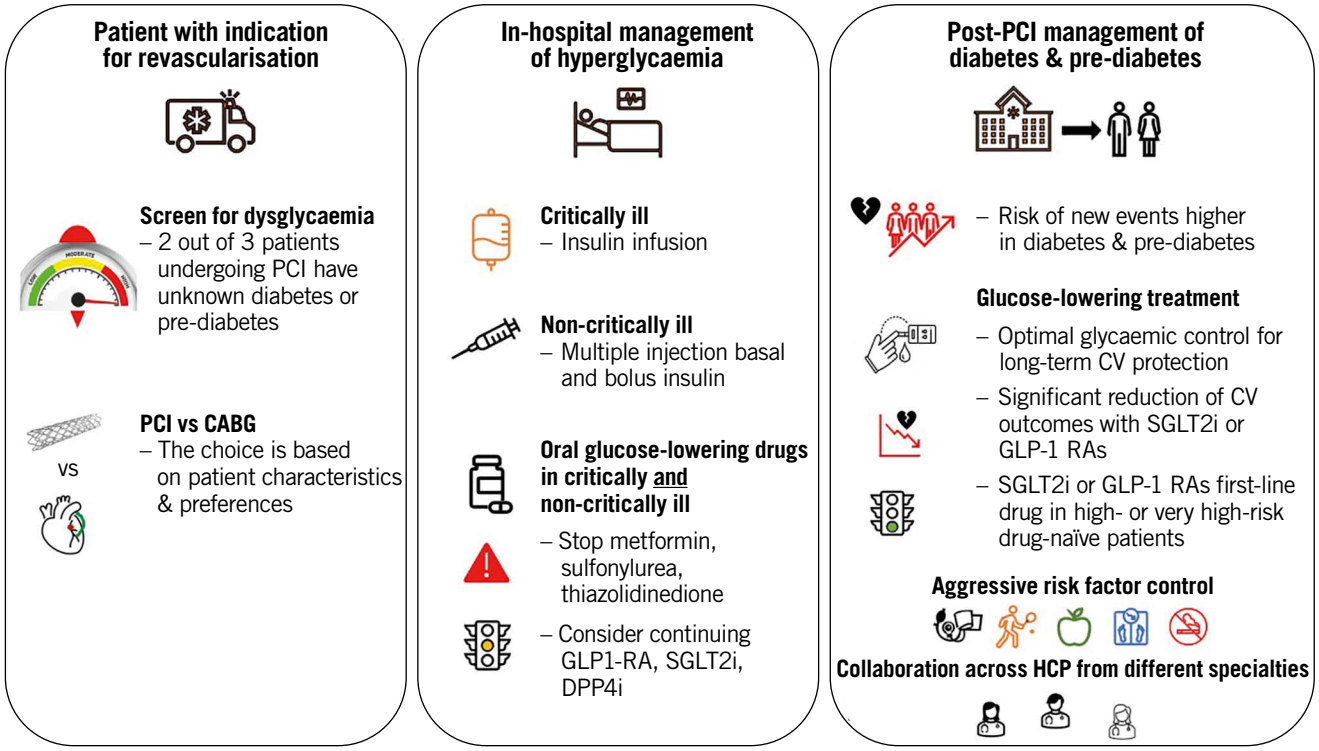

Central illustration. *Considerations relating to dysglycaemia in patients undergoing percutaneous coronary intervention. The left panel highlights that diabetes and pre-diabetes are overrepresented in patients undergoing percutaneous coronary intervention (PCI). Patients with an indication for revascularisation therefore should be screened for dysglycaemia at presentation and attention should be given to the most appropriate revascularisation method. The middle panel highlights important considerations for glucose-lowering therapy in these patients during and after PCI. The right panel highlights that patients with dysglycaemia have a higher risk of new events after PCI and points to the importance of optimal long-term control of dysglycaemia as well as other risk factors post PCI.*

accurate medical history allows the detection of the majority of cases of known diabetes in patients undergoing PCI. A determination of plasma glucose at hospital admission (irrespective of fasting) is mandatory for the detection of previously unknown diabetes. In the case of dysglycaemia at admission, further determinations of glycaemia at different times of the day will allow a better definition of the metabolic status of the patient. In case of dysglycaemia in patients without known diabetes, the determination of HbA1c allows the discrimination of diabetes from stress hyperglycaemia. An OGTT is recommended if HbA1c and/or fasting glucose are inconclusive[18]. Of note, in ACS the OGTT should not be performed earlier than 4-5 days after PCI to minimise false-positive results caused by stress hyperglycaemia, and may be performed during the polyclinic rehabilitation depending on the length of hospital stay[23,24].

Table 1. Criteria for the diagnosis of pre-diabetes and diabetes based on recommendations from the World Health Organization (WHO) and the American Diabetes Association (ADA)[20,21].

	Pre-diabetes	Diabetes
HbA1c	5.7-6.4% (39-47 mmol/mol)	≥6.5% (48 mmol/mol)[a]
Fasting plasma glucose	100-125 mg/dL (5.6-6.9 mmol/L)	≥126 mg/dL (7.0 mmol/L)[a]
2-hr glycaemia following a standard oral glucose tolerance test	140-199 mg/dL (7.8-11.0 mmol/L)	≥200 mg/dL (11.1 mmol/L)[a]
Random plasma glucose		≥200 mg/dL (11.1 mmol/L)[b]

[a]In the absence of unequivocal hyperglycaemia, diagnosis requires two abnormal test results from the same sample or in two separate samples. [b]Only diagnostic in a patient with symptomatic hyperglycaemia.

Indications for PCI in patients with T2DM

The indications for myocardial revascularisation, for both symptomatic and prognostic reasons, are the same in patients with diabetes as in patients without[18,25]. The anatomical pattern of CAD in diabetes influences prognosis and response to revascularisation. Patients with diabetes more frequently develop left main and multivessel critical stenoses, with diffuse disease also involving the small vessels[17,26,27]. Furthermore, common comorbidities of diabetes such as renal impairment and peripheral vascular disease adversely affect outcomes after coronary revascularisation[28-30]. Therefore, individual cardiac and extra-cardiac characteristics as well as patient preferences will determine when PCI is the appropriate revascularisation modality in patients with diabetes and CAD[18,25]. **Figure 1** outlines an algorithm for the recommended revascularisation modality in patients with diabetes based on the current European guidelines[18,25].

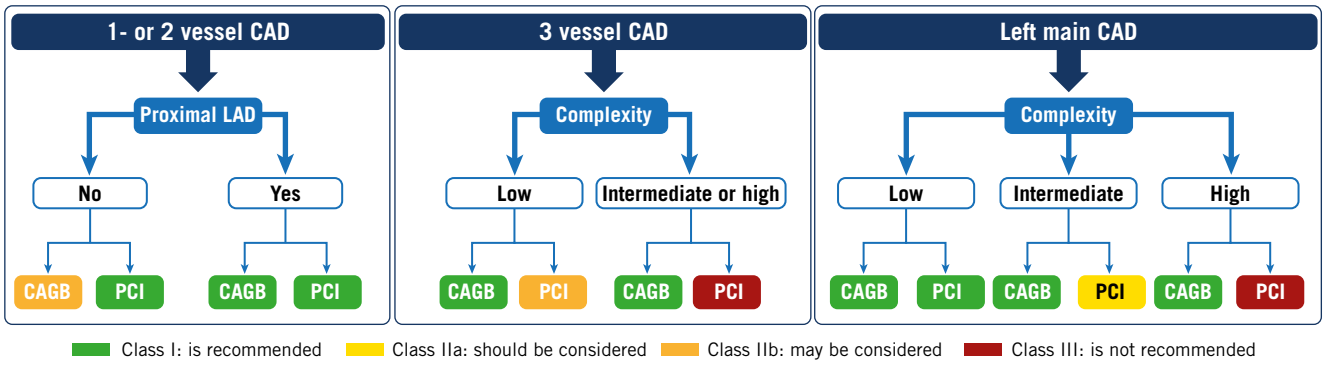

Figure 1. *Recommendations for coronary revascularisation adapted from the 2019 ESC guidelines on CVD and pre-diabetes and diabetes[18]. Low disease complexity coronary anatomy (SYNTAX score 0-22), intermediate disease complexity (SYNTAX score 23-32) and high disease complexity (SYNTAX score ≥33). CABG: coronary artery bypass graft; CAD: coronary artery disease; PCI: percutaneous coronary intervention*

Optimising glucose control during hospital admissions for ACS and elective PCI

AGGRESSIVE VERSUS NON-AGGRESSIVE GLUCOSE LOWERING

The benefits of an accurate glycaemic control in patients with diabetes and ACS was first demonstrated by the results of the DIGAMI trial, which showed that a more aggressive, insulin-based approach, compared with conventional treatment of hyperglycaemia at hospital admission and maintained long term, was associated with a significant reduction of mortality at 1, 3, and 5 years[31]. Notably, the trial results did not discriminate the benefits of accurate glycaemic control in the acute phase from those determined by the longer-term reduction of hyperglycaemia. Further, the differences in outcomes between the two arms could be attributed either to a positive effect of better glucose control, or to a beneficial action of insulin *per se*, or both. The DIGAMI-2 trial tried to address the limits of the DIGAMI trial by randomising patients to three treatment arms (intensified treatment in both the acute and chronic phase; intensified treatment in the acute phase only; conventional treatment)[32]. At the study's end however, glycaemic control was similar in the three groups and no difference in CV outcomes or mortality was demonstrated, leaving the question unanswered. Notably, the patients on intensified insulin treatment during hospitalisation and after discharge did not show better outcomes than the other two groups, where the majority of individuals received oral glucose-lowering drugs, suggesting that benefits of intensified insulin therapy are due to the improvement of glycaemic control, rather than to a direct effect of insulin *per se*[31,32]. Available data from trials in non-diabetic, normoglycaemic patients with ACS show that the intravenous infusion of insulin and glucose in the acute phase does not affect clinical outcomes[33,34], confirming that the benefits of intensified insulin treatment in ACS are entirely attributable to the reduction of hyperglycaemia and not to the glucose-independent protective effects of insulin.

The improvement of glucose control still has potential benefits both in the acute and chronic phases of coronary syndromes. However, as discussed above, the assessment of the effects of accurate glycaemic control during the acute phase is limited by the paucity of available data from randomised trials. Observational studies suggest that both hyperglycaemia and hypoglycaemia in the acute phase are associated with a poorer prognosis[35,36]. Randomised trials, often performed on patients in intensive care units with different medical conditions, and usually including patients with stress hyperglycaemia together with those with diabetes, have provided discordant results, with either reduced[37,38], unchanged[39], or increased[40] mortality. In addition, intensified glucose control reduced restenosis, without modifying mortality, in patients with diabetes undergoing PCI[41]. It is reasonable to believe that the results of each trial are determined by the balance between the benefits of improved glycaemic control and the risks of hypoglycaemic episodes induced by the intensification of therapy. For this reason, current guidelines recommend an accurate treatment of hyperglycaemia in ACS, providing therapeutic targets well above normoglycaemia, in order to minimise the risk of hypoglycaemia[17,42,43].

GLUCOSE-LOWERING AGENTS DURING PCI

Insulin is considered the drug of choice for the treatment of hyperglycaemia in the acute setting because of its pharmacokinetic and pharmacodynamic profile, allowing prompt correction of blood glucose levels[42]. Patients undergoing elective PCI may be treated either with intravenous insulin infusion or with multiple daily subcutaneous insulin injections, depending on their dietary regimen and glucose control[42]. Oral glucose-lowering treatments could theoretically affect the prognosis after PCI in patients with diabetes and should be given careful consideration both in the acute setting and when planning elective PCI. In those patients who are already treated with glucose-lowering agents at admission, some of the non-insulin drugs, such as sulfonylureas and thiazolidinediones, should be withdrawn for safety reasons. Metformin increases the risk of lactic acidosis in case of heart failure or renal failure[44]. The current recommendation is that metformin should be stopped prior to elective PCI in patients with renal failure[18,25]. However, the actual risk of lactic acidosis is minimal[45,46]; therefore, concern for

lactic acidosis in metformin-treated patients should not interfere with the clinical decision to perform primary PCI in patients with ACS[18,25]. Sulfonylureas are associated with a high risk of hypoglycaemia[47]; in addition, sulfonylureas reduce myocardial function in ischaemic conditions[48]. Thiazolidinediones induce fluid retention, exacerbating clinical manifestations of heart failure[49]. The possibility of maintaining a pre-existing treatment with DPP4 inhibitors, GLP-1 RAs or SGLT2 inhibitors is still controversial, with little available evidence of their effects in the acute phase. Pilot trials with GLP-1 agonists in the acute phase of coronary syndromes were inconclusive[50,51], whereas intervention studies with SGLT2 inhibitors are still ongoing.

GLUCOSE-LOWERING AGENTS DURING HOSPITAL STAY

Non-critically ill ACS patients who are able to eat regular meals may be treated either with intravenous insulin infusion or with multiple daily subcutaneous insulin injections, depending on their dietary regimen and glucose control. For patients with ACS who are critically ill, hyperglycaemia is usually managed via intravenous infusion of regular human insulin[42]. The determination of the insulin infusion rate is based on measurements of blood glucose (from samples of arterial, venous, or capillary blood). Several algorithms have been developed for the calculation of appropriate insulin doses[52-54].

Recovering patients who are able to eat regular meals can be shifted to standard basal-bolus insulin therapy with subcutaneous injections of rapid-acting insulin at meals and a single administration (usually at bedtime) of a long-acting insulin. In this latter approach, rapid-acting analogues are preferable to regular human insulin as bolus insulin, due to their superiority in post-prandial glucose control[55,56]; similarly, long-acting insulin analogues are preferable to NPH insulin for the lower risk of hypoglycaemia[57]. The accuracy in the determination of insulin doses depends on an appropriate frequency of glucose testing (usually, 5-6 tests daily); the use of devices for continuous monitoring of interstitial glucose could theoretically facilitate the management of insulin therapy, but it needs to be validated further[58].

The flow chart for the management of glycaemia in patients with ACS and in patients undergoing elective PCI is shown in **Figure 2**. Notably, although a large majority of patients are treated with insulin during hospitalisation, the pharmacological therapy for diabetes must be revised at discharge or shortly afterwards, in order to warrant a satisfactory glycaemic control and an optimal cardiovascular protection in the longer term.

Diabetes management post PCI

MULTIFACTORIAL TREATMENT

Following PCI, the rate of adverse events remains higher in patients with diabetes than in those with normal glucose metabolism. Hence, these patients will benefit from early identification and treatment of comorbidities and factors that increase CV risk[59]. Aggressive treatment of risk factors associated with hyperglycaemia is beneficial for long-term reduction of microvascular and macrovascular complications in T2DM as demonstrated by several trials, including the UKPDS, STENO 2, ADDITION and JDOIT3 studies[60-65]. From observational data provided by the Swedish National Diabetes Register, the excess risk of all-cause death, acute myocardial infarction (MI) and stroke, respectively, decreases by bringing each

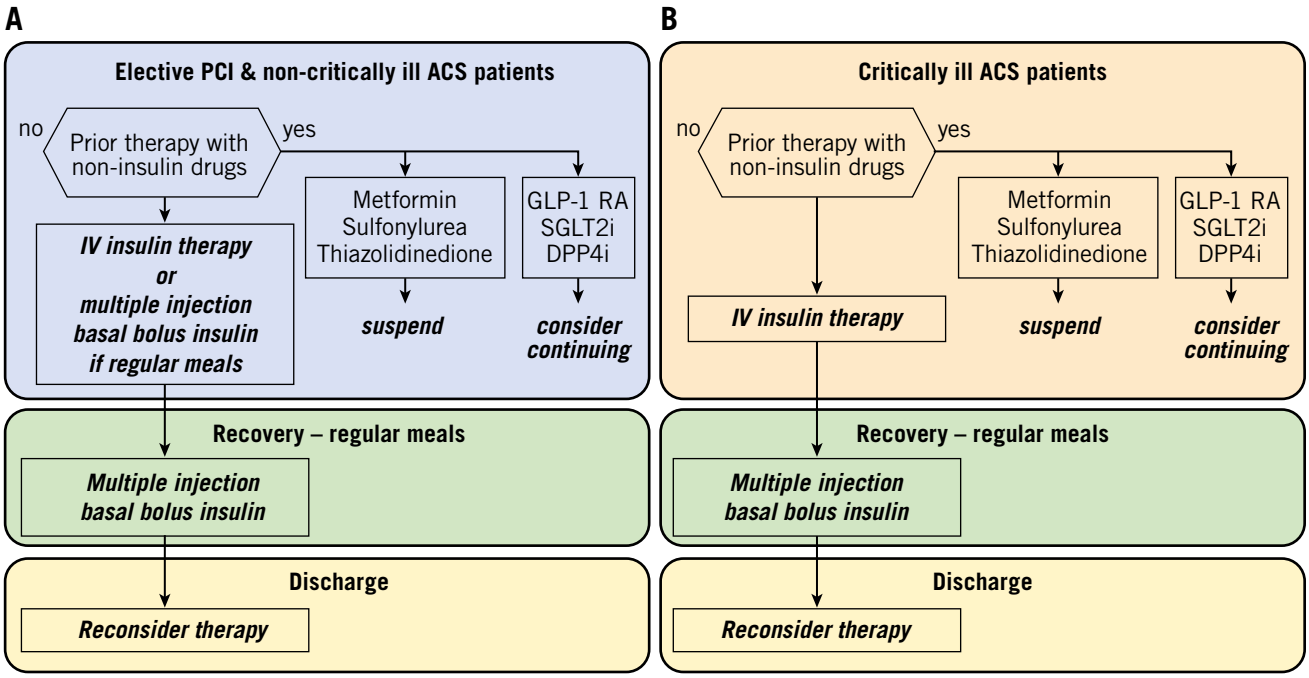

Figure 2. *Flow chart for the management of hyperglycaemia. A) In non-critically ill ACS patients and patients undergoing elective PCI. B) In critically ill ACS patients. ACS: acute coronary syndrome; DDP4: di-peptidyl peptidase 4; GLP-1 RA: glucagon-like peptide-1 receptor agonist; PCI: percutaneous coronary intervention; SGLT2: sodium-glucose transporter 2 inhibitor*

risk factor (HbA1c, low-density lipoprotein cholesterol [LDL-C], albuminuria, smoking, and systolic blood pressure [SBP]) within target range. Risk of heart failure (HF) hospitalisation consistently proved to be higher among patients with diabetes as compared with controls without (hazard ratio [HR] 1.45, 95% confidence interval [CI]: 1.34-1.57)[66]. The Euro Heart Survey found that, among 1,425 patients with known diabetes and CAD, the combination of aspirin, a beta-blocker, a renin-angiotensin-aldosterone system (RAAS) blocker, and a statin was associated with a significantly lower all-cause mortality (3.5 vs 7.7%; p=0.001) and incidence of CV events (11.6 vs 14.7%; p=0.05) after one year of follow-up[67]. Depending on individual risk level, the 2019 ESC guidelines on DM and CVD have set different recommended targets for risk factor control. Targets relating specifically to secondary prevention post revascularisation in patients with diabetes are outlined in **Table 2**[18].

Table 2. Treatment targets for managing patients with diabetes post coronary intervention adapted from the 2019 ESC Guidelines for CVD in diabetes or pre-diabetes[18].

Risk factor	Target
Blood pressure	– Target SBP 130 mmHg for most adults, <130 mmHg if tolerated, but not <120 mmHg – Less stringent targets, SBP 130-139 in older patients (>65 years)
Glycaemic control HbA1c	– HbA1c target for most adults is <7.0% (<53 mmol/mol) – More stringent HbA1c goals (e.g., <6.5% [48 mmol/mol]) may be suggested on a personalised basis if this can be achieved without significant hypoglycaemia or other adverse effects of treatment – Less stringent HbA1c goals (e.g., <8% [64 mmol/mol] or up to 9% [75 mmol/mol]) may be adequate for elderly patients.
Lipid profile: LDL-C	– Target LDL-C to <1.4 mmol/L (<55 mg/dL) and at least >50% reduction.
Platelet inhibition	To all patients with DM post coronary intervention.
Smoking	Cessation obligatory.
Physical activity	– Early after a coronary intervention, patients should be referred to an exercise-based cardiac rehabilitation for 8-12 weeks. – Following cardiac rehabilitation, the target is moderate to vigorous, ≥150 min/week, combined aerobic and resistance training. Individual adaptations may apply.
Weight	Aim for weight stabilisation in overweight or obese patients with DM.
Dietary habits	Reduction in caloric intake is recommended in obese patients with DM to lower body weight; there is no ideal percentage of calories from carbohydrate, protein, and fat for all people with DM.

BP: blood pressure; CV: cardiovascular; DM: diabetes mellitus; HbA1c: haemoglobin A1c; IGT: impaired glucose tolerance; LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure; T2DM: type 2 diabetes mellitus

GLUCOSE-LOWERING TREATMENT

Evidence indicates that improved glycaemic control defers the onset and reduces the progression of microvascular complications in diabetes. CV benefits from the use of glucose-lowering drugs in patients with macrovascular complications, including patients post PCI, have recently emerged from several cardiovascular outcome trials (CVOTs). Accordingly, early, effective, and sustained glycaemic control is advocated in the diabetes guidelines to mitigate the risks of hyperglycaemia[18]. The choice of treatment should be made with consideration of the balance between benefits induced by reduction of hyperglycaemia and harm determined by treatment side effects, particularly hypoglycaemia. Such a balance is determined by individual patient characteristics, and the pharmacological profile of the available treatment. In general, the more advanced the CVD, the older the patient, the longer the diabetes duration and the more comorbidities that are present, the less stringent the glucose control should be, because of the higher risk related to the adverse effects of treatment **(Table 2)**.

ESTABLISHED ORAL GLUCOSE-LOWERING DRUGS

CV effects of glucose-lowering agents have been extensively evaluated in clinical trials for newer drugs, but not for some long-established drugs. For example, there are no recent large-scale randomised CVOTs assessing the effect of metformin or sulfonylureas on CV events. The cardiovascular safety of sulfonylureas has been discussed for decades, because of the risk of hypoglycaemia, which induces sympathoadrenergic activation[68]. In addition, sulfonylureas interact directly with myocardiocytes, blocking an ATP-dependent potassium channel involved in myocardial adaptation to ischaemia[69]. Available clinical trials with sulfonylureas failed to produce significant effects (either detrimental or beneficial) on the incidence of major adverse cardiovascular events (MACE)[70-72]. Of note, combined data from all available randomised trials show an increase of all-cause mortality associated with sulfonylureas[71]. The alpha-glucosidase inhibitor acarbose did not alter MACE in patients with IGT and CVD over five years in the ACE trial[73]. The thiazolidinedione pioglitazone was neutral for the primary composite outcome. Despite a signal of reduced risk of subsequent MI or recurrent stroke, this drug should be avoided in patients with HF because of an increased risk of HF incidence[49,74-76]. A large, unblinded randomised comparison (TOSCA.IT) of pioglitazone versus sulphonylurea as add-on to metformin showed similar rates of the composite of MACE endpoint as well as its individual components; however, the trial was stopped for futility and, hence, results should be interpreted with caution[72]. Among long-established drugs for diabetes, insulin has been studied in several CV outcome trials. The results of studies performed in patients with diabetes and MI (i.e., DIGAMI and DIGAMI-2) have been reported above. In the UKPDS, long-term insulin treatment failed to provide a significant CV protection[70]; in another trial in high-risk patients, glargine insulin did not modify the incidence of major cardiovascular events[77].

NEWER ORAL GLUCOSE-LOWERING DRUGS

Following a meta-analysis of CV events with the thiazolidinedione rosiglitazone[78], the regulatory landscape for diabetes drugs underwent a major change in 2009[79]. Thereafter, all future diabetes drugs were required to demonstrate designated margins of

CV safety to achieve or maintain regulatory approval. As a consequence, a large number of trials to assess CV outcome were performed[80,81], most of which were designed to confirm non-inferiority of the experimental therapy versus placebo, added to background antihyperglycaemic treatment. Since the primary reason for performing these trials was the demonstration of safety, the study design was often not ideal for the detection of beneficial effects[82]. Despite these limitations, several CV safety trials have provided results suggesting that some of these drugs are capable of reducing CV complications substantially in patients with T2DM. These are summarised in **Table 3** and **Table 4**.

Five large prospective trials in T2DM populations with different baseline risk have assessed the CV effects of dipeptidyl peptidase 4 (DPP4) inhibitors: saxagliptin (SAVOR-TIMI 53)[70,83], alogliptin (EXAMINE)[84], sitagliptin (TECOS)[85], and linagliptin (CARMELINA and CAROLINA[86]) as reported to date. Four of the five trials confirmed statistical non-inferiority versus placebo (and alternative glucose-lowering therapy for glycaemic equipoise) for their primary composite CV outcome, but none of them showed significant CV benefits. Saxagliptin was associated with an increased risk of HF hospitalisation[83], especially in those with a high baseline NT-proBNP, pre-existing HF, or chronic kidney disease (CKD)[87], while there was a numerical, yet non-significant increase with alogliptin[84].

Seven CVOTs have examined the effect of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) on CV events in patients with DM and CVD: lixisenatide (ELIXA)[88], exenatide (EXSCEL)[73], liraglutide (LEADER)[89,90], injectable semaglutide (SUSTAIN-6)[91], oral semaglutide (PIONEER-6)[92], albiglutide (Harmony Outcomes trial, no longer marketed)[93] and dulaglutide (REWIND)[94]. A reduction in CV outcomes has been documented for liraglutide, injectable semaglutide and albiglutide. Liraglutide was associated with a reduction in both CV death and total mortality. Reductions in renal outcomes have been documented for liraglutide and injectable semaglutide[89,90]. A recent meta-analysis of these trials suggests that GLP-RAs reduce three-point MACE by 13% (HR 0.87, 95% CI: 0.83-0.92; p<0.001)[95]. Although the mechanisms by which some long-acting GLP-RAs reduce CV outcomes are still unclear, their effect could be partly mediated by direct vascular and cardiac action, beyond the improvement of traditional risk factors such as blood pressure and body weight[96]. Further, the gradual separation of the event curves in the trials suggests that the CV benefit is mediated by a reduction in atherosclerosis-related events.

Table 3. Trials with GLP1-RAs.

	CV OUTCOMES TRIALS IN T2DM						
	ELIXA	LEADER	SUSTAIN-6	EXSCEL	Harmony Outcomes	REWIND	PIONEER 6
Number of patients	6,068	9,340	3,297	14,752	9,463	9,901	3,182
Drug (dose)	Lixisenatide vs placebo 10-20 ug sc	Liraglutide vs placebo 1.8 mg sc	Semaglutide vs placebo 0.5 mg or 1.0 mg sc	Exenatide vs placebo 2 mg sc weekly	Albiglutide vs placebo 30 to 50 mg sc weekly	Dulaglutide vs placebo 1.5 mg sc weekly	Oral semaglutide vs placebo 14 mg
Inclusion criteria							
T2DM	100%	100%	100%	100%	100%	100%	100%
Cardiovascular	CVD	CVD or CKD or RF	CVD or CKD or RF	CVD, CHD or RF	CVD or RF	CVD or RF	CVD or CKD or RF
Renal	eGFR ≥30	N/A	N/A	eGFR ≥30	eGFR ≥30	eGFR ≥15	eGFR ≥30
Cardiovascular outcomes (HR)							
Follow-up (years)	2.1	3.8	2.1	3.2	1.6	5.4	1.3
MACE	1.02 (0.89-1.17)	0.87 (0.78-0.97)	0.74 (0.58-0.95)	0.91 (0.83-1.00)	0.78 (0.68-0.90)	0.88 (0.79-0.99)	0.79 (0.57-1.11)
Death (any cause)	0.94 (0.78-1.13)	0.85 (0.74-0.97)	1.05 (0.74-1.50)	0.86 (0.77-0.97)	0.95 (0.79-1.16)	0.90 (0.80-1.01)	0.51 (0.31-0.84)
Death (CV)	0.98 (0.78-1.22)	0.78 (0.66-0.93)	0.98 (0.65-1.48)	0.88 (0.76-1.02)	0.93 (0.73-1.19)	0.91 (0.78-1.06)	0.49 (0.27-0.92)
HHF	0.96 (0.75-1.23)	0.87 (0.73-1.05)	1.11 (0.77-1.61)	0.94 (0.78-1.13)	N/A	0.93 (0.77-1.12)	0.86 (0.48-1.55)
Renal outcomes (HR)							
Composite renal	N/A	N/A	1.28 (0.64-2.58)	N/A	N/A	0.85 (0.77-0.93)[b]	N/A
Loss of renal function	N/A	0.78 (0.67-0.92)[a]	1.28 (0.46-0.88)	N/A	N/A	N/A	N/A
ESRD	N/A	N/A	0.91 (0.40-2.07)	N/A	N/A	N/A	N/A
Acute kidney injury	N/A	N/A	N/A	N/A	0.87 (0.75-1.02)	N/A	N/A

[a]Nephropathy: defined as the new onset of macroalbuminuria or a doubling of the serum creatinine level and an eGFR of ≤45 ml per minute per 1.73 m^2, the need for continuous renal replacement therapy, or death from renal disease. [b]New macroalbuminuria, a sustained decline in estimated glomerular filtration rate of 30% or more from baseline, or chronic renal replacement therapy. CKD: chronic kidney disease >stage 3; CVD: cardiovascular disease; eGFR: estimated glomerular filtration rate; ELIXA: Evaluation of Lixisenatide in Acute Coronary Syndrome; ESRD: end-stage renal disease; EXSCEL: Exenatide Study of Cardiovascular Event Lowering; GLP1-RA: glucagon-like peptide-1 receptor agonist; Harmony Outcomes: albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease; HHF: hospitalisation for heart failure; HR: hazard ratio; LEADER: Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results; MACE: major adverse cardiovascular events (composite of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke); MI: myocardial infarction; N/A: not available; PIONEER 6: A Trial Investigating the Cardiovascular Safety of Oral Semaglutide in Subjects With Type 2 Diabetes; PVD: peripheral vascular disease; REWIND: Researching Cardiovascular Events With a Weekly Incretin in Diabetes; RF: risk factors; SUSTAIN-6: Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes; T2DM: type 2 diabetes mellitus

Table 4. Trials with SGLT2 inhibitors.

	CV OUTCOMES TRIALS IN T2DM				RENAL TRIALS			HF TRIALS		
	EMPA-REG OUTCOME	VERTIS-CV	CANVAS Program	DECLARE-TIMI58	CREDENCE	DAPA-CKD	SCORED	DAPA-HF	EMPEROR-reduced	SOLOIST-WHF
Number of patients	7,020	8,246	10,142	17,160	4,401	4,304	10,584	4,744	3,730	1,222
Drug	Empagliflozin vs placebo 25 or 10 mg	Ertugliflozin vs placebo 5 or 15 mg	Canagliflozin vs placebo 300 or 100 mg	Dapagliflozin vs placebo 10 mg	Canagliflozin vs placebo 100 mg	Dapagliflozin vs placebo 10 mg	Sotagliflozin vs placebo 400 mg	Dapagliflozin vs placebo 10 mg	Empagliflozin vs placebo 10 mg	Sotagliflozin vs placebo 400 mg
Inclusion criteria										
T2DM	100%	100%	100%	100%	100%	68%	100%	42%	50%	100%
Cardiovascular	CVD	CVD	CVD or RF	CVD or RF	–	No	CVD or RF	HFrEF, NYHA II-IV High NT-proBNP	HFrEF, NYHA II-IV High NT-proBNP	HF admission, any EF High NT-proBNP, oral diuretics
Renal	eGFR >30	eGFR ≥30	eGFR >30	eGFR >60	eGFR 30-90	eGFR 25-75	eGFR 25-60	eGFR ≥30	eGFR ≥20	N/A
Cardiovascular outcomes (HR)										
Follow-up (years)	3.1	3.5	2.4	4.2	2.62	2.4	1.3	1.52	1.33	0.75
MACE	0.86 (0.74-0.99)	0.97 (0.85-1.11)	0.86 (0.75-0.97)	0.93 (0.84-1.03)	0.80 (0.67-0.95)	N/A	N/A	N/A	N/A	0.72 (0.56-0.92)
Death (any cause)	0.68 (0.57-0.82)	N/A	0.87 (0.74-1.01)	0.93 (0.82-1.04)	0.83 (0.68-1.02)	0.69 (0.53-0.88)	0.99 (0.83-1.18)	0.83 (0.71-0.97)	0.92 (0.77-1.10)	0.82 (0.59-1.14)
Death (CV)	0.62 (0.49-0.77)	0.92 (0.77-1.11)	0.87 (0.72-1.06)	0.98 (0.82-1.17)	0.78 (0.61-1.00)	0.81 (0.58-1.12)	0.90 (0.73-1.12)	0.82 (0.69-0.98)	0.92 (0.75-1.12)	0.84 (0.58-1.22)
HHF	0.65 (0.50-0.85)	0.70 (0.54-0.90)	0.67 (0.52-0.87)	0.73 (0.61-0.88)	0.61 (0.47-0.80)	0.71 (0.55-0.92)	0.67 (0.55-1.82)[c]	0.70 (0.59-0.83)	0.69 (0.59-0.81)	0.64 (0.49-0.83)
Renal outcomes (HR)										
Composite renal*	0.54 (0.40-0.75)	0.81 (0.63-1.04)	0.60 (0.47-0.77)	0.53 (0.43-0.66)	0.66 (0.53-0.81)	0.56 (0.45-0.68)	0.71 (0.46-1.08)	0.71 (0.44-1.16)	0.50 (0.32-0.77)	N/A
Loss of renal function	0.56 (0.39-0.79)[a]	N/A	0.50 (0.30-0.84)[b]	0.54 (0.43-0.67)[a]	0.60 (0.48-0.76)[a]	0.53 (0.42-0.67)	N/A	N/A	N/A	N/A
ESRD	0.45 (0.21-0.97)	N/A	0.77 (0.30-1.97)	0.31 (0.13-0.79)	0.68 (0.54-0.86)	0.64 (0.50-0.82)	N/A	N/A	N/A	N/A
Acute kidney injury	0.76 (0.62-0.93)	N/A	0.66 (0.39-1.11)	0.69 (0.55-0.87)	0·85 (0·64-1·13)	N/A	N/A	N/A	N/A	N/A

*Composite renal outcomes defined as substantial loss of kidney function (doubling serum creatinine or 40% decrease in eGFR), ESRD (dialysis, transplantation, or a sustained eGFR of <15 ml/min/1.73m^2) or renal death. [a]Defined as doubling serum creatinine. [b]Defined as 40% eGFR reduction. [c]Composite endpoint hospitalisation for heart failure or cardiovascular death. CANVAS: Canagliflozin Cardiovascular Assessment Study; CKD: chronic kidney disease >stage 3; CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation trial; CV: cardiovascular; CVD: cardiovascular disease; DAPA-CKD: The Dapagliflozin And Prevention of Adverse outcomes in Chronic Kidney Disease; DAPA-HF: Study to Evaluate the Effect of Dapagliflozin on the Incidence of Worsening Heart Failure or Cardiovascular Death in Patients With Chronic Heart Failure; DECLARE–TIMI 58: Dapagliflozin Effect on Cardiovascular Events? Thrombolysis In Myocardial Infarction 58 trial; eGFR: estimated glomerular filtration rate; EMPA-REG OUTCOME: Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients-Removing Excess Glucose, EMPEROR-Reduced, ESRD: end-stage renal disease; HHF: hospitalisation for heart failure; HR: hazard ratio; MACE: major adverse cardiovascular events (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke; N/A: not available; SCORED: Effect of Sotagliflozin on Cardiovascular and Renal Events in Patients With Type 2 Diabetes and Moderate Renal Impairment Who Are at Cardiovascular Risk; SOLOIST-WHF: Effect of Sotagliflozin on Cardiovascular Events in Patients With Type 2 Diabetes Post Worsening Heart Failure; T2DM: type 2 diabetes mellitus; VERTIS-CV: Cardiovascular Outcomes Following Ertugliflozin Treatment in Type 2 Diabetes Mellitus Participants With Vascular Disease

Four CVOTs with sodium glucose transporter-2 (SGLT2) inhibitors, empagliflozin (EMPA-REG OUTCOME)[97], canagliflozin (CANVAS)[98], dapagliflozin (DECLARE–TIMI 58 trial)[99], and ertugliflozin (VERTIS-CV)[100], plus three trials on renal events with canagliflozin (CREDENCE)[101], dapagliflozin (DAPA-CKD)[102] and sotagliflozin (SCORED)[103] respectively, have been performed to date. CV benefits have been observed for three-point MACE for empagliflozin and canagliflozin; empagliflozin additionally showed mortality benefit, whereas all five agents have shown reductions in HF hospitalisation[98,99,101,104,105]. In addition, this class of drugs has been shown to have salutatory effects on renal function. It is believed that the CV benefits of SGLT2 inhibitors are mostly unrelated to the extent of glucose lowering and occur too early to be the result of weight reduction. Instead, the achieved beneficial effects more likely result from a reduction in HF-associated events. This is further supported by two recent superiority trials, DAPA-HF[106] and EMPEROR-reduced[107], in which patients with HF and reduced ejection fraction with and without DM were randomised to dapagliflozin or empagliflozin versus placebo, respectively. Both trials showed reductions of HF hospitalisation, irrespective of diabetes status[106,107]; in addition, a reduction of mortality was observed with dapagliflozin[106].

Further, the SOLOIST-WHF trial[108], although ended prematurely due to lack of funding, showed that sotagliflozin versus placebo was safe and beneficial in patients with diabetes and acute HF, irrespective of whether the patient had reduced or preserved ventricular function. The underlying mechanisms for SGLT2 inhibitor cardioprotective effects are not the object of the present article and remain to be fully elucidated[109-112].

IMPLICATIONS OF RECENT CVOTs

Based on the available evidence, SGLT2 inhibitors and GLP-1 RAs are considered the best options for the long-term treatment of T2DM in patients with established atherosclerotic CVD or at high/very high CV risk. These drugs are safe, effective, and generally well tolerated and can be started already during the hospitalisation for ACS or elective PCI, if indicated. Data from trials with liraglutide and empagliflozin suggest that at least some of the drugs of these two classes could also reduce mortality. Benefits with GLP-1 RAs seem to be related to an anti-atherosclerotic effect, whereas SGLT2 inhibitors appear to reduce HF-related endpoints and have specific advantages in patients with or at high risk for HF. Although the trial-based evidence for metformin monotherapy from UKPDS is not as strong as with the novel drugs tested in recent CVOTs, it is supported by extensive observations from everyday clinical practice[70,113-115]. There are a few precautions that should be kept in mind when selecting candidates for SGLT2 inhibitors and GLP1-RAs, respectively, in order to limit the risk of unexpected adverse events, as summarised in **Table 5**.

Table 5. Practical tips for the use of SGLT2 inhibitors and GLP-1 receptor antagonists.

	SGLT2i	GLP-1 RA
Avoid in case of	Recurrent genital infections	Pancreatitis
Beware of	Risk of ketoacidosis (avoid ketogenic diets)	Frequent initial nausea (dose titration with some agents)
Adjust doses of	Insulin (risk of severe hypoglycaemia) Diuretics (risk of dehydration)	Insulin (risk of severe hypoglycaemia)

In a 2018 Consensus Report by the American Diabetes Association (ADA) and the EASD, metformin was confirmed as first-line drug, with SGLT2 inhibitors and GLP-1 RA as preferred add-on treatments in patients at high cardiovascular risk in case of inadequate control on monotherapy[16]. In 2019, ESC guidelines recommended the use of SGLT2 inhibitors or GLP-1 RAs as first-line drugs in CV patients at high or very high risk with T2DM who do not receive any glucose-lowering treatment and the addition to current glucose-lowering therapy of SGLT2 inhibitors or GLP-1 RAs in those patients regardless of glucose control **(Figure 3)**[18]. The 2020 ADA/EASD Consensus Report, in agreement with ESC guidelines, confirmed that current glucose-lowering therapy has to be integrated either with GLP-1 RA or SGLT2 inhibitors, irrespective of the achievement of glucose targets **(Table 6)**[19]. These apparent differences are mainly theoretical, considering that the vast majority of patients need more than one drug in order to achieve an acceptable glucose control.

Conclusion

The number of individuals with diabetes and pre-diabetes is constantly increasing. Given that these conditions are overrepresented in patients with an indication for coronary revascularisation, it is important that colleagues stay up to date. We have outlined the current state of the art related to glucose lowering in patients with diabetes undergoing PCI. An accurate glycaemic control in the acute phase of ACS is a relevant factor for the improvement of longer-term outcomes. In addition, appropriate pharmacological therapy, including some newer drugs, for glucose control in the longer term can have a remarkable impact on recurrence of events, hospitalisations for heart failure and mortality and should be considered early in the patient's disease trajectory. Extensive research efforts have led to improved outcomes for patients with dysglycaemic states in recent decades. Still, the rate of adverse events remains higher in patients with diabetes following PCI. Some important open issues that future research efforts must address are the following:

1. Optimal glycaemic control for the outcome of ACS, CCS and post-coronary revascularisation interventions remains to be established.
2. The role of hypoglycaemia in the occurrence of CV events/mortality remains to be fully elucidated.
3. Further trials with SGLT2 inhibitors and GLP-1 RAs in patients with coronary syndromes/undergoing PCI without diabetes would eventually provide further knowledge as to the potential benefits of these drugs irrespective of glucose control, possibly expanding their present indications.

Table 6. Comparison of 2018 ADA/EASD, 2019 ESC and 2020 ADA/EASD recommendations for the long-term treatment of type 2 diabetes mellitus in patients with established or at high/very high risk for atherosclerotic cardiovascular disease (ASCVD).

	First-line drug(s) in drug-naïve patients	Add SGLT2i/GLP-1 RA to current glucose-lowering drugs irrespective of glucose control
2018 ADA/EASD Consensus Report[16]	Metformin	No
2019 ESC Guidelines[18]	SGLT2i, GLP-1 RA	Yes
2020 ADA/EASD updated Consensus Report[19]	Metformin	Yes

Conflict of interest statement

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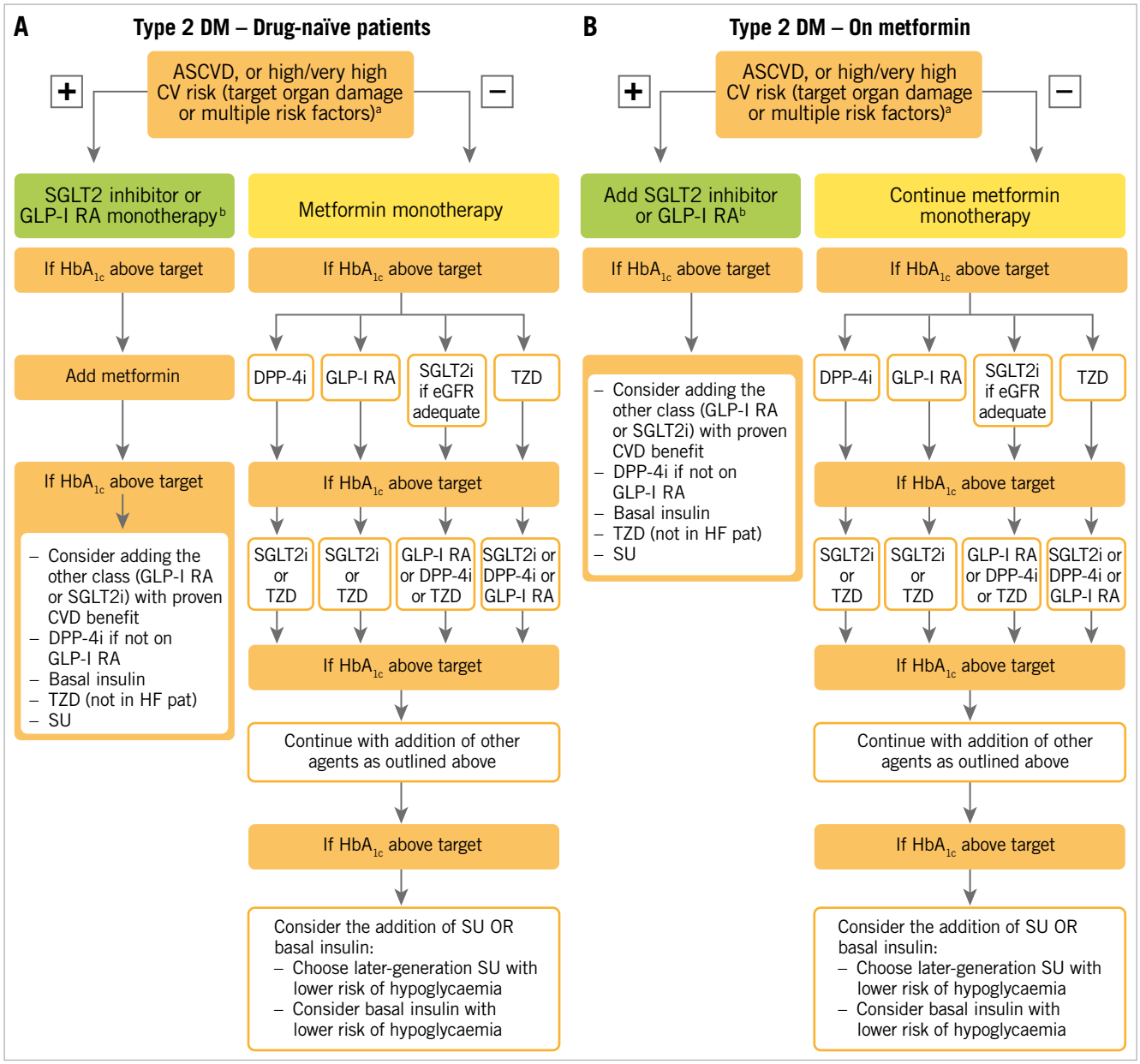

Figure 3. *Treatment algorithm in patients with T2DM and ASCVD or high/very high CV risk. A) Drug-naïve patients. B) Metformin-treated patients. Treatment algorithm proposed by the 2019 ESC guidelines on CVD, pre-DM and DM, reproduced from reference 18 with permission from Oxford University Press on behalf of the European Society of Cardiology. ASCVD: atherosclerotic cardiovascular disease; CV: cardiovascular; CVD: cardiovascular disease; DPP4i: dipeptidyl peptidase-4 inhibitor; eGFR: estimated glomerular filtration rate; GLP1-RA: glucagon-like peptide-1 receptor agonist; HbA1c: haemoglobin A1c; SGLT2i: sodium-glucose co-transporter-2 inhibitor; T2DM: type 2 diabetes mellitus; TZD: thiazolidinedion*

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