT is defined as 2hPG $\geq$7.8 mmol/L (140 mg/dL) and <11.1 mmol/L (16). The American Diabetes Association has recommended decreasing the FPG threshold from 6.1 to 5.6 mmol/L (100 mg/dL) to define IFG and therefore to replace the OGTT with the new FPG criterion (21). The current French diagnostic criteria that define prediabetic states (IFG and/or IGT) and diabetes are summarized in Table 1.

An international Expert Committee has recently proposed to use HbA1c as a diagnostic criterion for diabetes (HbA1c $\geq$ 6.5%) and to identify subjects with a risk for future diabetes using a threshold $\geq$ 6.0% (22), which was lowered to 5.7% by the experts of the American Diabetes Association (21). To date, the use of HbA1c as a diagnostic criterion for intermediate hyperglycaemia or diabetes is not recommended in France.

Screening for undiagnosed glucose metabolism disorders

Which diagnostic test?

European epidemiological studies show that the prevalence of abnormal glucose metabolism at discharge (6), two (23), three (6) and twelve months thereafter (24) is very high not only in ACS patients with known diabetes, but also in those without known diabetes: about 1/3 have diabetes and another 1/3 intermediate hyperglycaemia. This prevalence was

reported to be almost twice as high in patients with ACS as in matched controls (25), and very high in series of patients referred for coronary angiography (26) or for an elective consultation in cardiology (23). The OGTT is needed for the appropriate classification of glucose tolerance in patients with ACS (5,27). Very consistently, performing the FPG test alone leads to the underdiagnosis of dysglycaemic states in 2/3 of patients with ACS (6,18, 25). This is also true when 5.6 rather than 6.1 mmol/l is used as the FPG threshold to define impaired fasting glucose (28). OGTT has recently been recommended by a European expert committee in all patients after an ACS (20).

There are few data about the use of HbA1c as a diagnostic criterion for diabetes or intermediate hyperglycaemia after an ACS. In theory, HbA1c is very interesting as it reflects exposure to hyperglycaemia during the previous 2-3 months and therefore the result is not influenced by the stress due to the ACS. However, studies on series of patients without acute disease show that strategies using OGTT or HbA1c do not diagnose the same patients: there is increasing evidence of discrepancies between the two screening methods for the classification for dysglycaemia (29-32). It has been reported that admission HbA1c correlates with the presence of diabetes after the ACS (6) and with an abnormal OGTT three months after the ACS, with an adjusted odds ratio of 3.8 [1.8-7.8] for an HbA1c > 5.7% (33). However, admission HbA1c values in patients with or without diabetes three months thereafter largely overlap (6,33). For example, admission HbA1c was 4.9±0.5% in patients without and 5.2±0.7% in patients with diabetes three months later (6).

Nonetheless, after an ACS, HbA1c ≥ 6.5% has been shown to have a positive predictive value of 100% to predict a 2hPG value ≥ 11.1 mmol/l and might therefore be used instead of the OGTT to diagnose diabetes after an ACS (18).

When to test?

The admission glucose level does not appear to be a predictor of the long-term glucometabolic state (18). Furthermore, an OGTT performed very early after a myocardial

infarction with ST-elevation does not provide reliable information on the long-term glucometabolic state (33). OGTT results at hospital discharge in patients with ACS were compared with those three months thereafter (34). Of those with a normal OGTT at discharge, 48% had IGT and 4% diabetes 3 months thereafter. Among those with diabetes, according to OGTT, at discharge, 53% still had diabetes, 32% had IGT and 15% had normal OGTT 3 months thereafter. The result of an OGTT performed in ACS patients at hospital discharge also provides reliable information on the glucometabolic state at 12 months. For example, among 42 patients with diabetes at discharge, the OGTT was still abnormal, in almost all cases, 12 months after the ACS: 12 patients had IGT and 27 still had diabetes (24).

Should the OGTT be reassessed later after the ACS when patients are in a stable condition? Wallander *et al.* reported the results of the OGTT 3 and 12 months after an ACS. The 38 subjects with a normal OGTT 3 months after the ACS had the following OGTT results 9 months thereafter: 22 normal, 12 IGT and 4 type 2 diabetes (24). Thus a repeat OGTT could identify 42% of subjects with abnormalities.

Who to screen?

The very high prevalence of abnormal glucose metabolism after an ACS may justify a very systematic diagnostic approach. However, there are some predictive factors, such as age (28,33), female gender (33), metabolic syndrome (34), high body mass index (6), hypertension (34), insulin resistance (34), low HDL cholesterol level (28), FPG (6,28,33) and HbA1c (6,28,33). But, the values of these parameters greatly overlap and they are therefore not clinically relevant in a screening strategy.

A model to classify patients into normal glucose tolerance, IGT and diabetes was built from FPG, HDL-cholesterol, age and log-HbA1c (28). This model misclassified 44% of the patients, of whom 18% were overdiagnosed and 26% were underdiagnosed. Furthermore, low HbA1c cannot predict a normal OGTT. For example, an HbA1c < 5.0% has a negative predictive value of around 50% for an abnormal 2hPG 3 months after an ACS (18).

Consensus statement

1- *Admission glucose* (Level A) as *fasting plasma glucose* (Level A) and *HbA1c* (professional agreement) on the first day after the ACS should be measured in all patients.

2- *Admission glucose* diagnoses stress hyperglycaemia and leads to initiate early insulin treatment if admission glucose ≥ 180 mg/dL (10.0 mmol/L) (Level A). However, the admission glucose level cannot predict glucose metabolism disorders in stable conditions after the ACS (Level B).

3- *Fasting plasma glucose* should be used to manage treatment (Level A).

4- Subjects with HbA1c ≥ 6.5% may be considered diabetic (professional agreement).

5- In patients with no known diabetes and HbA1c < 6.5%, glucose metabolism disorders after an ACS should be assessed using the OGTT (Level A), as measuring only FPG leads to the underdiagnosis of dysglycaemic states in 2/3 of patients (Level A). The OGTT should be performed 7 to 28 days after the ACS, in stable conditions (Level B), often after discharge because the mean duration of hospitalization after an ACS is usually less than 7 days. The diagnostic criteria are similar as those used in subjects without a cardiovascular history (Table 1).

Fasting plasma glucose in mg/dL (mmol/L)	2 hours after an oral glucose load (75g) 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

Table 1: Criteria for the diagnosis of glucose metabolism disorders. IGT: Impaired Glucose Tolerance; IFG: Impaired Fasting Glucose. (The OGTT should be performed 7 to 28 days after the ACS, in stable conditions)

II) Diabetes care in cardiology intensive care units

Patients with diabetes mellitus are at an increased risk for myocardial infarction (2). Poor glycaemic control in diabetic patients and stress hyperglycaemia in non-diabetic patients are associated with worse outcomes after acute myocardial infarction (MI) (9) but it is not yet clear whether strict glycaemic control during acute MI hospitalizations improves outcomes.

Does intensive antidiabetic treatment in a cardiology intensive care unit provide any benefit?

Glycaemic control is not optimal in hyperglycaemic patients hospitalized for an ACS. It has been shown that 28% of the patients hospitalized for an ACS and with admission glucose $\geq$ 11 mmol/L (200 mg/dL) received no antidiabetic treatment (35). However, does intensive antidiabetic treatment in a cardiology intensive care unit provide any benefit?

Some studies have shown that intensive insulin treatment is beneficial. In the DIGAMI trial**,** 620 diabetic patients with an acute MI and a blood glucose concentration > 11 mmol/l (200 mg/dL) were randomly assigned to an insulin-glucose infusion for 24 hours followed by subcutaneous insulin four times daily for $\geq$ 3 months or standard treatment with insulin therapy only if clinically indicated (36). The target blood glucose level for patients assigned to the insulin-glucose infusion was 126 to 196 mg/dL (7 to 10.9 mmol/L). At randomization, the mean blood glucose was about 280 mg/dL (15.6 mmol/L). The mean blood glucose was significantly lower with intensive insulin at 24 hours (173 vs. 211 mg/dL [9.6 vs. 11.7 mmol/L]) and hospital discharge (148 vs. 162 mg/dL [8.2 vs. 9.0 mmol/L]) At randomization, HbA1c was 8.1%. The reduction in HbA1c at three months (1.1 vs. 0.4%) and one year (0.9 vs. 0.4%) was significantly greater in patients with intensive insulin therapy. Mortality at one year (19 vs. 26%) and at 3.4 years (33 vs. 44%) was significantly lower in the group assigned

to the more aggressive insulin therapy (36). The greatest reduction in mortality was seen in low-risk patients who had not been receiving insulin prior to the infarction. Since DIGAMI also included outpatient insulin therapy, the isolated effect of in-hospital glycaemic control could therefore not be easily assessed. The observational study of *Weston et al*, conducted in 50,205 patients hospitalized for an ACS, showed that insulin treatment was beneficial in patients with no history of diabetes but an admission blood glucose level ≥ 200 mg/dL (11.0 mmol/L) (35). Compared with those who received insulin, after adjustment for age, gender, co-morbidities and admission blood glucose concentration, patients who were not treated with insulin had a relative increased risk of death of 56% at 7 days and 51% at 30 days (HR 1.56, 95% CI 1.22 to 2.0, p, 0.001 at 7 days; HR 1.51, 95% CI 1.22 to 1.86, p, 0.001 at 30 days) (35).

Critically ill medical and surgical patients who are hyperglycaemic have a higher mortality rate than patients who are normoglycaemic (37)**.** Patients who died had significantly higher admission blood glucose levels (175 vs. 151 mg/dL [9.7 vs. 8.4 mmol/L]), mean blood glucose levels (172 vs. 138 mg/dL [9.5 vs. 7.7 mmol/L]), and maximum blood glucose levels (258 vs. 177 mg/dL [14.3 vs. 9.8 mmol/L]) than those who survived (37). There was a graded effect, with higher mortality among patients who had higher blood glucose levels. Mortality ranged from 10 % in patients with a mean blood glucose level between 80 and 99 mg/dL (4.4 and 5.5 mmol/L) to 43 % in patients with a mean blood glucose level greater than 300 mg/dL (16.6 mmol/L). Hyperglycaemia is also associated with worse outcomes in several subgroups of critically ill medical patients, including patients with stroke or acute myocardial infarction.

However, the benefit of intensive insulin treatment has not been observed in other studies. The value of insulin therapy was further studied in the DIGAMI-2 trial, in which patients with type 2 diabetes and acute MI were randomly assigned to one of three glucose management strategies: group 1, inpatient insulin infusion/outpatient intensive subcutaneous insulin therapy; group 2, inpatient insulin infusion/outpatient standard treatment; or group 3,

inpatient/outpatient routine glucose management according to local practice (38). Although it was anticipated that mortality rates would be lowest in group 1, they were similar in all three groups. However, there were a number of problems with this study that interfere with the interpretation of the results. Glycaemic control, which was expected to be the best in group 1, was also similar in the three groups. The overall event rate was lower than expected in all groups (perhaps due to improved benefit from reperfusion procedures and to the implementation of other secondary prevention strategies), which may have attenuated any statistical differences between groups. The trial was stopped earlier than planned due to a failure to recruit an adequate number of patients; since less than 50% of the required patients were recruited, the power to detect a difference among the treatment groups was substantially reduced. The possible benefit of more intensive glucose control in patients with an acute MI and either a history of diabetes or an admission blood glucose level $\geq$ 140 mg/dL (7.8 mmol/L) was evaluated in the Hyperglycemia Intensive Insulin Infusion in Infarction (HI-5) study (39). In this trial, 240 such patients were randomly assigned to conventional therapy or to an insulin/dextrose infusion to maintain the blood glucose level between 72 and 180 mg/dL (4 and 10 mmol/L) for at least 24 hours. After 24 hours, the patients were managed with standard care by their own physicians with a recommended HbA1c of less than 7%. There was no difference in the primary end-point of mortality in-hospital or at three or six months. However, HI-5 was seriously flawed by the small number of patients, the lack of blinding, the maintenance of glycaemic control for only 24 hours, and the failure to attain a significant difference in mean 24-hour blood glucose between the intensive therapy and control groups (149 vs. 162 mg/dL [8.3 vs. 9.0 mmol/L]) (39). Subset analysis found that mortality, in-hospital (0 vs. 7%) and at three and six months (2 vs. 11%), was considerably lower in patients who had a mean blood glucose level $\leq$144 mg/dL (8.0 mmol/L) during the first 24 hours.

Meta-analyses have been performed in an effort to consolidate the data from numerous randomized trials. One such meta-analysis of 15 randomized trials (10,140 patients) compared the effect of tight glucose control (defined as a target blood glucose level ≤150 mg/dL [8.3 mmol/L]) to less stringent glycaemic control in mixed medical and surgical ICU patients (40). Mortality in patients with tight glucose control was similar to that in patients with less stringent glycaemic control (26.7 vs. 25.6%, relative risk 0.99, 95% CI 0.87-1.12) (40).

Risk of hypoglycaemia

Intensive insulin treatment has been shown to be associated with an increased risk of hypoglycaemia (37). During such treatment, hypoglycaemia, when defined as blood glucose <40 mg/dL (2.2 mmol/L), occurs in up to 19% of patients, or up to 32% of patients when defined as blood glucose <60 mg/dL (3.3 mmol/L) (37). Hypoglycaemia can lead to seizures, brain damage, depression, cardiac arrhythmia or death (41). As part of a retrospective cohort study of more than 5000 medical and surgical critically ill patients, a nested case-control study found that blood glucose <40 mg/dL (2.2 mmol/L) was an independent risk factor for death after adjustment for severity of the illness, age, mechanical ventilation, renal failure, sepsis, and diabetes (adjusted odds ratio 2.28, 95% CI, 1.41-3.70) (42). The risk of hypoglycaemia was also evaluated in the large multicenter Normoglycemia in Intensive Care Evaluation Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial, which randomly assigned 6,104 medical and surgical ICU patients to either intensive insulin treatment (target blood glucose level of 81 to 108 mg/dL [4.5 to 6 mmol/L]) or conventional glucose control (target blood glucose of <180 mg/dL [<10 mmol/L]) (43). Although the conventional glucose control group was defined only by a maximal blood glucose target, the insulin infusion was reduced and then discontinued if the blood glucose level dropped below 144 mg/dL (8.0 mmol/L). Compared with the conventional glucose control group, the intensive insulin treatment group had a significantly lower time-weighted blood glucose level

(115 vs. 144 mg/dL [6.2 vs. 7.9 mmol/L]), a significantly higher incidence of severe hypoglycaemia (6.8 vs. 0.5%), defined as a blood glucose <40 mg/dL and significantly higher 90-day mortality (27.5 vs. 24.9%, odds ratio 1.14, 95% CI 1.02-1.28) (43). In the subgroup of 2,232 surgical patients, mortality was significantly higher in those who received intensive insulin treatment than in those who received conventional glycaemic control (24.4 vs. 19.8%, odds ratio 1.31, 95% CI 1.07-1.61). The Volume Substitution and Insulin Therapy in Severe Sepsis (VISEP) trial was a multicenter two-by-two factorial trial conducted in medical and surgical ICU patients with severe sepsis (44). It compared intensive insulin treatment (target blood glucose level of 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) with conventional glucose control (target blood glucose level of 180 to 200 mg/dL [10 to 11.1 mmol/L]), as well as comparing two methods of volume resuscitation. The intensive insulin treatment arm of the trial was stopped after 488 patients had been enrolled because intensive insulin treatment significantly increased the rate of hypoglycaemia (12.1 vs. 2.1%) and serious adverse events (10.9 vs. 5.2%). The trial then continued with only patients in the conventional therapy group until 537 patients had been enrolled. Analysis of the data at the end of the study showed that patients in the intensive insulin treatment group had significantly lower mean morning blood glucose (112 vs. 151 mg/dL [6.2 vs. 8.4 mmol/L]) and more frequent hypoglycaemic events (blood glucose ≤40 mg/dL [2.2 mmol/L]; 17 vs. 4.1%) than did those in the conventional glucose control group. There was no significant difference between the two groups for 28-day mortality (24.7 vs. 26.0% in the conventional glucose control group), morbidity, or organ failure, and a non-statistically significant increase in 90-day mortality in the intensive insulin treatment group (39.7 vs. 35.4%) (44). The Glucontrol trial was a multicenter trial that randomly assigned 1,101 critically ill medical and surgical patients to intensive insulin treatment (target blood glucose of 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) or conventional glucose control (target blood glucose of 140 to 180 mg/dL [7.8 to 10 mmol/L]) (45). The trial was terminated early because of a high rate of unintended protocol violations. Intensive

insulin treatment significantly increased the rate of hypoglycaemia (8.7 vs. 2.7%) (45). There was no difference in ICU mortality, although the intensive insulin treatment group had a non-significant trend towards higher 28-day mortality and in-hospital mortality. A retrospective study performed in 7820 patients hospitalized for acute MI has reported that hypoglycaemia was associated with increased mortality in patients not treated with insulin, but not in those treated with insulin (46).

In summary, data from the literature show that, in mixed populations of critically ill medical and surgical patients, intensive insulin treatment (target blood glucose of 80 to 110 mg/dL [4.4 to 6.1 mmol/L]) increases the incidence of severe hypoglycaemia and may increase mortality, when compared with the more permissive blood glucose ranges of 140 to 180 mg/dL (7.8 to 10 mmol/L).

Which insulin infusion protocol?

Intravenous infusion of insulin is usually recommended, with concomitant infusion of glucose. In the review of *Wilson et al.,* twelve different insulin infusion protocols, used in critical care, were reported and showed great variability. The areas of variability included differences in initial insulin dose, titration of insulin, use of insulin bolus, glycaemic targets and method of insulin protocol adjustments (47). The quantity of insulin injected ranged from 26.9 units/day to 115 units/day with a mean of 66.7 units/day. In most of the reported procedures, 75% of the daily insulin dose was administered when blood glucose was above 200 mg/dL (11.0 mmol/L). This great variability in protocols reflects the lack of consensus in the delivery of intravenous insulin in critical care.

Consensus statement

1- In cases of *unknown diabetes*, continuous insulin treatment has to be initiated when admission blood glucose level is ≥ 180 mg/dL (10.0 mmol/L) (level A).

2- In cases of *previously-known diabetes*:

♦ Continuous insulin treatment has to be initiated when admission blood glucose level is ≥ 180 mg/dL (10.0 mmol/L) and/or pre-prandial glucose level is ≥ 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 hospitalisation in cardiology intensive care unit (professional agreement)

♦ If the patient had known diabetes treated with insulin and admission blood glucose < 180 mg/dL (10.0 mmol/L) and/or pre-prandial glucose < 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 a more stringent target of 110 to 140 mg/dL (6.1 to 7.7 mmol/L) (Level A).

4- A blood glucose target < 110 mg/dL (6.1 mmol/L) is not recommended (Level A).

5- The recommended insulin treatment is continuous IV insulin infusion with a pre-prandial bolus (see proposed protocol below). Insulin dosage will be adapted to capillary glucose measurements (level A).

6- In patients on continuous IV insulin infusion, blood (capillary) glucose will be monitored 1 hour after initiation, then every 2 hours (level A).

7- In hyperglycaemic/diabetic patients not on continuous IV insulin infusion, blood (capillary) glucose will be monitored before each meal, 2 hours after meals and at bed time (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 cardiology intensive care unit** and a **protocol** for **transition from intravenous to subcutaneous insulin** are given in the **addendum**.

III) Diabetes care during hospitalization in a post-intensive care unit

Following the period in intensive care unit, insulin treatment is not mandatory for every patient with diabetes, and other antidiabetic treatments may be considered. The choice of the optimal treatment for diabetes depends on the metabolic profile of the patient. In situations of uncontrolled diabetes (HbA1c ≥ 8%), referral to a diabetologist is recommended.

Metformin

In UKPDS, monotherapy with metformin (with a mean dose of 2550 mg/day), in diabetic patients with a BMI ≥25 kg/m^2 was associated with a significant decrease in overall mortality (-36%), in myocardial infarction (-39%), and there was a non-significant decrease in stroke (-41%) when compared with treatment with sulfonylureas or insulin (48). These data led to recommendations for the use of metformin in all overweight or obese patients with type 2 diabetes. However, patients in UKPDS were newly-diagnosed type 2 diabetic patients mostly in primary prevention. Very few data on metformin after myocardial infarction are available. Many case-control studies have shown reductions in cardiovascular morbidity and mortality with metformin (versus sulfonylureas) (49). One meta-analysis showed that metformin treatment was associated with a significant decrease in cardiovascular mortality (OR: 0.74; IC 95%: 0.62-0.89) when compared with other antidiabetic treatments (50). The association between metformin treatment and mortality has recently been analyzed in 19,699 patients with type 2 diabetes and a history of cardiovascular disease from the REACH (Reduction of Atherothrombosis for Continued Health) registry (51). During the two-year follow-up a significant reduction in mortality (HR = 0.67 p < 0.0001) was observed with

metformin (51). After adjustment for age, gender, and other potential confounding factors, metformin treatment remained associated with a significant reduction in all-cause mortality (adjusted HR = 0.76; p < 0.001) (51). This benefit was also observed in patients with renal failure or with a history of congestive heart failure, which are usually considered contra-indications for metformin (51). In the DIGAMI 2 study, metformin was associated with a significant reduction in non-fatal cardiovascular events after two years of follow-up, (myocardial infarction, stroke) (HR 0.63, IC 95%: 0.42-0.95; p = 0.03) (52). In the same study, after 4 years of follow-up, treatment with metformin was associated with a significant decrease in all-cause mortality (HR: 0.62; IC 95%: 0.47-0.90, p=0.01) and a significant decrease in cancer mortality (53). Although no prospective studies with metformin have been performed in patients with type 2 diabetes after an ACS, data from case control studies and DIGAMI 2 suggest that the use of metformin in such situations may be recommended. In a Danish study performed in 10,920 patients hospitalized for heart failure between 1997 and 2006, treatment with metformin was associated with a low risk of mortality in diabetic patients compared with treatment with a sulfonylurea or insulin (54). However, its use is not recommended in situations of uncontrolled cardiac failure or renal failure. In addition, metformin has to be stopped before coronary angiography.

Sulfonylureas

Results obtained from the UGDP trial showed a potential increase in cardiovascular risk in patients treated with first-generation sulfonylurea (55). Controversial experimental studies have suggested that as sulfonylurea binds to K+ channels it might impair myocardial preconditioning, a natural cardioprotective mechanism, to varying degrees. In experimental models of ischemia, coronary artery vasodilatation was impaired in animals subjected to sulfonylurea treatment (56).

Several observational studies were unable to establish an association between sulfonylurea treatment and the occurrence of ACS. However, a recent retrospective observational study based on the UK General Practice Research database suggested a greater incidence of cardiovascular death and congestive heart failure in patients on sulfonylurea than in those on metformin (57). In intensification trials such as UKPDS and ADVANCE no increase in cardiovascular risk was found when treatment was intensified by sulfonylurea (58,59), and in an earlier study no association was reported between the size of myocardial infarction and previous treatment with glibenclamide (60). However, observational studies in patients who underwent coronary angioplasty after myocardial infarction have shown an increase in cardiovascular mortality in those on sulfonylurea, which was attributed to a deterioration in preconditioning (61). Similar findings were obtained in a case-control study, which reported a 30% increase in cardiovascular death following myocardial infarction in patients treated with first-generation sulfonylurea, including glibenclamide (62). Several recent pharmaco-epidemiological studies failed to reveal any increase in cardiovascular risk due to exposure to second-generation sulfonylurea after ACS (63-66). However, in the Danish registry, cardiovascular risk was higher in patients treated with sulfonylurea, with the exception of gliclazide, than in those on metformin (67). Data from the sulfamide-treated patients of the nationwide French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction in 2005, have shown that in-hospital mortality was significantly lower in patients receiving pancreatic cells-specific sulfonylureass (gliclazide or glimepiride) (2.7%), compared with glibenclamide (7.5%) (P = 0.019), indicating potential differences between the different sulfonylurea drugs (65). However, all of these non-randomized studies are prone to inclusion bias despite multiple adjustments. In the DIGAMI 2 trial, no increase in cardiovascular complications was observed in the arm treated with oral antidiabetic agents following an ACS. Nonetheless, only one third of the patients were treated with sulfonylurea in this arm (53).

Glinides

Repaglinide is able to bind myocyte K+ channels with a lower specificity toward beta cell K+ channels than is the case with second-generation sulfonylurea. Only limited and/or indirect data are available about cardiovascular risk following ACS. In the NAVIGATOR trial designed to compare nateglinide with placebo in order to assess cardiovascular risk and the occurrence of diabetes in glucose-intolerant subjects at high cardio-vascular risk, no increase in cardiovascular morbidity and/or cardiovascular mortality was found (68). In the Danish registry, no firm conclusions can be drawn due to a lack of statistical power, though there was a trend towards a higher cardiovascular risk with glinides than with metformin (OR 1.29 (0.86-1.94)) (67). No data about glinides were available in the French registry of intensive care units.

Acarbose

Acarbose acts mostly to decrease blood glucose in the post-prandial phase. In experimental models of ischemia reperfusion a decrease in the size of the necrotic lesion was reported (69) and type 2 diabetic patients on acarbose showed a greater improvement in endothelial function in the post-prandial phase than did those on nateglinide (70). A lower risk of cardiovascular adverse events was observed in glucose-intolerant patients treated with acarbose versus placebo in the STOP-NIDDM trial (71,72). Treatment with acarbose was associated with a lower risk of myocardial infarction in a meta-analysis of 7 clinical trials performed in patients with type 2 diabetes (hazards ratio=0.36 [95% CI 0.16–0.80], P=0.012) (73). Acarbose is currently being tested in China in patients with CVD and prediabetes in a placebo-controlled study looking at cardio-vascular events and the new-onset of diabetes.

Pioglitazone

Pioglitazone, by its action on the nuclear PPAR-γ (peroxisomal proliferator activated receptor) receptor ameliorates insulin sensitivity and glucose control. In addition, pioglitazone decreases plasma triglycerides and increases HDL cholesterol. Pioglitazone does not modify plasma level of LDL cholesterol whereas rosiglitazone, which was withdrawn from the European market in 2010, was known to increase plasma LDL cholesterol. Several studies have shown a reduction in inflammatory markers (such as CRP) and an improvement in endothelial dysfunction in patients on pioglitazone. In the PROactive study, pioglitazone was combined with the usual antidiabetic treatment (versus placebo) in patients with type 2 diabetes and cardiovascular disease. Pioglitazone induced a non-significant reduction in the primary endpoint, which included leg amputation and leg revascularization, and led to a significant reduction in major cardiovascular events (-16%) (74). In addition, in the PROactive study, among the 2445 patients with a history of myocardial infarction, pioglitazone induced a significant 28% reduction in recurrent myocardial infarction (p=0.04) and 37% reduction in ACS (p=0.03) (75). A meta-analysis confirmed the benefit of pioglitazone on ischemic cardiovascular events, but also showed an increase in heart failure (76). Another meta analysis of controlled studies (randomized trials and cohort studies) in patients with diabetes and heart failure showed that glitazones were associated with increased risk of hospital admission for heart failure but with reduced all cause mortality (77). In the PROactive study, the incidence of heart failure was increased with pioglitazone versus placebo (7.5% vs. 5.2%), but with no increase in heart failure-induced mortality (1.4% vs. 0.9%) (74). Pioglitazone promotes sodium retention and thus may inflate blood volume and decompensate pre-existing heart failure without increasing mortality.

All the available data confirm the global cardiovascular benefit of pioglitazone in patients with type 2 diabetes and a history of myocardial infarction, with a significant reduction in the risk for a recurrent fatal or non-fatal event. One complementary analysis

suggested that the cardiovascular benefit of pioglitazone in PROactive may partly be due to the increase in plasma HDL cholesterol (78). The use of pioglitazone has recently been suspended in France due to concerns on bladder cancer risk, but pioglitazone is still available in most of the countries in the world with the approval of European (EAMA) and American (FDA) drug agencies.

GLP-1 (Glucagon-Like Peptide-1) agonists

GLP-1 agonists reduce hyperglycaemia by enhancing glucose-induced insulin secretion and inhibiting glucagon production. They also reduce gastric emptying and appetite. Some experimental and clinical studies suggest that GLP-1 may protect the heart against ischemia/reperfusion injury and improve left ventricle contractility and endothelial function (79-82).

Exenatide. In a 12-week controlled study versus placebo, exenatide did not significantly modify heart rate or blood pressure, although mean body weight was significantly reduced (-1.5 +/-0.6 kg vs. placebo) (83). Patients with a recent cardiovascular event were excluded from the study. A recent analysis of data from health insurance organizations suggests, after adjustment for potential confounding factors, a cardiovascular benefit of exenatide (adjusted HR=0.81 [0.68-0.95]; p = 0.01) (84). Here also, patients with a recent cardiovascular event were excluded from that study. In a meta-analysis of 12 controlled randomized studies with exenatide, which also included diabetic patients with a history of cardiovascular disease, a non-significant decrease in the pre-specified endpoint (cardiovascular death, myocardial infarction, ischemic stroke, revascularization) (OR= 0.70 [0.38-1.31]; *p* > 0.05) was observed (85).

Liraglutide. An analysis of the pooled data from clinical trials with liraglutide did not show any significant effect of liraglutide on cardiovascular events (86).

Head to head comparison. A study comparing exenatide (10 µg BID) with liraglutide

(1.8 mg once daily) in 464 patients with type 2 diabetes not controlled by metformin and/or sulfonylureas showed a greater reduction in HbA1c with liraglutide (−1.12% [0·08] vs. −0.79% [0·08], p<0.0001) (87). A greater reduction in triglycerides was also observed with liraglutide whereas no differences between the two drugs were noted for body weight, blood pressure, LDL cholesterol, HDL cholesterol or the incidence of cardiovascular events (87).

Combined analysis. When data from clinical trials with both exenatide and liraglutide were combined, a significant reduction in the risk for major cardiovascular events was observed (OR=0.46 [0.26-0.83], p=0.009), when they were compared with placebo, whereas the risk for major cardiovascular events was no different when they were compared with active antidiabetic treatment (OR=1.05 [0.63-1.76], p=0.84) (88).

DPP-4 (Dipeptidyl peptidase-4) inhibitors

DPP-4 inhibitors reduce GLP-1 enzymatic degradation leading to moderate increases in its plasma concentration. The pooled analysis of the data from 19 clinical trials with sitagliptin, which compared 5,429 patients on sitagliptin with 4,819 on placebo or other active antidiabetic treatments showed a non-significant difference for the incidence of major cardiovascular events (inter-group difference –0.3 [-0.7- 0.1), p>0.05) (89). In an analysis of the pooled data from 25 clinical trials with vildagliptin, the relative risk of major cardiovascular events (cardiovascular death, myocardial infraction, stroke) as compared with the control group (placebo or active antidiabetic treatment) was 0.88 (0.37-2.11) (90). In the subgroup of patients in secondary prevention, the relative risk was 0.78 (0.51-1.19) (90). In an analysis of pooled data from trials with 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]) (91). Another meta analysis including available randomized controlled trials, either published or unpublished, performed in type 2 diabetic patients with DPP-4 inhibitors, with a duration >12 weeks showed a non significant decrease of the risk of cardiovascular

events and all-cause death (92).

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Consensus statement

1- Metformin is not contra-indicated after an ACS, in the absence of renal failure (professional agreement).

2- Following an ACS, due to the increase in cardiovascular risk reported in observational studies it is recommended not to use first generation sulfonylurea and glibenclamide (Level C).

3- Glinides are not contra-indicated following an ACS (professional agreement).

4- Acarbose may be used following an ACS when needed according to the metabolic phenotype of the patient (predominant post-prandial hyperglycaemia) (professional agreement).

5- Pioglitazone, when available, is not contra-indicated following an ACS. It must not be used in cases of congestive heart failure or when LVEF < 45% (professional agreement).

6- GLP-1 agonists are not contra-indicated following an ACS (professional agreement).

7- DPP-4 inhibitors are not contra-indicated following an ACS (professional agreement).

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IV) Diabetes care during cardiac rehabilitation

A comprehensive cardiac rehabilitation program should include:

– supervised physical activity after cardiac assessment,

– education on all cardiovascular risk factors (including diabetes)

– promotion of physical activity as a therapeutic means

– psychological support

– nutritional counselling

–   planning of long-term regular physical activity after cardiac rehabilitation

This multifaceted and multidisciplinary intervention improves functional capacity. Cardiac rehabilitation decreases all-cause and cardiovascular morbidity and mortality in patients after ACS (93,94). 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 percent improvement in survival in several subgroups, including type 2 diabetic subjects (95). However, it has been shown that hyperglycaemia during cardiac rehabilitation is associated with a smaller improvement in exercise capacity (96).

In addition, cardiac rehabilitation improves psychological well-being (97), patients' adherence to pharmacological advice and lifestyle modifications and patients' motivation for future long-term physical activity. Furthermore, cardiac rehabilitation is a cost-effective intervention after an acute coronary event (98).

Many studies have shown the benefit of physical activity on glycaemic control. It is estimated that physical activity may reduce glycated hemoglobin levels by 0.6% (99). As a consequence, one might expect a reduction in the risk of diabetic complications (100). Moreover, physical activity reduces weight and visceral adipose tissue, leading to reduced insulin resistance. Thus, physical activity during cardiac rehabilitation improves glycaemic control in patients with type 2 diabetes. In addition, regular physical activity in patients with IGT can prevent or delay the onset of type 2 diabetes (101, 102).

Cardiac rehabilitation reduces depression in diabetic patients and increases patients' motivation for lifestyle modifications (97).

Cardiac rehabilitation should start soon after clinical stabilization and patients' assessment by a submaximal exercise stress. The exercise component of the program, prescribed by a cardiologist, is a combination of endurance and light resistance training sessions associated with flexibility training, chest physiotherapy, 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 (103). The hypoglycaemic effect of physical activity lasts up to 30 hours following exercise (104). Self-monitored blood glucose (SMBG) provides a potential tool to control blood glucose and to prevent significant hypoglycaemia during and after physical activity (105). Moreover, blood glucose testing is also helpful to adjust antidiabetic treatments, if necessary, and for educational purposes (106).

Indeed, cardiac rehabilitation represents a unique opportunity to refer a patient for education

- not only for "usual" education on diabetes and self management, but also on the benefit of physical activity on diabetes
- on how to manage diabetes during physical activity (with SMBG help)

It has been shown that such education is important to reinforce patients' empowerment (107).

General nutritional counselling to prevent cardiovascular disease is important for patients with diabetes. It is no different from cardiovascular nutritional counselling given to non-diabetic patients. In patients with diabetes, additional information will be given on weight reduction, prevention and the treatment of hypoglycaemic episodes (108).

Cardiac rehabilitation provides an opportunity to optimize the treatment of diabetes. Referral to a diabetologist/diabetology team, during this period, may be useful, particularly in situations of uncontrolled diabetes with significant hyperglycaemia and/or repeated hypoglycaemia (109).

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

Consensus statement

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 a similar benefit in patients with diabetes.

2. Cardiac rehabilitation is an opportunity to show the patients the benefit of regular physical activity not only for cardiovascular prevention but also to improve glycaemic control and to prevent diabetes (Level A).

3. Blood glucose must be checked before exercise, in each patient with diabetes. In addition, blood glucose testing should also be performed at the end and 4 to 6 hours after each physical activity session, in patients treated with insulin or insulin secretagogues (sulfonylureas or glinides) in order to reduce the risk of hypoglycaemic episodes (professional agreement).

4. When blood glucose before exercise is above 250 mg/dl (13.9 mMol/L), ketonuria has to be checked. If the patient is without ketosis, feeling well and correctly hydrated, physical activity can be performed with caution, and regular capillary blood testing is recommended, at least every hour during the training session (professional agreement).

5. During cardiac rehabilitation, the patient should be referred to a diabetologist/diabetology team in the following situations:

- uncontrolled diabetes with significant hyperglycaemia (HbA1c> 8%)
- and/or severe/repeated hypoglycaemia (professional agreement).

V) Nutrition/Diet

Nutrition plays an important role in the treatment of patients with diabetes. It is important for optimal glycaemic control and also plays an important role in the primary and secondary prevention of cardiovascular disease (110). The nutritional treatment has to be

discussed with the diabetic patient, and cultural and ethnical specificities have to be taken into account. The diet program must be adapted to each patient. It has been shown that nutritional education provided by care providers familiar with diabetes and nutritional cardiovascular prevention and trained for patient education gives beneficial results in the control of glycaemia and cardiovascular risk factors (111-113).

A balance between ingested carbohydrates and insulin (endogenous or therapeutically administered) is critical for post-prandial blood glucose control. Thus, the proportion of carbohydrates in the diet is a crucial point for glycaemic control in patients with diabetes and the quantity of carbohydrate in a meal is the major determinant of post-prandial glycaemia (114,115). 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 may be modified, but the dose of insulin for the meal must be adjusted accordingly. For this, the patient needs to be educated by a trained diabetology team.

For the prevention of coronary artery disease, it is recommended to reduce risk by reducing saturated fat, trans fatty acids and sodium and by adopting a Mediterranean-style diet (rich in mono-unsaturated fat, 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 (116-118).

In patients with type 2 diabetes, hypertriglyceridemia is frequent. In situations of frank hypertriglyceridemia (over 400 mg/dL), fructose (which promotes hepatic triglyceride production) should be restricted and the consumption of fruits limited. After an ACS, a consultation with a dietician is mandatory in patients with overt hypertriglyceridemia.

Consultation with a dietician may be useful in all patients with diabetes after an ACS in order to obtain diet recommendations for diabetes, prevention of atherosclerosis and, when necessary, weight reduction.

The nutritional recommendations will be limited, here to the coronary syndrome period without embracing all of the diet recommendations in patients with diabetes.

Consensus statement

During hospitalization:

1. No specific recommended carbohydrate level for patients with diabetes. The proportion of carbohydrate in the diet does not have 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 intensive care unit, it is recommended to use a fixed carbohydrate dose for each meal (professional agreement).

3. Patients with diabetes are recommended to have 3 meals a day (in the absence of a concomitant procedure) (Level A).

4. Unnecessary fasting should be avoided (professional agreement).

5. Low glycaemic index food should be preferred to high glycaemic index food (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 must 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 fruit and vegetables and monounsaturated fatty acids is recommended (Level A).

4. In situations of overt hypertriglyceridemia, the patient has to be referred to a dietician (professional agreement).

5. A consultation with a dietician is recommended in patients with diabetes after an ACS

VI) When should a patient with diabetes be referred to a diabetologist?

Several consensus statements have emphasized the benefit of referring a patient to a diabetologist during hospitalization for conditions other than diabetes (13,119,120). Referral to a diabetologist in a situation of hospitalization for an ACS is likely to give substantial benefits to patients with diabetes. Hospitalization for an ACS provides a unique opportunity to optimize the treatment of diabetes and to educate patients in diabetes self-management (121).

It is advised, 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 usually advised to refer a patient with diabetes to a diabetologist before discharge or within one month after discharge (120).

The importance of the patient's education is emphasized in the ADA and the AACE (American Association of Clinical Endocrinologists) consensus statement (119). Because the length of hospital stay for an ACS is usually short, during hospitalization, it is recommend to limit diabetes-related education to an inventory of basic "survival skills" (level of understanding related to the diagnosis of diabetes, self-monitoring of blood glucose 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, identification of health care provider who will be responsible for diabetes care after discharge). Several studies have shown that medication errors and adverse drug events have been linked to poor communication of instructions to the patient at the time of discharge (122,123). Clear instructions at time of discharge and during outpatient care are needed and provide a reference for patients and their outpatient providers. It has been shown that an insulin-specific discharge instruction form provided greater clarity and more consistent directions for insulin dosing and self blood glucose monitoring in comparison with a generic hospital discharge form (124). Several studies have shown that an education program on diabetes during hospitalization provided better outcomes such as improved glycaemic control (125,126), fewer hospitalizations (125,126), fewer episodes of keto-acidosis (126) and reduced length of hospital stay (127). Moreover, in patients hospitalized in medical and surgical cardiac care units, an intervention program on diabetes, including clear self-care instructions before discharge, significantly decreased the frequency of prolonged and severe hyperglycaemia and the frequency of nosocomial infections (128). Thus, a clear educational program on the basic points of diabetes is highly recommended before discharge. This can be performed by a diabetologist and /or a diabetes educator.

In addition, diabetes care delivered by an endocrinologist/diabetologist, during hospitalization, has been shown to provide better outcomes such as better glycaemic control (129), fewer readmissions for diabetes (129,130), reduced length of hospital stay (130) and reduced cost (130). 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 days to 5.5 days (131). These data clearly show the benefit of an endocrinologist/diabetologist consultation in patients with diabetes hospitalized for conditions other than diabetes.

Consensus statement:

1. In the *intensive care cardiology unit*, the treatment of diabetes or stress hyperglycaemia that requires insulin needs to be delivered by an experienced team including a diabetologist (professional agreement).

2. *Referral to a diabetologist <u>before</u> hospital discharge*: the patient should be referred to a diabetologist **before discharge** from the hospital in the following situations:

   - unknown diabetes, diagnosed during the ACS hospitalization (HbA1c ≥ 6.5%)

   - and/or known diabetes with admission HbA1c ≥ 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 in order to organize a hospitalization following the hospitalization in the cardiology department (professional agreement).

3. *Referral to a diabetologist <u>after</u> hospital discharge*:

   - In patients without known diabetes at discharge (no known diabetes at admission and admission HbA1c <6.5%), it is recommended to perform an OGTT between day 7 and 28. If diabetes is diagnosed with 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).

   - The follow-up of the patient with diabetes will be coordinated with the primary care physician (professional agreement).

   - After discharge, the patients with diabetes may be referred to centres specialized in diabetes education, if available (professional agreement).

4. *Referral to a diabetologist during <u>cardiac rehabilitation</u>:* the patient should be referred to a diabetologist in the following situation:

- uncontrolled diabetes with significant hyperglycaemia

- and/or severe / repeated hypoglycaemia (professional agreement).

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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 hour 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 post-prandial 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 (according to Avanzini et al) (132)**:**

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 2h before the first meal and the discontinuation of intravenous glucose infusions.

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.

Unknown diabetes

Acute coronary syndrome

Known diabetes

Admission

Admission glucose

Stop antidiabetic drugs if any

Admission glucose ≥ 180 mg/dL

No   **Yes**

Continuous IV insulin

Admission glucose ≥ 180 mg/dL and/or
preprandial glucose ≥ 140 mg/dL at follow-up

No   **Yes**

Non insulin-treated diabetes | Insulin-treated diabetes | Non insulin-treated diabetes | Insulin-treated diabetes

Day 1

Fasting glucose

Fasting glucose → Adapt treatment

Continue / adapt previous insulin regimen

continuous IV insulin

continuous IV insulin

HbA1c

HbA1c

<6.5%   **≥ 6.5%**

Diabetes is diagnosed
See diabetologist*

At discharge

According to follow-up
Antidiabetic drugs to be adapted
± insulin treatment*

Insulin treatment*

Coordinated follow-up

Coordinated follow-up   Coordinated follow-up

Oral glucose tolerance test

Day 7 – Day 28

OGTT

Normal   **Impaired fasting glucose and/or Impaired glucose tolerance**   **Diabetes**

Reassessment
1 year later

Diabetes prevention
Referral to cardiac rehabilitation center

Coordinated follow-up

*A diabetologist should see the following patients:
• before discharge:
 -Diagnosis of unknown diabetes
 -Known diabetes with
        -new onset insulin therapy
        -and/or HbA1c ≥ 8.0%
        -and/or severe / repeated hypoglycemia
• after discharge:
 -Diabetes diagnosed with the OGTT
 -During cardiac rehabilitation, if significant hyperglycaemia
and/or severe/repeated hypoglycaemia

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