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Is percutaneous coronary intervention useful in non-flow-limiting vulnerable plaques? PREVENT trial

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Rupture and thrombosis of lipid-rich coronary atherosclerotic lesions (known as vulnerable plaques) have been described as the most common cause of acute coronary syndrome and sudden cardiac death. Vulnerable plaques often have no hemodynamic consequence and do not limit flow. On intravascular imaging they are recognized as thin-cap fibroatheromas, containing a large plaque and a lipid-rich necrotic core, separated from the lumen by a thin fibrous cap. We know that vulnerable plaques increase the risk of major adverse cardiac events. Until now, clinical practice guidelines recommend the use of pharmacological treatment (antiplatelet agents, high-intensity statins) for vulnerable plaques, but do not consider percutaneous coronary intervention (PCI), unless they limit flow or have caused an acute coronary syndrome. Theoretically, PCI could seal and passivate vulnerable plaques, reducing the risk of acute coronary events. Until now, a single randomized trial in 182 patients showed that PCI of vulnerable plaques could enlarge the coronary lumen and thicken the fibrous cap in 2 years, but this study was not powered to demonstrate clinical outcomes (major adverse cardiac events in 4.3% with PCI vs 10.7% with exclusive medical treatment at 2 years, p=0.12). It is not clear whether it is advisable to revascularize vulnerable plaques without hemodynamic repercussion, that is, they do not generate ischemia.

The multicenter, open-label, randomized, controlled PREVENT trial was conducted at 15 hospitals in South Korea, Japan, Taiwan, and New Zealand. Its objective was to evaluate the effects of PCI on major adverse cardiovascular events in patients with vulnerable, high-risk, non-flow-limiting plaques identified by intracoronary imaging. It included patients with stable coronary artery disease or acute coronary syndromes undergoing cardiac catheterization. Flow-limiting lesions, with a fractional flow reserve (FFR) ≤0.80, and lesions causing acute coronary syndrome were treated with PCI with drug-eluting stents before randomization. All untreated, non-culprit lesions, which were clearly not responsible for the presenting clinical syndrome, with a stenosis ≥ 50% by visual estimation were functionally evaluated by FFR. Any intermediate, non-flow-limiting lesion with FFR >0.80 and non-culprit was evaluated with gray-scale intravascular ultrasonography (IVUS), radiofrequency IVUS, a combination of gray-scale intravascular IVUS with near-infrared spectroscopy or optical coherence tomography (OCT). Vulnerable plaques were defined as lesions with at least two of the following four characteristics: a minimum luminal area <4 mm², defined by IVUS or OCT; a plaque burden >70% by IVUS; a lipid-rich plaque defined by near-infrared spectroscopy, or a thin-cap fibroatheroma detected by radiofrequency IVUS or OCT. The main exclusion criteria included previous surgical or stent revascularization, three or more target lesions, or two lesions in the same artery, highly calcified or angulated lesions, or bifurcation lesions requiring treatment with two stents. Initially, resorbable scaffolds were used; when they were withdrawn from the market, everolimus-eluting cobalt-chromium metal stents were used. Patients with one or two vulnerable non-flow-limiting plaques were randomly assigned (1:1) to a strategy of PCI plus optimal medical therapy or optimal medical therapy alone. After PCI, dual antiplatelet therapy was administered for 6 or 12 months depending on clinical presentation and anatomical complexity. Treatment with high-dose statins was recommended. Clinical follow-up was performed 1, 6, 12, and 24 months after randomization and every year thereafter.

The primary endpoint was a composite of cardiovascular death, target vessel myocardial infarction, or target vessel revascularization due to ischemia, or hospitalization for unstable or progressive angina, at 2 years after randomization. Secondary endpoints were the individual components of the primary composite endpoint, death from any cause, any myocardial infarction, any revascularization, stent or scaffold thrombosis, stroke, bleeding events, and the combination of death from all causes, myocardial in-

farction, or repeated revascularization. To calculate the sample size, an incidence of the primary endpoint at 2 years of 8.5% in the preventive PCI group and 12% for the medical treatment alone group was assumed, which implies a relative risk reduction of 30%. With 1600 patients included there would be a power of 80%, with a two-tailed p value of 5%, assuming a loss to follow-up and a crossover rate of 7%. Between September 2015 and September 2021, 5,627 patients were assessed for eligibility; 3,562 patients had intermediate non-flow-limiting lesions (FFR >0.80) that were evaluated with intracoronary imaging. Vulnerable plaques were found in 1608 (45%), and 1606 patients were included in the trial, with 1672 qualifying lesions; 803 patients with 831 lesions in the preventive PCI plus optimal medical treatment group and 803 patients with 841 lesions in the optimal medical treatment alone.

The median age was 65 years (interquartile range 58-71); 73% were men, 31% had diabetes, 84% had stable coronary artery disease, 12% unstable angina, and 4% a myocardial infarction within 1 week. Vulnerable plaques were assessed by grayscale IVUS in 95% of patients; radiofrequency IVUS was used in 71%, near-infrared spectroscopy in 42%, and OCT in 5%. Regarding the predefined criteria for plaque vulnerability, in 97% of the patients a minimum luminal area <4 mm² was verified, in 96% a plaque load >70%, in 11% a high lipid content and in 5% thin-cap fibroatheromas. Eighty-nine percent had at least two defined images characteristic of vulnerable plaque.

PCI of non-flow-limiting lesions was performed in 91% of the 803 patients assigned to preventive PCI, with bioabsorbable scaffolds in 33%, and with cobalt-chromium everolimus-eluting metallic stents in 67%. In the preventive PCI group, 9% crossed to receive medical treatment only. In the medical therapy group, 1% switched to PCI. The use of dual antiplatelet therapy was higher in the PCI group. More than half of the patients in both groups received high-intensity or moderate-intensity statins plus ezetimibe. The mean LDL cholesterol was 64±21 mg/dL in both groups at the last follow-up.

The 2-year follow-up was completed in 97% of patients. The median duration of follow-up was 4.3 years. The maximum duration of follow-up was 7.9 years in both groups. At 2 years, the primary endpoint occurred in 0.4% of patients in the preventive PCI group and 3.4% in the optimal medical therapy group, p=0.0003. The effect was directionally consistent for each component of the primary composite endpoint. The composite risk of death from all causes, myocardial infarction, or any revascularization was also lower. The number needed to treat with preventive percutaneous coronary intervention was 45.4 to prevent one primary endpoint event in 2 years and 87.7 to prevent cardiac death or target vessel myocardial infarction in 2 years. Stroke and hemorrhagic events did not differ between the two groups. The per-protocol and real-treatment analysis yielded similar results.

The concept of preventive PCI to render vulnerable high-risk plaques passive assumes that neointimal development over the stent or scaffold would functionally thicken the fibrous cap, reducing the risk of rupture. We know that a high plaque burden, a small minimum lumen area, a high lipid content, and a thin fibrous cap are associated with future cardiac events, and the risk increases with the number of adverse features present. Currently, clinical guidelines recommend PCI only for flow-limiting lesions or those responsible for acute coronary syndromes. However, studies have shown that cardiovascular events arise from vulnerable plaques, whether or not they are flow-limiting. The PREVENT trial challenges conventional wisdom by demonstrating reduced risk of major events with preventive PCI in commonly untreated lesions.

Importantly, patients in both groups were treated with optimal medical therapy and strict control of risk factors, achieving low LDL concentrations.

We can cite several limitations. First, the trial was open, which introduces observation bias. It is true that this does not apply to hard endpoints such as death or heart attack, but it does not rule out that some components of the cotreatment could differ. In fact, there was a difference in the use of double antiaggregation, and it is striking that the main body of the publication does not quantify this difference. The low incidence rate of the primary endpoint (in the medical treatment arm 3.4% at 2 years when expected 8.5%) may be due to the fact that the majority of patients had chronic coronary syndromes and the excellent control of risk factors.

But it is essential to highlight that the very concept of vulnerability is under discussion. Plaque vulnerability is a dynamic condition: some vulnerable plaques could stabilize without events, while stable plaques could transition and become vulnerable later, and plaques of different maturity often coexist. Up to three-quarters of vulnerable plaques could evolve to a more stable phenotype. Less than 5% of vulnerable plaques evolve with major events. In contrast, more than 95% of autopsies of patients with sudden death show myocardial hypertrophy and fibrosis. The phenomenon of plaque erosion (endothelial desquamation adjacent to the atherosclerotic plaque, without rupture of the fibrous cap) appears to be a more frequent phenomenon than traditional rupture. While rupture occurs in plaques with the characteristics evaluated in the trial and is accompanied by red thrombi rich in blood cells and fibrin, erosion occurs in lesions with the fibrous cap intact,

lower lipid content, and white thrombi rich in platelets. Viewed in this way, it is clear that our ability to predict events and which of all the manifestations of atherosclerotic disease in a particular patient will be responsible for a serious event seems illusory. The concept of vulnerable patient (vulnerable plaque, with vulnerable blood, prone to thrombotic phenomena, and vulnerable myocardium, with structural alterations that predispose to malignant ventricular arrhythmia) implies a much broader vision of cardiovascular risk. In this sense, strict metabolic control and lifestyle modification emerge as probably more cost-effective behaviors.

REDUCE-AMI trial: lack of evidence about the benefit of treating with beta-blockers patients with myocardial infarction and preserved left ventricular ejection fraction.

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Clinical trials from the 1980s and 1990s demonstrated that long-term beta-blocker therapy after acute myocardial infarction (AMI) reduces mortality by approximately 20%. These trials primarily involved patients with large infarcts and low left ventricular ejection fraction (LVEF), and this occurred at a time before the routine use of percutaneous coronary interventions, dual antiplatelet therapy, high-intensity statin therapy, and renin angiotensin aldosterone system antagonists. A meta-analysis by S. Bangalore et al. in 2014 suggested that in the era of modern reperfusion strategies, beta-blockers did not significantly reduce mortality. Data are lacking on the effect of long-term treatment with beta-blockers in patients with AMI and preserved LVEF. Divergent conclusions have emerged from extensive observational studies and meta-analyses of such studies. Despite this, current guidelines recommend the use of beta blockers after an AMI.

The REDUCE-AMI trial investigated whether long-term beta-blocker treatment in patients with AMI and preserved LVEF reduces a composite endpoint of death from any cause or new AMI. It was a prospective, randomized, open-label, pragmatic, registry-based clinical trial, conducted in Sweden (38 centers), Estonia (1 center), and New Zealand (6 centers). It enrolled patients between 1 and 7 days after an AMI who had undergone coronary angiography and who had LVEF ≥50% on echocardiogram. They also had to have documented obstructive coronary artery disease (stenosis ≥50%, or a fractional flow reserve ≤0.80 at any time before randomization). The main exclusion criterion was indication or contraindication for treatment with beta-blockers. Randomization was carried out using a web-based system. The beta-blockers used were metoprolol (at least 100 mg daily) as the first option and bisoprolol (at least 5 mg daily) as an alternative. Patients were required to continue beta-blocker treatment after discharge until a contraindication appeared. Patients randomly assigned to the group without beta-blockers were discouraged from using them unless there was a compelling indication.

The primary endpoint was a composite of death from any cause or new AMI. Secondary endpoints were death from any cause, death from cardiovascular causes, new AMI, and hospitalization for atrial fibrillation or heart failure as primary diagnoses. Safety endpoints were hospitalization for bradycardia, second- or third-degree atrioventricular block, hypotension, syncope, or pacemaker implantation; hospitalization for asthma or chronic obstructive pulmonary disease (as primary diagnosis), and hospitalization for stroke. The data were obtained from different national registries. The bulk of the information comes from the Swedish SWEDEHEART registry.

To calculate the sample size, it was assumed that the annual incidence of the primary end point would be 7.2% in the group without beta-blockers, and that these would reduce the risk by 16.7% (1.2% absolute risk reduction per year, considered the least important difference to detect). During the trial, total event counts by blinded adjudicators indicated an actual event rate of 3% per year. The sponsor and the steering committee then modified the assumptions: they assumed 25% the minimum important difference to detect a lower risk, which corresponds to a 0.7% absolute risk reduction. With a power of 80% and a 2-tailed p value <0.05, it was calculated that 379 events of the primary endpoint would be necessary, which was expected to occur after including 5000 patients.

From September 2017 to May 2023, 5020 patients were randomized, 95.4% in Sweden. The median age was 65 years, 22.5% were women, and 35.2% had an ST-segment elevation AMI; 46.2% had hypertension, 14% diabetes, 7.1% had previous AMI. Near 11 % of patients were already receiving beta blockers. The median systolic blood pressure was 150 mm Hg; 55.4% had one-vessel disease, 27% had two-, and 16.6% had three-vessel or left main coronary artery disease. Percutaneous coronary intervention (PCI) was performed in 95.5% and coronary artery bypass grafting in 3.9%. At discharge, 97.4% were receiving aspirin, 95.8% a P2Y12 receptor inhibitor, 80.2% a renin angiotensin system inhibitor or antagonist, and 98.5% a statin.

Of the 2508 patients assigned to beta-blockers, 62.2% received metoprolol (a median dose of 100

mg daily) and the rest received bisoprolol (a median dose of 5 mg daily).

The median follow-up was 3.5 years (interquartile range, 2.2 to 4.7) in each trial arm. The primary endpoint occurred at 2.4% per year in the beta-blocker arm and at 2.5% per year in the non-beta-blocker arm (HR 0.96, 95% CI 0.79-1.16; p=0 ,64). There was also no reduction in the incidence of each of the secondary end points. Adjustment for age, diabetes, or prior AMI did not change the results. There was no difference in the incidence of safety endpoints.

The REDUCE-AMI trial calls into question the conduct of prescribing beta-blockers to all patients with AMI, since it points out that in patients with AMI and LVEF ≥ 50% there is no clear benefit from the intervention. Although it does not rule out a small beneficial or harmful effect, the time-to-event curves were overlapping throughout follow-up and there was no difference in the primary endpoint or each of the secondary endpoints, making a clinically relevant difference very improbable. It is interesting to remember that also in the case of heart failure with preserved LVEF, the benefit of beta-blockers is under discussion, and appears reduced compared to other interventions.

But we want to make some observations. The doses of beta-blockers used in this trial were lower than in previous trials. Fourteen percent of those assigned to the no-beta-blocker group crossed arms and were taking beta-blockers after 1 year of follow-up. We cannot rule out the possibility that this crossover may have contributed to the null effect of the intervention. And we want to highlight that included patients had a high median systolic blood pressure, high prevalence of one-vessel disease, two-thirds an AMI without ST- segment elevation, and almost universal use of PCI. That is, a population with low risk of events, with a very low pretest probability of obtaining benefit from beta-blocker treatment. Although the favorable effect of these drugs in patients with LVEF ≤ 40% is clear (a fact confirmed by different meta-analyses in the context of AMI or heart failure), we should not even extrapolate the results of PREVENT trial to patients with AMI. and LVEF between 41% and 49%, where some analyzes suggest benefit. Other ongoing trials (including BET-AMI and REBOOT) are examining long-term treatment with beta-blockers in patients with AMI and a broader definition of preserved LVEF, with a cut-off value of 40%. Presumably, the lower the LVEF of the patients included, the greater the benefit of the treatment.

One last comment about the design: a pragmatic (reduction of procedures complexity) and registry-based trial (easily accessible data), as a way to facilitate the investigation of clinically relevant topics, with lower costs.

No impact of empagliflozin on the prognosis of acute myocardial infarction: the EMPACT-MI trial

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In recent decades, the treatment of acute myocardial infarction (AMI) has experienced a series of advances that have significantly reduced in-hospital and long-term mortality: antiplatelet agents, early reperfusion treatment (with fibrinolytics and now mainly with coronary angioplasty), the use of neurohormonal antagonists (renin-angiotensin system inhibitors or antagonists, beta-blockers, of mineralocorticoid receptor antagonists) and statins in high-intensity treatment. For a decade, sodium-glucose cotransport 2 inhibitors (SGLT2i) or gliflozins have demonstrated strong effects in patients with diabetes, heart failure or renal failure on cardiovascular adverse events, and specifically heart failure progression of renal dysfunction and cardiovascular mortality. So, it was expected that the study of SGLT2i effect in AMI patients would be considered. Let us remember that patients experiencing an AMI, or a very recent AMI were excluded from studies with gliflozins in diabetes, heart failure or kidney failure. The mechanisms by which these drugs could be beneficial in AMI are multiple: decrease in sodium entry into the myocardial fiber, increase in mitochondrial calcium content, attenuation of reperfusion injury and cell necrosis, reverse remodeling, energy improvement by promoting the consumption of ketone bodies, decreased fibrosis, reduction of epicardial fat and improvement in diastolic function. In addition, the attenuation of endothelial dysfunction, the improvement of coronary flow, the decrease in oxidative stress, the attenuation of inflammatory phenomena and neurohormonal activation, the promotion of autophagy, the decrease in glomerular hyperfiltration, the restoration of tubuloglomerular feedback, and the increase in the production of erythropoietin and the oxygen supply to the tissues. In different observational studies on the use of gliflozins in patients with AMI, publication bias led us to know generally positive results, especially in patients with AMI and diabetes, in whom reduction of the in-stent restenosis, the size of the AMI and even cardiovascular mortality were advocated.

After the publication of the randomized trials EMMY (empagliflozin vs placebo in patients with large AMI, in which the use of the drug generated a decrease in the values of natriuretic peptides and a slight increase in the left ventricular ejection fraction, LVEF) and DAPA -MI (dapagliflozin vs placebo in AMI patients without diabetes, generally with

LVEF < 50%, in which the drug did not demonstrate a clear effect on hard clinical endpoints, only a reduction in diabetes incidence and weight) , we now know the results of the EMPACT-MI trial.

EMPACT-MI was a randomized, multicenter, parallel-group, placebo-controlled clinical trial designed to evaluate the safety and efficacy of empagliflozin in patients at high risk of developing heart failure after AMI with or without ST-segment elevation. The AMI had to have occurred within 14 days prior to admission to the study and coincide with signs and/or symptoms of pulmonary congestion requiring treatment, or new development of ventricular dysfunction, with LVEF <45%. Additionally, the presence of at least one enrichment factor was required: age ≥65 years; that the new LVEF was <35%; myocardial infarction prior to the current one; estimated glomerular filtration rate <60 ml/min/1.73 m^2; atrial fibrillation; type 2 diabetes; elevated natriuretic peptides; uric acid ≥ 7.5 mg/dL; systolic pulmonary pressure ≥ 40 mm Hg; patient not revascularized for AMI, and without plans to do so; 3-vessel coronary lesion; peripheral vascular disease. Patients with a history of heart failure or reduced LVEF before the index AMI, those with estimated glomerular filtration rate <20 ml/min/1.73 m^2, patients with cardiogenic shock, and those who planned to start treatment with SGLT2i were excluded.

The primary endpoint was a composite of time to first hospitalization for heart failure or death from any cause. Secondary endpoints hierarchically established were the times to all hospitalizations for heart failure or death from any cause; all unscheduled cardiovascular hospitalizations or death from any cause; all hospitalizations from any cause or death from any cause; all hospitalizations due to AMI or death from any cause. It was established that the trial would continue until 532 events of the primary end point were recorded, which would ensure, with an annual incidence of the primary end point in the placebo arm of 12.5% and a relative reduction of 23% with empagliflozin, a power of 85% with a 2-tailed p value of 0.05. Considering an annual loss of 1% of the included patients, it was estimated that 3312 patients were necessary, with an inclusion period of 12 months and a similar follow-up period. The analysis was done by intention to treat. It was proposed that if the inclusion of patients was slower than expected, or the event rate lower than expected, the number of included patients could be increased to 5000. This was accompanied by an extension of the inclusion and follow-up periods. Despite everything, it finally became necessary, to reach the desired power, to include 6500 patients.

Between the end of 2020 and March 2023, 6522 patients at 451 centers in 22 countries were randomly assigned to empagliflozin at a dose of 10 mg daily or placebo. The median age was 64 years; 75.1% were men, 74.3% corresponded to AMI with ST-segment elevation. Sixty-nine percent had a history of high blood pressure, 31.7% of diabetes. 78.3% of patients met the inclusion criterion of LVEF <45%, and 56.9% met the criterion of congestion requiring treatment. There was an overlap of both criteria in 35.6% of the cases. In 75.8% of the patients in whom there was accurate measurement of LVEF, the average was 40%.

Near 29 % of patients had one enrichment criterion, 28.1% 2, 20.7% three, the rest between 4 and 7. The most frequent enrichment factors were age ≥65 years, diabetes type 2 and 3-vessel injury. The median from admission to randomization was 5 days. In 89.3% of the cases, a revascularization procedure was performed (almost all of them coronary angioplasty) and in 10.7%, thrombolytics were used. Treatment at discharge consisted of renin angiotensin system inhibitors/antagonists or sacubitril valsartan in 82% (most cases an angiotensin converting enzyme inhibitor), beta blockers in 86%, and mineralocorticoid receptor antagonists in 47.2%; loop diuretics in 37.8% and some diuretic in 64.7%. Ninety-eight percent received antiplatelet therapy, 90% dual antiplatelet therapy, and 94.7% received statins.

In a median follow-up of 17.9 months, the annual incidence of the primary end point was 6.6% in the placebo arm and 5.9% in the empagliflozin arm (HR 0.90; 95% CI 0.76-1,06; p=0.21). There were no differences in any of the subgroups considered (according to age, LVEF; diabetes, kidney function, blood pressure, congestion, etc.). The analysis of the composite primary endpoint components shows no difference in the annual incidence of mortality (3.8% vs 3.6%) and suggests an effect on the incidence of hospitalization for heart failure (3.4% in the placebo, 2.6% in the empagliflozin arm, HR 0.77; 95% CI 0.60-0. 98). It should be clarified, however, that hospitalization for heart failure was not a prespecified individual endpoint. Statistical significance was not reached in any secondary endpoint. The total number of hospitalizations for heart failure (an exploratory endpoint) was significantly reduced, from 207 to 148 (RR 0.67; 95% CI 0.51-0.89).

Although DAPA-MI and EMPACT-MI trials share common characteristics (patients of similar age, with equivalent prevalence of male sex and ST-segment elevation infarctions, and, in general, similar treatments, close to perfection), EMPACT-MI included more ill patients: patients with diabetes were not ruled out, the LVEF and the glomerular filtration rate were somewhat lower. But most importantly: the annual mortality rate and the annual incidence of hospitalization for heart failure in the placebo arm doubled those of DAPA-MI trial. However, as in this case, the SGLT2i did not modify the incidence of the

composite primary endpoint, basically because all-cause mortality (more than half of the primary endpoint events) did not change with the gliflozin, most likely due to the excellent treatment instituted, which makes it very difficult for a specific intervention to generate an additional and significant reduction in mortality. The effect on hospitalization for heart failure was not a prespecified endpoint, so, from a methodological point of view, it is only enough to generate hypotheses. As it is highly unlikely that studies like those cited will be repeated, we will have to rely on post hoc analysis to act. In this sense, patients who we know benefit most from gliflozins (kidney dysfunction, diabetes, persistent heart failure) may eventually be candidates for treatment after AMI. It is clear that there is no room in the information available for a universal indication of gliflozins, but undoubtely there are patients who are candidates to be treated. Clinical trials have not been able to give us a definitive answer.