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Functional or anatomical approach to diagnose coronary artery disease? The PROMISE trial

Douglas PS, Hoffmann U, Patel MR, Mark DB, Al-Khalidi HR, Cavanaugh B, et al. Outcomes of anatomical versus functional testing for coronary artery disease. **N Engl J Med 2015;372:1291-300.http://doi.org/46m.**

Different strategies can be adopted in a patient who, without prior coronary artery disease, presents with chest pain suggestive of angina. If the condition does not require hospitalization or urgent decision-making, and the probability of coronary artery disease before testing is intermediate, a functional approach has been usually taken, with ischemic-evocative testing, from exercise stress test (EST) to imaging, nuclear medicine or echocardiography studies, all with exercise or pharmacologic stress. In the last years, a new study has been incorporated: coronary computed tomography angiography (CTA), allowing the non-invasive study of coronary anatomy. Each of the mentioned methods has its advocates, conditions in which it is more useful and well-known sensitivity and specificity. The PROMISE trial postulated the comparison between both the anatomical and functional approach in stable patients with chest pain and undiagnosed coronary artery disease. The proposal did not aim at comparing the diagnostic ability of both strategies, but the outcome of patients submitted to either approach.

The study included patients with symptoms suggestive of coronary artery disease, over 54 years of age in men and 64 years in women, or between 45 and 54 years in men and 50 and 64 years in women, presenting any major coronary risk factor or evidence or peripheral vascular or cerebrovascular disease. They were randomly assigned to CTA or functional testing (FT). The primary endpoint was the composite of all-cause mortality, acute myocardial infarction (AMI), hospitalization for unstable angina and major procedural complications occurring within 72 hours after their performance. The study aimed at demonstrating the superiority of the strategy based on CTA, assuming a rate of events of 8.5% at 2.5 years in the FT group, with 20% reduction in the CTA group. The study was planned so that in the event of nonsignificant superiority, at least noninferiority could be demonstrated, accepting up to 10% excess of events in the CTA group, i.e that the upper limit of the HR 95% CI arising from comparing TCA vs. FT was not greater than 1.10.

A total of 10,003 patients were included in the study, 5,007 in the FT group. Mean age was 60.8 years, 52.7% were women, 21.4% were diabetic, 65% hypertensive, 67.7% dyslipidemic, 51.1% were past or current smokers and 32.1% had a family history of coronary artery disease. Slightly over 73% of patients reported chest pain, 14% dyspnea on exertion and the remaining patients other symptoms. Angina was classified as typical in 77.7% of patients, typical in 11.7% and nonanginal pain in the remaining patients. Two-third of patients had a 10-year calculated risk of events ≥7.5%. Twenty-five percent of patients were receiving beta-blockers and between 43% and 46% each of the following: aspirin, statins, or renin-angiotensin system inhibitors or blockers.

In the FT group, nuclear stress testing was used in 67.5% of cases, echocardiography in 22.4% and EST in 10.2%. In 25% of imaging studies the stress was pharmacological. Coronary artery disease was diagnosed only in 10.7% of cases with CTA and 11.7% with FT. In a median follow-up of 25 months the incidence of the primary endpoint was 3.3% with TCA and 3% with FT (HR 1.04, 95% CI 0.83-1.29; p=0.75). It can be seen that no superiority or inferiority could be demonstrated in the TCA group. Also, no significant results were found for the secondary endpoint, including the primary endpoint plus coronary catheterization to demonstrate nonobstructive coronary artery disease: 6.6% vs. 7.1%. Within 90 days after inclusion, 12.2% of patients in the TCA group underwent catheterization and 3.4% of these patients showed no evidence of obstructive coronary artery disease. In the FT group, these values were 8.1% and 4.3%, respectively, with significant differences between both strategies. Among patients undergoing studies requiring radiation, median exposure was slightly less in patients submitted to TCA than to nuclear stress testing.

The PROMISE study should be complimented for focusing on a topic of clinical interest: what are the consequences of choosing an anatomical versus a functional approach in patients with suspected coronary artery disease. The study could not demonstrate differences in the endpoints selected and some considerations should be formulated. Despite the high prevalence of risk factors and 53.3% calculated obstructive coronary disease, only 10% of tests were positive. This leads us to question the adequacy of current criteria. Concurrently, the rate of events was low. Two non-excluding explanations emerge: the symptom leading to test performance was atypical angina in three out of four cases, and/or the patients were adequately medicated. A question arises: if the outcome of patients submitted to different strategies was being explored, why was revascularization not an endpoint? Coronary computed tomography angiography led more patients to receive coronary angiography and there were more

revascularization procedures: 6.2% vs. 3.2%. In conclusion, there are no differences in hard events in a population as the one described in the study with either approach. In each case, the diagnostic method should be based on patient characteristics, clinical impression, decision on the conduct to follow according to results, and available resources.

The value of ultrasensitive troponin T in the real world. The SWEDEHEART Registry

Melki D, Lugnegard J, Alfredsson J, Lind S, Eggers KM, Lindahl B, et al. Implications of Introducing High-Sensitivity Cardiac Troponin T Into Clinical Practice: Data From the SWEDEHEART Registry. **J Am Coll Cardiol 2015;65:1655-64.http://doi.org/f27h2r**

Elevated troponin values are an essential part of acute myocardial infarction (AMI) diagnosis, and have a clear role in the decision for invasive conduct in a patient presenting with chest pain or equivalent condition. Recently, the introduction of high-sensitivity or fifth-generation troponin T (hsTnT) has become widespread. This assay has a 5 ng/ml limit of detection and the cut-off value for the diagnosis of myocardial necrosis is 14 ng/mL, which is correspondent to a healthy population´s 99th percentile. The cut-off value of the previous fourth generation assay was 30 ng/mL, which is equivalent to approximately 50 ng/mL of hs-TnT.

The national Swedish SWEDEHEART registry includes almost all patients admitted in a coronary care unit or equivalent for acute coronary syndrome (ACS). We considered patients hospitalized between 2009 and 2012, with diagnosis of ACS, and evaluated the role of hs-TnT assessment. A total of 48,594 were included during that period. Four groups were defined according to hs-TnT values on admission: a) group 1, hs-Tnt ≤5 ng/mL in 11.9% of cases; b) group 2, hs-TnT from 6 to13 ng/mL (detectable but below the cut-off value for necrosis) in 13.4% of cases; c) group 3, hs-Tnt from 14 to 49 ng/mL (over the cut-off value for necrosis, but still below the value equivalent to 30 ng/mL corresponding to the cut-off value of the previous assay) in 21.6% of cases; and d) group 4: hs-TnT ≥50 ng/mL (diagnosis of necrosis with any of the two assays) in 53.2% of patients.

Patients in groups 3 and 4 had similar age, sex and coronary artery risk factors. Notably, the incidence of history of AMI, coronary surgery and heart failure was higher in group 3, and hence, aspirin, statin or neurohumoral antagonist therapy was more prevalent. An ascending prevalence was found for coronary angiography (from 24.5% in group 1 to 69.7% in group 4), significant coronary artery disease (from 43% in group 1 to 71% in group 3 and 87.7% in group 4) and percutaneous coronary intervention (from 8.5% in group 1, to 23.1% in group 3 and 49.2% in group 4). The prevalence of left ventricular dysfunction also increased: from 9.8% in group 1 to 45% in group 4.

Finally, ACS diagnosis (AMI between brackets) in group 1 was 30.5% (2.2%); in group 2, 48.3% (2.6%); in group 3, 61.7% (18.2%) and in group 4, 89.6% (81.2%). One-year mortality was 1.6% in group 1, 2.4% in group 2, 10.3% in group 3 and 17.1% in group 4.

The value of this registry lies in exploring the use of hs-TnT in the real world. It can be seen that group 3 patients (those who would not have been diagnosed with necrosis using the previous assay, but had a positive result with hs-TnT) comprised more than 21% of the total number of patients enrolled in the study, 1 every 5 patients. They had more prevalence of coronary artery disease, ventricular dysfunction and worse prognosis than patients with lower hs-TnT values. However, it is also true than in almost 40% of these patients, ACS was not diagnosed and AMI was only diagnosed in 18%. And these data come from hospitalized patients with presumed diagnosis of ACS, that is, already selected patients! This point seems crucial and should be engraved with fire: hs-TnT expresses myocardial damage or injury, but it is not a synonym for AMI: many patients with structural cardiomyopathy, chronic coronary artery disease, heart failure, renal failure, etc, may present persistent troponin elevation not associated with AMI, or an acute coronary disorder, or acute elevations in the context of other disorders, from atrial fibrillation to pulmonary embolism. And though it is clear that higher values imply worse prognosis, it is also true that they are sometimes due to chronic processes, not needing urgent hospitalization but a deeper analysis of patient condition. The diagnosis of ACS or AMI must consider prior history, clinical condition, ECG and, of course, biomarkers. It has become common to rely on hs-TnT to make a diagnosis: its elevation seems for many to signify AMI, as well as low values sometimes leave without hospitalization patients who clearly have angina at rest. Only the careful use of hs-TnT will allow a better decision in each case: not preventing the hospitalization of an acute patient and not hospitalizing a patient just for finding a slightly elevated biomarker.

Relationship between low cardiac output and dementia: beyond the traditional predictors. A cohort study from the Framingham registry

Jefferson AL, Beiser AS, Himali JJ, Himali JJ, Seshadri S, O'Donnell CJ, et al. Low cardiac index is associated with incident dementia and Alzheimer disease: the Framingham heart study. **Circulation 2015;131:1333-9.http://doi.org/46n**

Different cross-sectional studies have demonstrated that small reductions in cardiac index (CI) are associated with cognitive impairment, lower cerebral volume and increased white matter intensity. However, this relationship might be affected by the greater prevalence of risk factors and cardiovascular disease found in patients with reduced CI that could be the

real responsible causes of such cognitive injury. A longitudinal sub-study among the descendants of the first Framingham Registry participants (which started in 1948), recruited between 1971 and 1975 (called the Framingham Offspring cohort) provides valuable information in this regard.

Among 3,539 participants examined between 1998 and 2001, 1,677 underwent cardiac magnetic resonance imaging (CMRI) between 2002 and 2006, assessing ventricular volumes and CI. On admission, demographic variables, risk factors, prior cardiovascular disease and educational level were collected. During follow-up, prospective neurologic and neurocognitive studies were performed to define the incidence of dementia and specifically Alzheimer disease.

After this analysis, 552 participants aged <60 years were excluded from the study, 29 with dementia or previous stroke and 57 with incomplete data, resulting in a final cohort of 1,039 subjects. Mean age was 69 years and 53% were women. Mean CI was 2.7±0.5 L/min/m2; a reduced CI (less than 2.5 L/min/m2) was found in 33% of all participants and in 31% after excluding those with previous cardiovascular disease. In a median follow-up of 7.7 years, 32 participants developed dementia, attributable to Alzheimer disease in 26 of them.

Considering CI as a continuous function and in a model adjusted for age, sex and education, each drop of one standard deviation in CI was associated to excess risk of developing dementia (HR 1.71 95% CI 1.14-2.57; p=0.01), with similar values for Alzheimer disease. Also, adjusting for the Framingham score or excluding from the analysis patients with atrial fibrillation or established cardiovascular disease (understanding that the risk of dementia is increased in these patients) did not modify findings.

When CI was treated in a categorical manner (higher or lower than 2.5 L/min/m2) and adjusting for age, sex, education and Framingham score, a low CI was again associated with greater risk of dementia (HR 2.07, 95% CI 1.07-4.19; p=0.04). In this case, the independent prediction of Alzheimer disease was in the limit of statistical significance (HR 2.10, 95% CI 0.96-4.61; p=0.06). Once again, the exclusion of patients with atrial fibrillation or cardiovascular disease did not change the association.

This study, due to its longitudinal and prospective character adds information to previous cross-sectional studies, showing the association of hemodynamic impairment with increased risk of dementia and indicating that this risk goes beyond prior cardiovascular disease. One limitation of the study is that findings can only refer to the population studied, i.e. to subjects over 60 years, and another is that the number of events during follow-up was low, reducing the analysis power. It is remarkable that one third of participants had CI below the value considered normal, leaving open the possibility that in many cases there was subclinical diastolic failure. The responsible mechanism seems to be, in principle, the loss of brain blood flow autoregulation secondary to hemodynamic impairment, favoring degenerative processes and accumulation of amyloid substance (associated to Alzheimer´s disease). Lack of neurologic images as well as an initial assessment of brain circulatory status do not allow defining whether the decrease in CI may act as an isolated factor in healthy individuals or if it is really manifested in those with subclinical cerebrovascular injury.

Does extended duration dual antiplatelet therapy increase mortality? A systematic review and meta-analysis

Elmariah S, Mauri L, Doros G, Galper BZ, O'Neill KE, Steg PG, et al. Extended duration dual antiplatelet therapy and mortality: a systematic review and meta-analysis. **Lancet 2015;385:792-8.http://doi.org/f259ts**

Dual antiplatelet therapy (DAT) with aspirin and thienopyridine is used in several cardiovascular diseases to decrease the risk if ischemic complications. Different randomized studies have evaluated the role of extended duration DAT: it increases the protection against ischemic events and at the same time the incidence of bleeding. The optimal duration of DAT therapy, with greater reduction of ischemic events and less incidence of bleeding, has not been clarified yet, and probably varies from patient to patient. A still unanswered question is whether extended duration DAT has an influence on vital prognosis. In some randomized studies there has been no effect on mortality; however, in the DAPT study, reviewed in a previous issue of the Journal, despite reduced incidence of stenting myocardial infarction and thrombosis, it evidenced increased overall mortality, at the expense of non-cardiovascular deaths.

The present meta-analysis considered randomized, controlled trials where extended duration DAT was compared with aspirin or was tested against short duration DAT, reporting on mortality. It included 14 trials with 69,644 patients. Baseline condition was acute coronary syndrome or percutaneous coronary intervention in 10 trials (among them, the CURE, CREDO and DAPT trials, n=42,616), peripheral vascular disease revascularization in the CASPAR trial, atrial fibrillation in the ACTIVE-A trial (n=7,554), recent lacunar stroke in the SPS-3 trial, or clinical conditions of high ischemic risk in the CHARISMA trial (n=15,603). In 8 trials (n=57,542) DAP was compared with aspirin, in some (as the CHARISMA trial) since study onset, in others (as the DAPT trial) after an initial period of DAP in all patients. In the remaining studies, extended duration DAT was compared with short duration DAT. The difference in the extent of treatment with extended duration DAT vs. the comparator ranged between 6 months (in studies with percutaneous coronary intervention comparing 6- vs. 12-month DAT) and 43 months in the ACTIVE-A trial.

In the meta-analysis, extended duration DAT did not increase mortality with respect to the comparator (HR 1.04, 95% CI 0.96-1.19). Results were similar after excluding the DAPT trial. Similarly, there was no evidence of increased cardiovascular (HR 1.01) or non-cardiovascular (HR 1.04) mortality in the 12 and 11 studies reporting them, respectively. Neither were there differences among the 10 studies evaluating coronary artery disease and the remaining studies. A sensitivity analysis excluding each study at a time and analyzing the rest showed similar results. Meta-regression, seeking to find a relationship between the difference in treatment duration with extended duration DAT versus the comparator and mortality also showed no significant result.

This meta-analysis rejects the idea that extended duration DAT is associated with excess mortality. It does not exclude it completely, as the 95% CI upper limit is 1.19, implying that up to 19% increase is possible. However, the consistency of results in various sub-analyses and the sensitivity analysis make it reliable. As it is not a meta-analysis of individual data it is not possible to know whether specific patient characteristics are associated with increased risk. Clopidogrel was the thienopyridine used for DAT in most patients; thus, conclusions are applicable to that specific drug. Populations, treatment regimens and DAT duration were dissimilar among studies, but with no heterogeneity in the results, reinforcing the credibility of findings. Therefore, the decision about the advantages and disadvantages of extended duration DAT should continue to be established in each individual case, and will still be focused on ischemic risk and hemorrhagic risk.

Overall cardiovascular mortality in the last 25 years: figures and determinants

Roth GA, Forouzanfar MH, Moran AE, Barber R, Nguyen G, Feigin VL, et al. Demographic and epidemiologic drivers of global cardiovascular mortality. **N Engl J Med 2015;372:1333-41.http://doi.org/46p**

Globally, the overall number of cardiovascular deaths worldwide has increased in the last decades. Different factors influence this phenomenon, among them the increase in population (logically implying more deaths), progressive aging (at older age, the chance of cardiovascular death is greater) and epidemiological and therapeutic modifications (prevalence of risk factors, progress in therapy, etc). The 2013 Global Burden of Disease Study (GBD 2013) assessed specific mortality by age in 188 countries grouped in 21 regions, and its variation between 1990 and 2013, considering 240 causes of death. The substudy presented here focused on cardiovascular mortality, taking into account 10 specific causes (ischemic, hypertensive and rheumatic heart disease, ischemic and hemorrhagic stroke, cardiomyopathy and myocarditis, endocarditis, atrial fibrillation and flutter, aortic aneurysm, and peripheral vascular disease) and a category comprising the remaining cardiovascular causes of death. The number of cardiovascular deaths, population growth, changes in population structure related to sex and age and epidemiological changes, taken as variation in specific mortality rate for age, sex and cause unexplained by population growth or aging, were assessed in each country between 1990 and 2013. Three scenarios were considered: a) one contemplating the number of expected deaths in 2013, when only the population increase between those two years was taken into account, considering the population structure of 1990. This first scenario provided information on the increased number of deaths attributable only to population growth; b) a second scenario in which the expected number of deaths in 2013 was calculated contemplating not only population growth but also its aging, keeping the specific rates of death for each cause, sex and age of 1990 constant. The difference in the number of deaths between the second and the first scenario would indicate the expected number of deaths exclusively due to population aging; c) a third scenario, with the number of deaths really observed in 2013, where the difference with respect to the number of expected deaths in the b) model would then represent the number of deaths attributable to epidemiological differences.

Therefore, in 2013, almost 17.3 million cardiovascular deaths represented an increase of almost 41% with respect to 1990, when 12.3 million had been registered. This increase in the number of deaths was attributable to 25% increase in population growth, 55% increase in population aging and 39% decrease in epidemiological changes. Among the 5 million extra deaths between both years, almost 50% were due to ischemic heart disease, although there was an estimated 34% reduction in its prevalence. The characteristic death increase by population growth and aging and decrease for epidemiological reasons was the same for almost all the causes of cardiovascular death, but in the case of rheumatic heart disease the epidemiological decrease was so high that the algebraic sum resulted in 26% reduction in the number of deaths between 1990 and 2013 (only cause presenting decrease in the total number of deaths over the study interval). Atrial fibrillation/flutter and peripheral vascular disease were exceptions to the above; in both cases, death increased due to the three factors, population growth and aging and also, for epidemiological reasons; therefore the increase in the number of deaths was 288% and 155%, respectively, above the other etiologies. In the analysis by regions, Southern Asia showed the highest increase of cardiovascular deaths (97%), whereas a decrease was found in Central and Western Europe. Our Latin American region showed no changes.

This analysis reveals that were it not for the increase in population growth and aging, the number of cardiovascular deaths would have been lower in 2009 than in 1990. Previous studies had attributed half of this descent to improved treatment. But, as seen, only

in some countries can this progress and epidemiological changes generate a true reduction in the number of deaths. Better life conditions and prevention of early deaths appear paradoxically to be mainly responsible for the increase in cardiovascular deaths. Shall we read reports in the future about the increase of deaths for cancer because those due to cardiovascular disease have decreased?

Monoclonal antibodies and LDL reduction: a new hope?

Sabatine MS, Giugliano RP, Wiviott SD,Raal FJ, Blom DJ, Robinson J, et al. Efficacy and safety of evolocumab in reducing lipids and cardiovascular events. **N Engl J Med 2015;372:1500-9.http://doi.org/46q**

Reduction of LDL cholesterol levels is a central part of primary and secondary prevention of cardiovascular events. Proprotein convertase subtilisin–kexin type 9 (iPCSK9) inhibitors have emerged as a new kind of drugs aimed at achieving this goal. Evolocumab (E) is one component of this family of drugs, already tested in several phase 2 (MENDEL 1, LAPLACE-TIMI 57, GAUSS 1, RUTHERFORD 1 and YUKAWA 1) and phase 3 (MENDEL 2, LAPLACE 2, GAUSS 2, RUTHERFORD 2, DESCARTES, THOMAS 1 and THOMAS 2) trials, where it has been shown to achieve approximately 60% reduction in LDL cholesterol values. After completing these studies, participants were invited to enroll in open-label, long-term follow-up studies: the OSLER 1 study for those who had participated in any phase 2 trial, and the OSLER 2 study for the ones who had taken part in the phase 3 trials. Patients with no adverse events leading to study drug discontinuation, no clinical unstable condition in the initial study, and in whom it would not be necessary to unblind lipid values or need adjustment of background lipid-regulating therapy during the first 12 weeks of participation in the OSLER trials could be included in these studies. Independently of the treatment they had received in the initial study, patients were assigned to receive E plus standard therapy for dyslipidemia versus open-label standard therapy in a 2:1 ratio. Evolocumab was administered subcutaneously: at a dose of 420 mg once a month in OSLER 1; at a dose of 140 mg every 2 weeks or 420 mg once a month in OSLER 2 (both schemes offer similar results). The primary endpoint was safety: incidence of adverse events. Other safety primary endpoints included major adverse events, need for E discontinuation, and abnormal lab tests. The secondary endpoint was efficacy: LDL cholesterol reduction; other efficacy endpoints were E effect on other lipid values. The effect on cardiovascular and cerebrovascular events was used as exploratory evaluation. The sponsor (Amgen) was responsible for the design, and data collection and analysis.

Between 2001 and 2014, 4,465 patients (74.1% of participants in any of the initial studies) were included in the OSLER program (1,324 in OSLER 1, and the rest in OSLER 2). Mean age was 58 years, 80% had at least one additional coronary risk factor and 70% were under statin therapy. Median LDL cholesterol at study onset was 120 mg/dL.

The incidence of adverse events was 69.2% in the E group and 64.8% in the other group (p=0.003), with similar incidence of major adverse events in both groups: 7.5%. In 7.2% of participants E had to be prematurely discontinued. Although with low incidence, the prevalence of neurocognitive adverse events was higher with E: 0.9% vs. 0.3%, as well as a certain excess of arthralgias, cephalea and limb pain. At the end of the first 12 weeks, E treatment plus standard therapy reduced LDL values by 61% with respect to standard therapy alone (p<0.001). This decrease was preserved during follow-up (median of 11 months). There was also a significant reduction in the other lipid values. The exploratory analysis of clinical impact showed advantages for E treatment in the incidence of cardiovascular events [0.95% vs. 2.18% (HR 0.47, 95% CI 0.28-0.78; p=0.003].

iPCSK9 agents have emerged as a new tool for the treatment of patients with dyslipidemia. Evolocumab produced a marked decrease of LDL values in the OSLER program. The reduction in clinical events must be regarded with caution, as this was not a primary endpoint of the study. However, a recently reported meta-analysis, by Savarese et al., considering 24 randomized studies with 10,159 patients and which did not include OSLER, showed similar results to this study: an average decrease of 47% in LDL values and a drop of 50% overall mortality risk and acute myocardial infarction. Independently of these results, some concerns can be expressed: OSLER was an open-label program, with a very low incidence of events because the population was not high risk. Hence, the annual overall event reduction was slightly over 1%, and specifically mortality, decreasing from 0.4% with standard therapy to 0.14% with E. The greater incidence of neurocognitive events must be clarified to dispel doubts. Properly designed studies should confirm the ability of these drugs to substantially modify the prognosis. Even if this were the case, the issue of costs will not be a minor concern in the future in case its use is authorized. Only cost-effectiveness analyses will define the place they merit in treatment guidelines and the specific groups of patients which may benefit from them.

Relation between door-to-balloon time and mortality in ST-segment elevation myocardial infarction: the relevance of an adequate analysis

Nallamothu BK, Normand SL, Wang Y, Hofer TP, Brush JE Jr, Messenger JC, et al. Relation between door-to-balloon times and mortality after primary percutaneous coronary intervention over time: a retrospective study. **Lancet 2015;385:1114-22.http://doi.org/f26rfh**

Door-to-balloon time (DBT, the time elapsing from pa-

tient arrival to hospital to balloon inflation) has been considered one of the strongest predictors of mortality in the context of ST-segment elevation acute myocardial infarction (STEMI). This has led to campaigns aimed at shortening this time, and all practice guidelines emphasize the need to achieve times under 90 minutes. However, in the last years, observational studies have shown that despite a significant reduction in DBT, this has not been accompanied by a decrease in mortality. In this sense, one of the most important studies is that of Menees et al (N Engl J Med 2013;369:901-9) based on The Catheterization and PCI Registry Data of the National Cardiovascular Data Registry of the United States, supplied by over 1,400 hospitals throughout the country. In this work, excluding patients referred for PCI from another center and those with DBT greater than 3 hours, the authors showed that although median DBT had fallen from 83 to 67 minutes between 2005 and 2008, mortality remained constant at 5% vs.4.7%. These results and others from similar communications led to the conclusion that DBT is a minor determinant of mortality and that therefore other predictors should be sought and worked on.

Conversely, the authors of the present study hypothesized that patient profile might have changed to explain lack of overall mortality reduction, and that at the individual level a lower DBT still results in better prognosis. With similar inclusion criteria as in the study of Menees et al. they considered patients from the same Registry, with STEMI and PCI, and performed a multiscale statistical analysis, allowing the simultaneous study of the population and each individual patient´s DBT. Moreover, taking into account Medicare and Medicaid data as reference they could predict the 6-month outcome of Registry patients 65 years of age or older.

They thus incorporated 151,116 PCI performed on 146,940 patients. Procedures ranged from 15,730 in 2005 to 24,449 in 2011, representing an increase of 55% between those 2 years. Over this period, there was a slight increase in age and prevalence of diabetes, dyslipidemia and prior revascularization procedures, and a marked decrease in the use of drug-eluting stents (from 76% to 53%) and glycoprotein IIb/IIIa inhibitors (from 73% to 45%). Conversely, use of direct thrombin inhibitors increased from 10% to 42% and that of manual thrombectomy from 12% to 39%. Concomitantly, between 2005 and 2011, median DBT fell from 86 to 63 minutes ($p<0.001$); in-hospital mortality adjusted by patient factors, AMI and the procedure showed a tendency to increase: from 4.7% to 5.3% ($p=0.06$), and in the subgroup of patients aged 65 years or older, the 6-month adjusted mortality increased from 12.9% to 14.4% ($p<0.001$). At the individual level, the adjusted DBT analysis showed a significant 8% reduction in annual in-hospital mortality risk and 6% in 6-month mortality risk for each 10 minute decrease in DBT. But, and this reveals the progressively poorer prognosis with passing years, the same DBT was associated with worse prognosis in successive years. For example, 10% of patients with the highest DBT in 2005 (median DBT of 154 minutes) showed 8.1% of in-hospital mortality; and equivalent patients in 2011 (with a lower median DBT of 127 minutes) had 11% in-hospital mortality. Therefore, each year, and adjusting for all the variables described and the individual DBT, the annual DBT, for each successive year, was associated with 12% in-hospital mortality risk and 11% 6-month mortality risk .

This thorough analysis reveals the multiplicity of factors influencing event assessment, and how another turn of the screw is always possible. Against the fact of considering that the decrease of DBT has no prognostic implication in STEMI, this analysis shows that this is not the case, and that, other factors associated with the annual increase of in-hospital and long-term mortality should also be taken into account. The conclusions of the studies that originated the latter are due to the various levels of assessing results, and an example of ecologic fallacy: the false inference that is made when applying at the individual level information that is valid for a certain special, temporal or social context. Thus, in wealthier countries, the body mass index is greater; but in each country, the poorer people have the highest values. In this case, in the year of lowest DBT, mortality was higher; but in each year, a lower DBT was associated with lower mortality. There are, however, some limitations: the relationship between a decrease in DBT and lower mortality arises from observation (although, could it emerge from a randomized study?); it is possible that such relationship is not linear and essentially, it is not clear which factors are responsible for higher mortality during the study period.

Do not smoke! And if you do, do it be far away from your children: smoke damages their arteries. A Finnish study

West HW, Juonala M, Gall SL, Kähönen M, Laitinen T, Taittonen L, et al. Exposure to parental smoking in childhood is associated with increased risk of carotid atherosclerotic plaque in adulthood: the Cardiovascular Risk in Young Finns Study. **Circulation 2015;131:1239-46.http://doi.org/46r**

There is a well-known association between parental smoking and increased vascular disease in their children when they reach adulthood, independently of their lifestyle and risk factors. A refined corroboration stems from the prospective Cardiovascular Risk in Young Finns Study, carried out in five university cities to show the association of risk factors in childhood and adolescence with cardiovascular disease at adulthood.

Among 3,596 children or adolescents aged 3, 6, 9, 12, 15 or 18 years assessed in 1980, 2,991 were reassessed in 1983. In both years, parents completed questionnaires on their smoking habits at the year of

interrogation and were divided, one or both parents, in never, occasional or current smokers. In 1980, cotinine dosage (expression of nicotine exposure) was available in 1,578 participants. Based on parental answers and cotinine dosage in children, three categories were generated: children whose parents did not smoke; children whose parents smoked but were not submitted to passive smoking (undetectable cotinine) and children whose parents smoked and were passive smokers (cotinine level between 0 and 3 ng/ml). Cotinine >3ng/ml was considered active smoking, and 248 participants presenting this condition were excluded from the analysis.

In 2001 and 2007, a carotid artery B-mode ultrasound was performed in 2,448 participants of the primitive population, assessing intima-media thickness. Mean age was slightly over 36 years. Evidence of carotid plaque was found in 2.6% of participants. In a multivariate model (adjusted for age, sex, vegetable and fruit intake and body mass index in childhood, smoking habit at the time of study, lipid level values, blood pressure and current body mass index) the fact that parents had declared in 1980 or 1983 having ever smoked was associated with 2.6 RR of carotid plaque in their offspring (95% CI 1.3 to -5.3;p=0.007); and if they had declared they were current smokers during that period with 1.7 RR (95% CI 1 to -2.8; p=0.04.

Compared with offspring of parents who had never smoked, children whose parents smoked but were not submitted to passive smoking presented a higher prevalence of carotid plaque (almost double), but without statistical significance. However, the association was significant, with a fourfold greater risk of carotid plaque due to passive smoking in childhood, which was even higher when maternal instead of paternal smoking was involved: among the offspring whose parents had declared being current smokers, the RR was 5.2 if the mother smoked and 2.7 if the father smoked.

Several factors can explain the link between smoking and atherosclerotic disease: lipid peroxidation, accumulation of cholesterol esters in the plaque, platelet activation, inflammation and endothelial dysfunction. Passive smoking is almost as harmful as active smoking. Policies restricting smoking in public areas may have displaced smokers to private places, and doubtless, the home is the ideal place. This study, commendable for its prospective design and the long-term follow-up, over 25 years, emphasizes a fundamental fact: the ability of adversely affecting the health of the most beloved ones by not taking the necessary precautions. We could wonder whether with a larger number of observations, the association of vascular disease with parental smoking habits would have been significant, even in cases when they did not smoke in front of their children. Study limitations are the observational nature of these findings and the possibility of residual confounding due to the presence of unaccounted variables.