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CARDIOVASCULAR RISK MANAGEMENT IN DIABETES MELLITUS INSIGHTS INTO PREVENTION AND TREATMENT OF CORONARY ARTERY DISEASE

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Abstract:
Background: Coronary artery disease (CAD) stands as the predominant cause of morbidity and mortality among individuals with diabetes mellitus. Concurrent risk factors in these patients accentuate cardiovascular risks, necessitating a comprehensive approach to their management.

Objectives:
1. To explore primary preventive measures, emphasizing lifestyle modifications and risk factor control, aimed at averting the onset of CAD in diabetic individuals.
2. To review recent clinical research elucidating indications for contemporary anti-diabetic therapies and distinctive considerations in coronary revascularization for diabetic patients.

Methods: The study encompasses a literature review focusing on preventive strategies and recent advancements in anti-diabetic treatments. Emphasis is placed on collaborative care involving cardiologists, endocrinologists, general practitioners, and nephrologists for comprehensive patient management.

Results: The findings highlight the importance of a multidisciplinary approach in addressing CAD risks in diabetic patients. Lifestyle interventions and stringent risk factor management emerge as pivotal in primary prevention. Furthermore, the study presents contemporary insights into anti-diabetic treatments and nuances in coronary revascularization tailored for this patient population.

Conclusion: The evolving role of cardiologists in the care of diabetic patients underscores the imperative for collaborative, holistic management strategies. Integrating the latest research findings with interdisciplinary expertise is crucial in optimizing outcomes for diabetic individuals at risk for CAD.

Keywords: SGLT2 inhibitors, GLP1 analogues, coronary revascularization, diabetes mellitus, coronary artery disease, cardiovascular risk.

INTRODUCTION:

Currently, one of the most common chronic diseases in the world is diabetes mellitus, which is also a global epidemic. 2014, there were 422 million diabetes patients worldwide, up from 108 million in 1980, according to the World Health Organization's (WHO) most recent World Report on Diabetes in 2016. According to estimates, 1.6 million deaths in 2016 could have been caused directly by diabetes. Diabetes is a significant risk factor for cardiovascular disease (CV) and is commonly accompanied by additional risk factors: 75-85% of diabetic patients have arterial hypertension, 80% have dyslipidemia, and 60-70% are obese. As a result, cardiovascular problems are the leading killer [1].

Diabetes is linked explicitly to a higher risk of developing coronary artery disease (CAD), which manifests at a younger age. According to estimates, clinical illness may manifest up to 15 years earlier in diabetic patients than non-diabetic people. Additionally, CD is more aggressive in people with diabetes, increasing the risk of stent thrombosis, recurrent myocardial infarction, stroke, and cardiovascular death. In non-diabetic patients, atherosclerosis begins with endothelial dysfunction; in diabetic patients, it develops due to insulin resistance and hyperglycemia. Both originated in decreased nitric oxide synthesis, an antiatherogenic factor and increased plasminogen activator inhibitor (PAI-1) production [2].

acsAdditionally, oxidative stress and an accumulation of free radicals by hyperglycemia harm the proteins, lipids, and nucleic acids of smooth muscle and endothelial cells. Through the migration of inflammatory cells, increased vascular permeability, impaired endothelium-dependent vasodilation, malfunction of endothelial progenitor cells, and endothelial cell death, accumulation of advanced glycation products also contributes to vascular damage. Currently, it is the responsibility of the cardiologist to be knowledgeable about the specifics of celiac disease in people with diabetes and to stay current on the methods available to reduce the risk of these patients [3].

Given the severity of the issue, a great deal of clinical research has been done recently, and clinical practice guidelines have been developed across several specialties to obtain agreement and optimize interdisciplinary care [4].

CORONARY DISEASE PREVENTION IN DIABETIC PATIENTS:

Our first focus should be to successfully prevent the onset of celiac disease, using the arsenal of preventative measures at our disposal and pouring our efforts into its care. The diabetic patient is the model for those who benefit from a comprehensive lifestyle intervention, both for those with full-blown celiac disease and those at risk of developing it. Diabetes is a condition in which many CV risk factors tend to converge. On the other hand, it's essential to actively stop people from going from pre-diabetes to diabetes [5].

Table 1: The benefits of exercise for diabetic individuals' hearts	
Hemodynamic effects	decreased heart rate Decreased blood pressure Increased maximal oxygen consumption Increased vagal tone decreased sympathetic activity
Anti-ischemic effects	Increased coronary flow

	Decreased myocardial oxygen demand Decreased endothelial dysfunction increased nitric oxide
Antithrombotic effects	decreased fibrinogen decreased blood viscosity Fibrinolysis potentiation Decreased platelet adhesiveness Decreased inflammatory markers
Effects on other associated risk factors	HDL increased, triglycerides decreased decreased adiposity Weightloss
**HDL: high-density lipoproteins*	

Lifestyle

Physical exercise

Higher levels of physical activity were related to decreased mortality and lower CV risk in the prospective EPIC study, which has demonstrated that physical activity can improve glycemic management and prevent CV complications. According to the Look AHEAD study, patients with type 2 diabetes who engaged in regular physical activity lost weight, had higher levels of high-density lipoprotein cholesterol (HDL-C), had lower levels of glycosylated hemoglobin (HbA1c), and required fewer antihypertensives, hypoglycemic, and lipid-lowering medications. He could not show a decline in CV events, perhaps due to lessened use of cardioprotective medication. The cardioprotective benefits of regular exercise are listed in Table 1 [6].

Diet

A balanced diet emphasizing fruit, vegetables, grains, and skimmed dairy products is often advised. A predetermined set of diabetic patients with similar outcomes were enrolled in the randomized PREDIMED trial, which showed a 30% reduction in cardiovascular risk in individuals following a Mediterranean diet. The effectiveness of a low-carb diet is still debatable; a recent meta-analysis revealed short-term improvements in glycemic control but no long-term differences in weight loss, glycemic control, or LDL cholesterol levels [7].

Loss of weight

The Italian IDES trial and the Look AHEAD study both showed improved factor control regarding weight loss [8].

cardiovascular

Although quitting smoking leads to weight gain afterward, a 2013 prospective analysis showed that this weight gain does not reduce cardiovascular risk [9].

MANAGEMENT OF RISK FACTORS:

Hypertension

In diabetic patients, antihypertensive treatment lowers the risk of CV events. In patients over 65 years of age, a target of 130-140 mmHg is advised if adequately tolerated; additionally, diabetic patients should maintain systolic blood pressure > 120 mmHg and diastolic blood pressure (DBP) > 80 mmHg, according to the most recent European Cardiology (E.S.C.) guidelines on diabetes, pre-diabetes, and cardiovascular diseases from 2019. Systolic blood pressure reductions under 130 mmHg were related to benefits but at the cost of increased cerebrovascular events. There was no discernible drop in other types of events [10].

In patients with end-organ damage, it is advised to pick an ACEI/ARA II over another antihypertensive medication. Diuretics and beta-blockers should not be used together in people with pre-diabetes since they may accelerate the onset of diabetes [11].

Lipid regulation

LDL cholesterol (LDL-C) targets 100 mg/dl in diabetic patients with moderate CV risk, 70 mg/dL and at least 50% reduction in patients at high CV risk, and 55 mg/dL and at least 50% reduction in patients with very high CV risk are all recommended by the most recent European guidelines. Also advised are HDL-C levels of 85 mg/dl in cases of extremely high risk and 100 mg/dl in patients with increased CV risk. Statins are still our primary instrument for achieving these objectives. They are typically well tolerated; myalgias are uncommon but should be avoided in pregnant women [12].

Although the potential CV benefit outweighs the potential CV risk associated with statin usage, diabetes linked with statin therapy is associated with the patient's age and prior risk. European guidelines advocate combination treatment with ezetimibe if objectives cannot be met with the maximally tolerated dose of statins. In case of statin resistance or continuation of increased LDL-cholesterol levels despite combination treatment, the guidelines advise using P.C.S.K. inhibitors. According to recommendations from the American Diabetes Association (A.D.A.) and S.E.C., Figure 1 illustrates the individualization of glycemic targeting in diabetic patients based on their baseline characteristics [13].

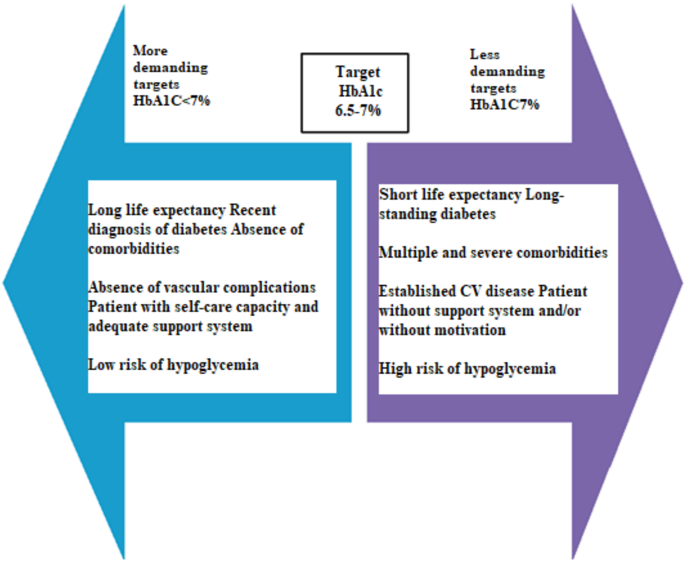

Figure 1. *Individualization of the glycemic target in diabetic patients according to their baseline characteristics, based on the recommendations of the American Diabetes Association (A.D.A.) and S.E.C.*

Antiplatelet therapy

The use of aspirin in the context of primary prevention is still debatable. In the recent ASCEND research, 15,480 patients with diabetes who had no CV illness were randomly assigned to receive or not receive 100 mg of aspirin daily. Aspirin use was related to a decreased risk of CV events, but an increased risk of severe bleeding balanced it. Only 1 in 4 patients in this trial were taking a proton pump inhibitor, which could augment the benefits of aspirin if used by these individuals. The use of low-dose aspirin is still the preferred method for secondary prevention [14].

In some diabetic patients after acute coronary syndrome, dual aspirin and ticagrelor or prasugrel therapy are more effective than dual aspirin and clopidogrel therapy. In a recent study, the T.H.E.M.I.S. trial, diabetic patients with Crohn's disease taking aspirin were randomly assigned to receive long-term (for 40 months) ticagrelor or a placebo. The ticagrelor group showed a lower risk of CV death, myocardial infarction, and stroke but at the cost of a higher risk of significant bleeding. Therefore, most diabetes patients today would not benefit from such a treatment. However, some individuals with higher ischemia risk and lower bleeding risk may find it interesting [13, 15].

GLUCOSE MANAGEMENT:

A definite advantage of strict glycemic control on macrovascular problems has not been proven, even though it has regularly been linked to reduced microvascular complications. While the Spanish Society of Cardiology supports tighter standards, proposing HbA1c 6.5% if there is no danger of hypoglycemia, European guidelines indicate a target of HbA1c 7% (Figure 1). The following sections further explain the suggested prescription drugs to achieve optimal glycemic control [16].

Table 2: Lists the findings of the primary clinical trials on iSGLT2 for CV safety

	EMPA-REG OUTCOME	CANVAS	DECLARE 58
Drug (vs. placebo)	Empaglyphozine	Canaglyphozine	Dapaglyphozine
Continuation (years)	3.1	2.4	4.5
Use of metformin (%)	74	77	82
Prevalence of sickness CV (%)	99	65	40
MACE (CV death, myocardial infarction, ischemic stroke) (H.R.H.R. [95% CI])	0.86 (0.74-0.99)	0.86 (0.75-0.97)	0.93 (0.84-1.03)
Myocardial infarction (H.R.H.R. [95% CI])	0.87 (0.70-1.09)	0.89 (0.73-1.09)	0.89 (0.77-1.01)
Death CV (H.R.H.R. [95% CI])	0.62 (0.49-0.77)	0.87 (0.72-1.06)	0.98 (0.82-1.17)

**CV: cardiovascular. H.R.H.R.: hazard ratio. 95%CI: 95% confidence interval*

CORONARY HEART DISEASE IN DIABETIC PATIENTS MANAGEMENT:

Treatment for diabetes

Glycemic control has always been the cornerstone of treating diabetes, traditionally viewed as a condition owing to elevated glucose levels. As was already indicated, showing a discernible decrease in CV events has not been feasible due to tight glycemic management, in contrast to microvascular problems. A significant shift in the treatment of diabetes has resulted from the recent discovery of molecules that show a decrease in cardiovascular events. Because current medicines must go beyond glycemic management, it has become vital to revisit pharmacological treatments to confirm their safety and cardiovascular benefits [17].

The most recent European guidelines and the 2018 A.C.C. expert consensus document already open this avenue. It is vital to reassess the traditionally used algorithms and prioritize those medications that imply a cardiovascular advantage for the coronary patient. We will now review the necessary anti-diabetic drugs that have reduced the risk of cardiovascular disease [18].

SGLT2 blockers

One of the primary anti-diabetic treatments is SGLT2 inhibitors (iSGLT2). 90% of glucose reabsorption is carried out by the sodium and glucose cotransporter SGLT2 found in the proximal tubule. Its blockage results in glycosuria, which lowers blood glucose, but it also has diuretic and natriuretic effects, weight loss, and a drop in blood pressure. Table 2 presents the findings of the three significant clinical trials using SGLT2-i on CV safety that have been reported to date (EMPA-REG, CANVAS, and DECLARE-TIMI). Studies were carried out either exclusively on diabetic individuals with established CV disease (EMPA-REG) or on diabetic patients with high CV risk or established CV disease (CANVAS and DECLARE-TIMI) [19].

Empagliflozin showed a 14% decrease in the primary MACE endpoint (CV death, non-fatal myocardial infarction, and ischemic stroke) in the EMPA-REG study, predominantly at the expense of a 38% decrease in CV death. On the other hand, the CANVAS research showed a 14% reduction in the same primary objective with canagliflozin but no appreciable drop in CV mortality. Dapaglizofine showed non-inferiority in the primary endpoint of the DECLARE-TIMI2 study, but it failed to attain statistical significance in the primary endpoint of MACE. According to a meta-analysis of the three studies, these medications lower the risk of CV death in diabetes individuals generally but only in those who already have established CV disease [20].

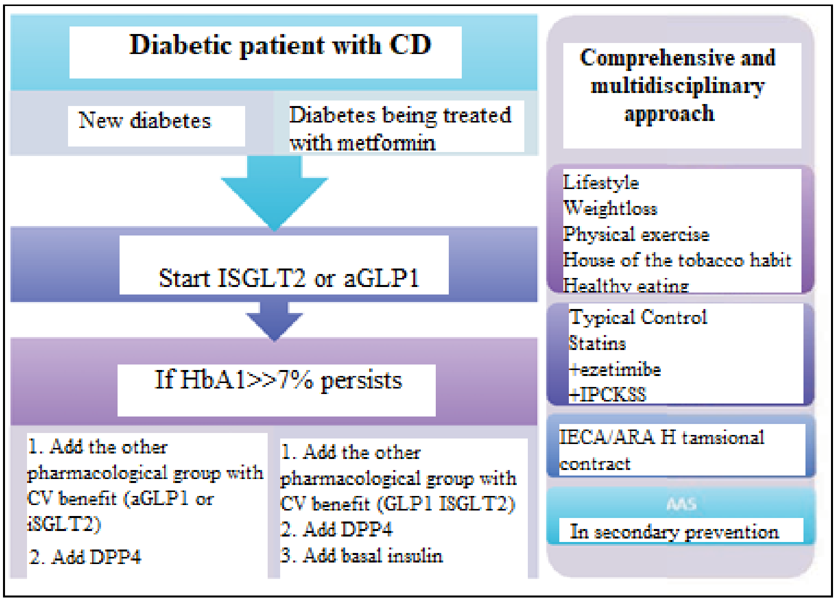

Figure 2: *Treatment algorithm for diabetic patients with coronary disease (CD).*

GLP1 equivalents

Seven sizable randomized clinical trials have been conducted to examine the CV effects of GLP1 (aGLP1) analogues. Among them, the LEADER study with liraglutide showed a significant reduction of 13% in the combined primary endpoint of CV mortality, stroke, and non-fatal myocardial infarction in patients with high CV risk (81% with established CV disease), as well as a reduction in CV mortality and total mortality. In contrast, semaglutide showed a 26% decrease in the same primary endpoint in the SUSTAIN-6 study and a decrease in CV mortality in its oral form in the PIONEER-6 study; both studies involved diabetic individuals at high CV risk [21].

Albiglutide showed a decrease in the primary endpoint of major cardiovascular events in diabetes patients undertaking secondary prevention in the HARMONY trial 2018. The fact that non-analogue agonists have not demonstrated a cardiovascular advantage in comparison to human analogue medicines could be explained by a potential immunological mechanism. Although it appears to be based on their prolonged half-lives, a decrease in S.B.P., and a noticeable weight loss, how the CV advantage of a GLP1 is achieved remains unclear [22].

Other diabetes medications

DPP-4 inhibitors' effects on the cardiovascular system have been examined in five sizable prospective studies, and they have typically shown non-inferiority against placebo, i.e., CV safety, without indicating CV risk reduction. In observational studies, the traditional diabetes medication metformin appears to improve the prognosis for cardiovascular disease. However, this has not been proven by randomized clinical research. Most patients in the aforementioned clinical studies with aGLP1 and iSGLT2 got metformin concurrently; however, this occurred similarly in both groups, so it would not add to the Effect [23].

A medical therapy algorithm for people with coronary artery disease

The traditional algorithms for the medical management of diabetes have been updated in light of this new information, and the use of iSGLT2 and aGLP1 is advised in patients with existing Crohn's disease or those who are at high risk of acquiring it (due to several risk factors or organ causes). The overall therapy regimen for these individuals is shown in Figure 2. iSGLT2s are used when the patient has heart failure since they have been demonstrated to reduce hospitalizations, but aGLP1s are favoured when weight loss is specifically desired [24].

HEART RESPIRATORY REVASCULARIZATION:

Diabetes patients' revascularization triggers

The type of coronary architecture involvement influences D.D.M.M. patients' prognosis and response to revascularization. These patients typically have multivessel disease and the left central coronary artery involvement at presentation. Additionally, coronary artery disease, which affects the small blood vessels, is more common. Comorbid conditions, including chronic renal disease, cerebrovascular illness, or peripheral artery disease, are also present and hurt the outcomes of coronary revascularization. In individuals with or without diabetes mellitus, the indications for coronary revascularization are the same [25].

Patients with D.D.M.M. with stable CD were randomized in the BARI 2D research to receive optimal medical or optimal medical therapy plus myocardial revascularization (percutaneous or surgical). No discernible differences between the two groups were seen in the composite endpoint of death, myocardial infarction, and stroke after 5 years of follow-up. Only one randomized clinical trial (n = 1212 patients) comparing (surgical) revascularization along with the best medical care versus medical care alone in the context of chronic ischemic heart failure discovered a significant survival benefit in patients revascularized with a left ventricular ejection fraction of 35% or less, with a mean follow-up of 9.8 years [26].

Patients with D.D.M.M. and ventricular dysfunction also saw this advantage. However, it did not prove statistically significant. With a mean follow-up of 6 months, a recent meta-analysis using data from 5,324 patients with non-ST-segment elevation acute coronary syndrome reveals that an early invasive strategy compared to a delayed invasive approach is linked with lower patient mortality. pePeopleith D.D.M.M. has a risk of recurrent myocardial infarction that is higher than average (hazard ratio (H.H.R.R.)=0.67; 95% CI: 0.45-0.99) [27].

Compared to coronary artery bypass grafting (CABG), percutaneous coronary revascularization (PCI)

When deciding on the best revascularization technique, the D.D.M.M. is a crucial factor that must be considered. Three randomized clinical trials evaluated the two revascularization approaches in D.D.M.M. patients, mainly in stable multivessel CD employing first-generation drug-eluting stents; however, one had to be stopped early. A one-year endpoint of death, myocardial infarction, or stroke was not found to differ between the surgical and percutaneous revascularization groups for 510 patients with multivessel CD or complex monovascular CD in the CARDia study [28].

This study lacked the power to identify these variations, though. Except for left central coronary artery stenosis, 1,900 diabetic patients with multivessel CD were randomly assigned to elective bypass surgery or percutaneous revascularization in the FREEDOM study. NNon-fatal myocardial infarction or stroke at 5 years, the primary endpoint of all-cause death, occurred in 26.6% of patients following percutaneous intervention and 18.7% of surgical patients. However, there were no appreciable differences between first-generation D.E.S. percutaneous coronary intervention and revascularization intervention in the composite endpoint of death, stroke, or myocardial infarction (MI) at 5 years old in the subset of 452 diabetic patients enrolled in the SYNTAX study [29].

The requirement for repeat revascularization and significant unfavourable cardiovascular and cerebrovascular event rates during 5 years was more critical in the percutaneous group. In the SYNTAX low (22) or intermediate (23-33) groups, patients with D.M.D.M. had a greater risk of recurrent revascularization after PCI than CABG. A greater incidence of cardiac death was noted in the group of patients with PCI who were insulin-dependent. DM was not an independent predictor of outcome in the SYNTAX study's multivariate analysis. As a result, D.M.D.M. is not listed as one of the 8 factors determining the choice of revascularization method in the SYNTAX 2 score [30].

The risk of death or myocardial infarction was higher with percutaneous intervention (relative risk [R.R.R.R.] = 1.51). However, the risk of stroke was reduced (RR=0.59) in a meta-analysis of 3,052 DM patients who were randomized to PCI (mainly with first-generation D.E.S.) against CABG [31]. These findings suggest that surgery, unlike PCI, has advantages for D.M.D.M. patients. For next-generation D.E.S., a meta-analysis of randomized clinical trials involving 8,095 DM patients found that patients who were randomized to next-generation everolimus-eluting stents experienced significantly lower rates of myocardial infarction, stent thrombosis, and MACE than those who received first-generation drug-eluting stents. It is unknown how much, if at all, the outcome gap in favour of CABG in patients with D.M.D.M. and multivessel disease will be reduced using next-generation D.E.S. [32].
There is not much data comparing PCI with CABG in ACS-NSTE. In a registry of 2,947 patients with D.M.D.M. with stable A.C.S., CABG and PCI with D.E.S. were compared. The benefit of CABG over PCI was shown at 30 days and 3.3 years of follow-up, with mortality, myocardial infarction, and non-fatal stroke as the primary endpoint [33].

In light of each patient's unique cardiac and extracardiac characteristics and preferences, who should be fully informed, the heart team should discuss the most suitable revascularization modality in patients with D.M.D.M. and multivessel disease. Based on the findings of the BARI 240 study and, more recently, the ISCHEMIA study, stable patients should generally receive optimal medical care unless their symptoms are intolerable, there are significant areas of ischemia, proximal disease in the anterior descending artery, or their left main coronary artery [34].

Table 3: Recommendations on the type of revascularization in patients with diabetes and E.C.E.C. stable (translated from the Guides of the E.S.C. 2019 on diabetes, pre-diabetes and cardiovascular enfermedades).

Recommendations according to the extension of the E.C.C.	CABG		PCI	
	Class of recommendation	Level of evidence	Class of recommendation	Level of evidence
A glass				
Without proximal A.D.A. stenosis	IIb	C	I	C
With proximal A.D.A. stricture	I	A	I	A
Two glasses				
Without proximal A.D.A. stenosis	IIb	C	I	C
With proximal A.D.A. stricture	I	B	I	C
Three glasses				
Low complexity (SYNTAX 0-22)	I	A	IIb	A
Intermediate – high complexity (SYNTAX > 22)	I	A	III	A
Left coronary trunk				
Low complexity (SYNTAX 0-22)	I	A	I	A
Intermediate-high complexity (SYNTAX 23-32)	I	A	IIa	A
Very high complexity (SYNTAX ≥ 33)	I	A	III	B

** CABG: coronary artery bypass grafting; PCI: percutaneous coronary intervention; A.D.A.: left anterior descending artery.*

Based on recent recommendations of the E.S.C. Guidelines, the revascularization strategy in diabetic patients can be structured as follows if revascularization is necessary, the coronary anatomy is technically amenable to revascularization by PCI or surgery, and the estimated surgical mortality is low [35]:
In patients with A.C.L. disease and intermediate SYNTAX score, coronary artery bypass surgery is preferred, though PCI may be considered a reasonable alternative. PCI and CABG are comparable alternatives in T.C.I. disease, low SYNTAX score, and two-vessel disease, including proximal L.A.D. involvement. PCI and CABG are not recommended in patients with T.C.I. disease and a high SYNTAX score, as well as in patients with trivessel disease and an intermediate. His alternatives can be considered in certain situations with a level IIb suggestion [36].
According to the E.S.C. Guidelines, Table 3 displays the strength of the evidence and the recommendation grade for each indication.

CONCLUSIONS:

Due to the high frequency of celiac disease in diabetic patients, the contemporary cardiologist is responsible for understanding the specific needs of these patients, whom he will regularly see in the operating room and catheterization room. According to the most recent research, they must also be aware of the main preventative measures to delay the beginning of celiac disease in diabetic patients, including lifestyle changes, managing their numerous risk factors, and the appropriate selection of anti-diabetic medications. Finally, depending on the coronary anatomy and the most recent recommendations, the cardiologist and cardiac surgeon must agree on the best revascularization technique for each patient as a heart team.

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