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How long should dual-antiplatelet therapy be extended after stent implantation? Three studies, one answer?

Dual-antiplatelet therapy (DAPT) with aspirin and a thienopyridine (clopidogrel, prasugrel, ticagrelor) is routinely indicated after stent implantation. Treatment guidelines generally suggest 1-month DAPT for bare-metal stents (BMS) and 6 to 12 months for drug-eluting stents (DES). Stent thrombosis (ST) is the most dreaded complication of stent implantation which, though infrequent, may be fatal. At the same time, the most serious complication of DAPT is bleeding, especially major bleeding and intracranial hemorrhage. Actually, the optimal duration of DAPT that may reduce all risks remains uncertain. Observational studies had shown that risk of ST increases after DAPT discontinuation. Different randomized studies published during the last years, as the PRODIGY trial (6 versus 24 months) and the OPTIMIZE trial (3 versus 12 months), using first- and second-generation BMS and DES, suggest that DAPT during short periods is not inferior to more prolonged therapy regarding event occurrence. Recently, 3 randomized studies were published which add new information and generate new questions.

ARCTIC-Interruption Study

Collet JP, Silvain J, Barthelemy O, Rangé G, Cayla G, Van Belle E, et al. Dual-antiplatelet treatment beyond 1 year after drug-eluting stent implantation (ARCTIC-Interruption): a randomised trial. **Lancet** 2014;384:1577-85.

The French multicenter, randomized, open-label ARCTIC trial included patients scheduled for planned percutaneous coronary intervention with DES. The initial phase (ARCTIC-Monitoring) compared 2 strategies for DAPT administration in the first year after the intervention: one in which the antiplatelet dose was decided based on platelet reactivity tests, and another in which the dose was conventionally chosen. This first phase (between 2009 and 2011) included 2,440 patients, and was unable to demonstrate difference between both strategies. Patients who during the course of the first year had neither presented an ischemic event nor significant bleedings, nor required a new procedure, were invited to participate in the second phase (ARCTIC-Interruption). They were similarly randomly allocated to 2 other strategies: DAPT continuation or thienopyridine interruption, continuing only with aspirin antiplatelet treatment. The primary efficacy endpoint was the composite of all-cause mortality, acute myocardial

infarction (AMI), ST, stroke or urgent revascularization. The safety endpoint was major bleeding. Sample size was calculated expecting a primary efficacy endpoint incidence of 6% in the first 6 months after thienopyridine interruption with 50% reduction in those who continued with DAPT.

Among the patients included in the first phase, only 1,259 (51.6%) participated in the second phase. They were generally patients at lower risk than those of the initial cohort (less diabetes and peripheral vascular disease, and lower platelet reactivity). Mean age was 64 years; first-generation DES was used in slightly more than 40% of cases, and second-generation DES in the rest of cases. DAPT included clopidogrel in 90% of cases and prasugrel in the remaining 10%.

For different reasons, after a median follow-up of 17 months, one fifth of cases discontinued clopidogrel and a third discontinued prasugrel in the group that continued with DAPT. Similarly, in the group that had to interrupt thienopyridine, 15% of patients resumed clopidogrel and 2%, prasugrel. Finally, there was no difference in the combined primary efficacy endpoint (4% in each group) or in any of its separate components. Conversely, the incidence of major and minor bleeding was lower in the interruption group (1% vs. 2%, $p = 0.04$).

The authors performed a meta-analysis of six studies (including the ARCTIC study) with 12,536 patients, comparing DAPT continuation vs. interruption after 6 to 12 months, whose results agreed with those presented in their study: there was no difference in mortality, but DAPT continuation was associated with a double risk of major bleeding.

In this study, the number of patients included and the rate of events was lower than the one calculated (because they were low risk patients and risk estimation was based on data from registries and studies with first-generation DES), so the power to detect a difference was low.

SECURITY study

Colombo A, Chieffo A, Frasheri A, Garbo R, Masotti-Centol M, Salvatella N, et al. Second-Generation Drug-Eluting Stent Implantation Followed by 6- Versus 12-Month Dual Antiplatelet Therapy: The SECURITY Randomized Clinical Trial. **J Am Coll Cardiol** 2014;64:2086-97.

The SECURITY trial was conducted to test the non-inferiority of 6- versus 12- month DAPT in patients treated exclusively with second-generation DES. It was a randomized, multicenter, international study,

including patients with at least one implanted DES with stable or unstable angina or silent ischemia. Patients with ST-segment elevation AMI in the last 48 hours or non-ST-segment elevation AMI in the previous 6 months, and those with DES or BMS implantation in the last 3 months were excluded from the study. Patients scheduled for unprotected left main coronary lesion, venous bridge lesion or intrastent restenosis interventions were not included in the study. Eligible patients were assigned to 6- versus 12-month-treatment with thienopyridine and aspirin indefinitely. Initially, the primary endpoint was ST, which was then replaced by a composite of death, AMI, stroke, ST and major or fatal bleeding. The study started in 2009. During follow-up, an interim analysis showed that the incidence of the primary endpoint was lower than expected: only 4.5% at one year, indicating the need of 1,370 patients per group, larger than the one originally calculated. Due to the slow inclusion of patients and budget restrictions, the study was finally terminated in June 2014.

At the moment of study termination, 1,399 patients had been included, 628 in the 6-month group and 717 in the 12-month group. Mean age was 65 years, 31% were diabetic, 21% had history of AMI and 61% were stable at the moment of the procedure. Forty-four percent of patients had more than one vessel lesion, and access was radial in almost 70% of cases. Follow-up at one year was completed in 91% and at 2 years in 82% of patients. At the end of the first year, 33.8% of patients that should have interrupted treatment at 6 months continued with DAPT and 96.1% of those assigned to 12-month DAPT.

At 12 months, the primary endpoint occurred in 4.5% of cases in the 6-month group and in 3.7% in the 12-month group (absolute difference 0.8%, 95% CI -2.4% to 1.7%; $p = 0.46$). As the upper limit of the 95% CI was lower than the pre-set noninferiority margin of 2%, the 6-month noninferiority hypothesis was accepted. At 12 months, no differences were found in the individual components of the composite endpoint or in the incidence of major or fatal bleeding. The incidence of ST at 12 months was low: 0.3% vs. 0.4% ($p = \text{ns}$). In the multivariate analysis, age ≥ 75 years and factors associated to the complexity of the lesion and the procedure (stent number, size and length) were independent predictors of events, but not DAPT duration.

The SECURITY study arrived at the same conclusions that other randomized studies, suggesting that lower DAPT duration is not inferior to more prolonged DAPT. Some results should be highlighted: the low incidence of events (attributable to the inclusion of low risk patients with generally non-complex lesions and to a lower rate of major events with second-generation than with first-generation DES), the low recruitment, and the fact that a third of patients in the 6-month group continued with DAPT beyond the expected time. All this led, as in the previous study, to a low power to detect differences.

DAPT Study

Mauri L, Kereiakes DJ, Yeh RW, Driscoll-Shempp P, Cutlip DE, Steg PG, et al. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. **N Engl J Med** 2014;**371**:2155-66.

The international, multicenter, randomized, placebo-controlled DAPT trial assessed the safety and efficacy of continuing DAPT beyond one year in patients with DES implantation. Among the nearly 26,000 initially enrolled patients scheduled for stent implantation, 22,866 received DES. They were treated with open DAPT, and if after that period they had not presented major cardiovascular or cerebrovascular events, repeat revascularization or moderate to severe bleeding, they were randomly assigned to continue DAPT up to 30 months, or to continue only with aspirin and a thienopyridine placebo. At the end of 30 months, patients were followed-up for an additional 3 months to assess the effect of thienopyridine discontinuation in patients who had received prolonged DAPT. The copriary efficacy endpoints were ST and the incidence of major events: death, AMI or stroke between month 12 and month 30. The primary safety endpoint was the incidence of moderate or severe bleeding.

A total of 9,961 patients were included (43.6% of those initially enrolled). Average age was slightly under 62 years, 75% were men and 31% were diabetic. Twenty-six percent of patients underwent percutaneous coronary intervention in the context of AMI, and nearly 17% additional patients for unstable angina. Approximately 51% of patients had at least one clinical or angiographic risk factor for ST. Sixty-five percent of patients received clopidogrel and the rest prasugrel. In 47.2% of cases, everolimus-eluting stents were used and in 26.7% paclitaxel-eluting stents; in the remaining cases, sirolimus-eluting or zotarolimus-eluting stents.

At 18-month follow-up, the group that continued with DAPT presented significantly lower incidence of ST (0.4% vs. 1.4%; HR 0.29, 95% CI 0.17-10.48; $p < 0.001$) and of major adverse events (4.3% vs. 5.9%; HR 0.71, 95% CI 0.59-0.85; $p < 0.001$). Not only the incidence of AMI associated to ST was lower (2.1% vs. 4.1%), but also the one unrelated to this phenomenon (1.8% vs. 2.9%). Of note, the incidence of AMI (related or not to ST) increased during the 3-month period after thienopyridine discontinuation, whether this occurred at month 12 or 30. Major adverse events were more markedly reduced when paclitaxel-eluting instead of everolimus-eluting DES was used, though it should be noticed that the choice of DES was not at random. The rates of death from cardiac causes (0.9% vs. 1%), vascular causes (0.1% in both groups) and stroke (0.8% vs. 0.9%) were not significantly different between both groups. Even all-cause death was more prevalent in the prolonged DAPT group (2% vs. 1.5%; HR 1.36, 95% CI 1-1.85; $p = 0.05$). In a secondary analysis considering follow-up for 33 months

(including the 3-month period after thienopyridine discontinuation), mortality was 2.3% vs. 1.8%; $p = 0.04$. Deaths from non-cardiovascular causes were responsible for the observed differences, especially those due to fatal bleeding (11 vs. 3, mostly in the context of trauma) and those associated to cancer (31 vs. 14). A post hoc analysis showed that, despite randomization, the number of patients with cancer had not been balanced between the two groups, with a larger number of patients in the group with prolonged DAPT. The differences in mortality disappeared after excluding these patients.

The rate of at least moderate bleeding was higher with prolonged DAPT (2.5% vs. 1.6%; HR 1.61, 95% CI 1.21-2.16; $p = 0.001$), with no difference in the incidence of severe or fatal bleeding.

It should be highlighted that the population selected was low risk with no complications or major events during the year after stent implantation. Patients who would have probably benefited most (due to a major event in the first year) were not included. While previous evidence indicated reducing DAPT duration, this study suggests that there could be some benefit with treatment prolongation, although with uncertain results about mortality and greater risk of bleeding (though not severe or fatal). A meta-analysis performed by the authors, considering this and other studies comparing brief DAPT (≤ 6 months) versus prolonged DAPT, conclude that this is not associated with higher mortality, with HR 1.05 95% CI 0.96-1.19; $p = 0.33$.

In conclusion, what is to be done? All studies, with lower or higher power, conclude that risk of bleeding increases as DAPT is more prolonged. In this sense, it seems sensible to shorten its duration in patients at greater risk of bleeding. In patients at high ischemic risk we should adopt more prolonged DAPT, since the DAPT study indicates that beyond the 70% decrease in the risk of ST, there is reduction of unrelated AMI. The final decision to use DAPT for a few months or extended for an indefinite limit may stem from the adequate balance between both risks, and from the evaluation of the type of lesion, context and type of DES (due to the unconfirmed information about the dissimilar ST incidence according to the eluted drug, independently of the known differences between first or later generation DES), until new data and longer follow-up contribute to clarify the scenario.

Opposing effects of intensive glycemic control in diabetic patients : increased mortality, reduced coronary events. The ACCORD trial.

Gerstein HC, Miller ME, Ismail-Beigi F, Largay J, McDonald C, Lochnan HA, et al. Effects of intensive glycaemic control on ischaemic heart disease: analysis of data from the randomised, controlled ACCORD trial. *Lancet* 2014;384:1936-41.

Patients with type 2 diabetes are at increased risk of

developing ischemic heart disease, whose incidence increases with higher glycosylated hemoglobin (HbA1c). Intuitively, an intensive strategy (IS) directed to achieve a marked decrease in HbA1c levels should translate into better prognosis than that achieved with standard care. However, known randomized studies at the end of the past decade questioned this assumption, by demonstrating that IS is associated with higher mortality, an apparently contradictory finding with the fact that it is simultaneously able to reduce the rate of non-fatal coronary events.

One of the most important cited studies was the ACCORD trial, conducted in the United States and Canada. It included 10,251 patients with type 2 diabetes and HbA1c $\geq 7.5\%$, with cardiovascular disease in those aged between 40 and 79 years, or with coronary risk factors, ventricular hypertrophy, albuminuria or evidence of atherosclerotic disease in those aged between 55 and 79 years. Patients were randomized to target HbA1c between 7% and 7.9% (standard therapy, ST) or $< 6\%$ (IS). The primary endpoint was the composite of cardiovascular death, non-fatal acute myocardial infarction (AMI) and non-fatal stroke. The secondary endpoint was death from any cause. Median follow-up was 3.7 years, at the end of which median HbA1c was 6.4% with IS and 7.5% with ST. Patients in the IS group received more anti-diabetic medication and hypoglycemic episodes were more frequent. No significant difference was found in the primary endpoint (6.9% vs. 7.2%), but there was greater incidence of all-cause death (5% vs. 4%; $p = 0.04$), leading to early discontinuation of the study. Patients from the IS group were then assigned to ST and follow-up was further extended for a median of 1.1 years, with final median HbA1c of 7.1% in the IS group and 7.6% in the ST group.

The following substudy explores the effect of IS on the rate of coronary events. During the 3.7-years of comparison between both strategies, the annual rate of non-fatal AMI was lower with IS (1.08% vs. 1.35%; HR 0.78, 95% CI 0.65-0.94; $p = 0.01$) and there was a trend towards lower prevalence of unstable angina and need for revascularization. Considering the complete follow-up period of 4.8 years, the annual rate of non-fatal AMI was considerably lower (1.18% vs. 1.42%; HR 0.81, 95% CI 0.71-0.95; $p = 0.01$), same as that of unstable angina (0.83% vs. 1%; HR 0.81, 95% CI 0.67-0.97; $p = 0.02$) and coronary revascularization (2.41% vs. 2.81%; HR 0.84, 95% CI 0.75-0.94; $p = 0.003$). In both periods there was a trend towards excess fatal AMI (0.10% vs. 0.06% in the first 3.7 years, 0.09% vs. 0.05% in the complete follow-up period). Interestingly, after adjusting by the HbA1c value achieved in the active phase of the study all the outcome differences between both strategies disappeared.

A meta-analysis of four large studies of IS versus ST confirms that the former reduces the rate of coronary events. This, in addition to the reduced difference between both modalities after adjusting by HbA1c,

strongly suggests that high glycemic levels might be per se a risk factor for the development of coronary disease in diabetic patients, independently of coexistent hypertension, other metabolic factors and insufficient treatment. The reduction in the incidence of coronary disease is no reason to install in all patients an aggressive hypoglycemic therapy if the increase in total mortality is taken into account. Nevertheless, as everything in medicine, it is probable that IS is justified in some cases: younger patients, with shorter time of disease evolution and less target organ injury, in whom a more aggressive treatment delays its appearance.

High fitness in adolescence is associated with reduced risk of acute myocardial infarction in adulthood.

Hogstrom G, Nordstrom A, Nordstrom P. High aerobic fitness in late adolescence is associated with a reduced risk of myocardial infarction later in life: a nationwide cohort study in men. **Eur Heart J** 2014;**35**:3133-40. <http://doi.org/f2wh25>

Several cohort studies agree that high physical or aerobic fitness is associated with lower cardiovascular risk. In general, monitoring in these studies has been short, and there is the possibility that in fact people with subclinical cardiovascular disease are those with lower exercise capacity, casting doubt on a causal relationship. Demonstrating that less physical fitness precedes by several years the incidence of cardiovascular events could help to prove this relationship. A Swedish national registry of conscripts studied between 1969 and 1984 provides evidence in this regard.

The study included 743,498 conscripts with a mean age of 18.5 years. Baseline clinical conditions, body mass index (BMI), aerobic fitness evaluated with cycle ergometer (in 62,0089 conscripts since 1972) and expressed in Watts (W), and muscle strength evaluated with dynamometer and expressed in Newtons, were determined as part of the admission studies to the military service. Mean BMI was 21.5 ± 2.7 kg/m². Individuals with lower aerobic fitness and muscle strength had lower BMI, higher prevalence of chronic diseases, and in the following 20 years had less annual income and university education.

At a median follow up of 34 years, those with lower aerobic fitness had greater incidence of acute myocardial infarction (AMI). Considering 5 quintiles according to the W values on ergometer testing, and taking as reference the highest W (HR 1), risk increased progressively as functional capacity decreased (HR from 1.27 in the quintile immediately below the highest, to 2.15 in the lowest, p for trend $p < 0.001$). Further analysis also considering education, socioeconomic factors and baseline conditions partly reduced the strength of the association, but preserved statistical significance. The analysis of muscle strength association with AMI incidence showed less clear results and lower HR. In an analysis in which aerobic fitness,

muscle strength and the mentioned covariates were jointly considered, the association of aerobic capacity with AMI incidence was maintained, but the association with muscle strength was lost. At any stage of fitness, 18-year-old obese men (BMI > 30) had a higher incidence of AMI during follow-up than lean men (BMI < 18.5). Furthermore, obese men in the highest quartile of aerobic fitness were at significantly higher risk than lean men in the lowest quartile.

There are several reasons for reduced risk of coronary events in highly trained subjects, associated to the effect of exercise on blood pressure, insulin resistance, lipid profile, incidence of diabetes, neurohormonal activation, inflammation and hemorheological parameters. The novelty of this epidemiological study is that it suggests that, in principle, higher aerobic fitness in adolescence may lead to a significant reduction of AMI incidence in middle age. In that sense it is a fact in favor of encouraging regular physical activity in children and teenagers. Since data on the follow-up of physical activity are missing, one can assume that increased aerobic fitness at 18 years identifies those who by habit will continue playing sports or training regularly throughout life. However, if regular physical activity had decreased or disappeared after adolescence, and still a low risk of AMI persisted, genetic or metabolic factors associating aerobic fitness and risk of events could be assumed.

Effect of beta-blockers in patients with heart failure, low ejection fraction and atrial fibrillation. A meta-analysis

Kotecha D, Holmes J, Krum H, Altman DG, Manzano L, Cleland JG, et al. Efficacy of beta blockers in patients with heart failure plus atrial fibrillation: an individual-patient data meta-analysis. **Lancet** 2014;**384**:2235-43. <http://doi.org/f2xnh6>

The advent of beta-blocker (BB) treatment for heart failure with reduced ejection fraction (HFREF) showed a significant change in patient outcome and disease prognosis. Several randomized studies clearly showed that BBs significantly decreased mortality and hospitalization in these patients. Therefore, BBs are an AI indication in all HFREF treatment guidelines.

Atrial fibrillation (AF) is an entity whose incidence and prevalence (like that of HF) increases with age. Atrial fibrillation and HF share common etiologic factors (hypertension, valvular disease, neurohormonal and inflammatory activation), and each of them is in itself a predictor of increased incidence of the other. If until 15 years ago it was argued that for the coexistence of HFREF and AF the drug of choice was digoxin, due to its ability to control ventricular response and reduce rehospitalization, in the past decade and a half and in the light of the mentioned studies, it became clear to all that in HFREF, with sinus rhythm (SR) or AF, BBs should be prescribed. A recently published meta-analysis strongly challenges this assumption.

This is a meta-analysis of individual data that included the MDC (metoprolol quick-release), MERIT HF (metoprolol extended-release), CIBIS I and II (bisoprolol), SENIORS (nebivolol), BEST (bucindolol), ANZ, US-HF, CAPRICORN and COPERNICUS (carvedilol) studies. The purpose was to explore the differential effect of BBs in patients with HFREF, with AF versus SR. The primary endpoint was all-cause mortality; secondary endpoints were cardiovascular death and a composite of cardiovascular hospitalization and death.

A total of 18,254 patients were included, of whom 13,946 (76%) had SR and 3,066 (17%), AF. These two groups are the basis of this report. The remaining 7% had other ECG rhythms or unaccountable data.

Compared with patients with SR, those with AF were 5 years older, more frequently in FC III-IV and with more diuretic, digoxin, amiodarone, aldosterone and oral anticoagulation treatment. Left ventricular (LV) EF was the same (median 27%), as was heart rate, (median of 81 vs. 80 beats/minute) and the use of angiotensin-converting enzyme inhibitors (ACEI). During the extent of the studies, the crude mortality rate was 18% with AF versus 14% with SR, and extending follow-up to the immediate phase after completion of the studies, the figures were 21% and 16%, respectively. In patients with AF, median hospitalization was 1.5 to 2 days longer.

In patients with SR, after adjusting for age, sex, LVEF, heart rate and ACEI treatment, BBs significantly reduced the time to overall mortality (HR 0.73, 95% CI 0.67 - 0.80), cardiovascular mortality (HR 0.72, 95% CI 0.65-0.79), the first cardiovascular hospitalization (HR 0.78, 95% CI 0.73-0.83) and the first hospitalization for HF (HR 0.71, 95% CI 0.65-0.77). In contrast, in patients with AF, the corresponding HR were in all cases higher than 0.90 (risk reduction below 10%) and consistently lacked statistical significance. Similar results were found in various sensitivity analyses and with different models to perform the meta-analysis.

What is the reason for these findings? Patients with AF are more severely ill, but this is not a reason to explain BB failure. In fact, in the severely ill patients of the COPERNICUS study, with mean LVEF of 20%, carvedilol produced a reduction in mortality of such a magnitude that the study had to be suspended. In this meta-analysis baseline LVEF and heart rate were similar in SR and AF, and so was the heart rate achieved (although there is some weakness in this respect because we have the heart rate measured in the last visit but lack the heart rate immediately prior to death). An interesting point is that only 58% of patients with AF were anticoagulated. This implies a risk of embolic events, some of them fatal, that BBs cannot prevent. Beyond that, several questions arise. Can death mechanisms differ in AF and SR, so that BBs are more effective in one context than in the other? Does heart rate reduction represent the same in either case? Studies

conducted in patients with AF (mostly with preserved LVEF) suggest that a target heart rate ≤ 80 beats / minute is not better than a target ≤ 110 beats / minute. If heart rate decrease per se is not enough to improve prognosis in HFREF with AF, are the rest of BB properties (anti-ischemic, antiarrhythmic, antiremodeling, metabolic, etc.) enough? How brief the eternal truths in medicine are!

Risk factors, subclinical cardiovascular disease and biomarkers: a univocal relationship?

Xanthakis V, Enserro DM, Murabito JM, Polak JF, Wollert KC, Januzzi JL, et al. Ideal cardiovascular health: associations with biomarkers and subclinical disease and impact on incidence of cardiovascular disease in the Framingham Offspring Study. *Circulation* 2014;130:1676-83. <http://doi.org/zcf>

A favorable profile of vascular risk factors (RF) has been associated with better clinical outcome in all observational studies. It is understood that the clinical manifestation of cardiac and vascular damage is preceded by the presence of subclinical disease. In recent years we have witnessed the discovery and analysis of a large amount of biomarkers (BM) expressing activation of phenomena even preceding preclinical disease, in some cases at least partly responsible for these phenomena. If these assumptions are correct it may be presumed that increased presence of RF must be associated with greater BM alteration, and that this unfavorable profile should initially be related to greater subclinical disease and over time to higher event rate. To confirm this hypothesis, an observational study was designed in the context of the Framingham cohort follow-up.

The study initially included 2,680 participants (sample 1), free of patent heart and vascular disease, with creatinine < 2 mg/dL and body mass index (BMI) ≥ 18.5 kg/m², who underwent clinical evaluation and BM assessment between 1995 and 1998. Among these patients, there was also information of subclinical cardiovascular disease in 1,842 participants (sample 2), and complete data that allowed exploring the relationship with the prognosis in 1,826 participants (sample 3).

The following studies were carried out:

1) Cardiovascular health profile, evaluated with the 7-point score proposed by the American Heart Association (AHA), conferring 1 point for each of these conditions: no smoking or quitting for more than 1 year; healthy diet; regular physical activity (at least 150 minutes of moderate exercise or 75 minutes of vigorous exercise per week); BMI < 25 kg/m²; blood pressure $< 120/80$ mm Hg, serum cholesterol < 200 mg/dL and fasting blood glucose < 100 mg/dL, all in the absence of specific treatment. Seven points imply perfect cardiovascular health.

2) Presence of subclinical disease, if at least one of the following conditions was found: ventricular hy-

pertrophy on ECG or echocardiogram; left ventricular ejection fraction (LVEF) < 50%; urinary albumin-creatinine ratio $\geq 25 \mu\text{g}/\text{mg}$ in men and $35 \mu\text{g}/\text{mg}$ in women; ankle brachial index ≤ 0.9 ; carotid intima-media thickness ≥ 80 th percentile or carotid lesion $\geq 25\%$

3) Expression of inflammatory BM (C-reactive protein), neurohormonal activation [renin, aldosterone, B-type natriuretic peptide (BNP) and N-terminal fragment of pro atrial natriuretic peptide], hemostatic factors [fibrinogen, D-dimer, plasminogen activator inhibitor type-1 (PAI-1) endothelial dysfunction (homocysteine), cardiac stress [high-sensitivity troponin I, ST2 and growth differentiation factor 15 (GDF-15)]

4) Follow up with endpoint of coronary event, heart failure, stroke or transient ischemic attack, or intermittent claudication.

In sample 1, 55% of participants were women and mean age was 58 years. Approximately 30% of participants had a score between 0 and 2; 52% between 3 and 4 and only 18% between 5 and 7 (only 1.4% of women and 0.4% of men had the highest score). The average score was slightly higher among women: 3.4 ± 1.4 vs. 3 ± 1.2 . Considering the 12 BM, only renin, ST2 and troponin showed no association with the AHA score. Adjusting for age and sex, all BM showed higher values when the score was lower (expressing greater activation of biological phenomena when the clinical profile of cardiovascular health was worse), except for natriuretic peptides (NP), where higher values indicated higher scores.

Among the 1,842 sample 2 participants, an inverse association was established between the AHA score and subclinical disease. In a maximum 16-year follow-up period, only PAI-1, BNP and GDF 15 were independent prognostic markers among the 9 BM associated with the AHA score. The cardiovascular health score was a predictor of clinical events, with higher scores associated with better outcomes after adjusting for age, sex, subclinical disease and the 3 BM mentioned.

This study attempted to validate several hypotheses. It confirms that a better risk profile is generally associated with a better BM profile, but it presents the unexpected result of a direct relationship between the AHA score and NP values, which only confirms the complexity of their interpretation. How can this result be explained? Because among patients with high AHA score women predominated (with higher NP values than men) and because NP have higher values, with the same LVEF in lean as in obese patients and not being obese is a criterion for a better score. Another point of note is that only 3 out of 12 BM had independent predictive value, confirming that measuring many of them for a better prognostic and therapeutic approach is, at least wrong. And finally, it should be stressed that even after adjusting for subclinical disease and BM, cardiovascular health score retains predictive value: what it expresses goes beyond our current ability to explain it. Unaccounted factors are immersed in that score, so easy to obtain, and yet unraveled.

Ventricular function and prognosis following percutaneous coronary intervention

Mamas MA, Anderson SG, O’Kane PD, Keavney B, Nolan J, Oldroyd KG, et al. Impact of left ventricular function in relation to procedural outcomes following percutaneous coronary intervention: insights from the British Cardiovascular Intervention Society. *Eur Heart J* 2014;35:3004-12a. <http://doi.org/zcg>

Observational studies have suggested that reduced left ventricular ejection fraction (LVEF) is an adverse prognostic factor in patients undergoing percutaneous coronary intervention (PCI). Between 10% and 30% PCI procedures are performed in patients with LVEF, generally with more extensive coronary disease and higher rate of comorbidities than those with preserved EF. Many of the cited studies are from a decade or two ago, and both the technical procedure and LVEF treatment have progressed significantly since then; hence, there are no current data to confirm or not the previous observations. A recent publication of the British Cardiovascular Intervention Society, which collects data on all PCI performed in the United Kingdom, comes to update knowledge on the subject.

This cohort study includes PCI undertaken between 2006 and 2011. The data were categorized in preserved EF (PEF $\geq 50\%$), moderately reduced EF (MEF, 30-49%) or low EF (LEF, < 30%). The primary endpoints were 30-day-, 1- and 5-year mortality. The incidence of cardiovascular and cerebrovascular major events (ME) and major periprocedural bleeding was also considered. Data adjusted for age, sex, medical history, risk factors and extent of coronary disease, PCI complications and need for circulatory support were analyzed. The prognosis was established according to the type of procedure, elective (E), unstable angina (UA), and ST-segment elevation or non-ST-segment elevation acute myocardial infarction (STEMI or NSTEMI).

Among the 460,124 PCI performed in the study period, 230,464 (50.1%) EF data were collected in the present study. Preserved EF was verified in 69.7% of cases, MEF in 24.7% and LEF in the remaining 5.6%. Worse EF was associated with older age, prevalence of male gender, diabetes, FC III-IV, and more complex coronary history. It was also more frequent to perform PCI in the context of an acute coronary syndrome in patients with LVEF. Specifically, in patients with LEF the radial access was less used and PCI in more than one vessel was more common. Unadjusted 30-day mortality was 0.5% with PEF, 2% with MEF and nearly 10% with LEF ($p < 0.0001$). In the multivariate analysis, and taking patients with PEF as reference, HR for mortality was 2.91 (95% CI 2.43-3.49) for MEF and 7.25 (95% CI 5.87-8, 96) for LEF, $p < 0.0001$ in both cases. Excluding patients with cardiogenic shock or in need for circulatory support did not change the results. There was a gradient of mortality according

to the clinical condition and EF, from 0.22% in E patients with PEF, up to 23.3% in those with STEMI and LEF. The influence of MEF on prognosis did not vary according to the clinical condition considered: it consistently doubled the risk of mortality with respect to PEF. In contrast, LEF compared with PEF implied a HR for mortality of 3.7 in E patients, 5 in those with UA/NSTEMI and 8.2 in STEMI patients. The incidence of ME and bleeding also increased significantly as EF worsened. The prognostic influence of EF on mortality remained at 1 and 5 years.

For various reasons RLVEF may be associated with poor prognosis already within the first month following PCI: sicker patients, diabetics and with more diffuse and complex coronary disease, reduced tolerance to pre and periprocedural ischemia, increased risk of bleeding, and more frequent acute and severe co-morbid conditions. It is clear that the presence of RLVEF should be cause for alert during PCI, and should be valued in all its magnitude as a risk marker beyond coronary anatomy and electrocardiographic changes.