JORGE THIERER

Angina with normal coronary arteries: an entity with a distinct outcome?

Radico F, Zimarino M, Fulgenzi F, Ricci F, Di Nicola M, Jespersen L, et al. Determinants of long-term clinical outcomes in patients with angina but without obstructive coronary artery disease: a systematic review and meta-analysis. **Eur Heart J 2018;39:2135-46. http://doi.org/gdd2g7**

Angina with normal coronary arteries or without obstructive coronary artery disease is defined as the presence of this symptom in the absence of ≥ 50% diameter stenosis in any major epicardial vessel. This condition has controversial prognostic implications. Many studies claim that it is associated with greater incidence of adverse events, while others have only documented impaired quality of life. A recently published meta-analysis deals with some precisions on this matter.

The meta-analysis included observational studies published in English between 1980 and 2017 reporting the incidence of events with follow-up duration of at least one year. Studies enrolling asymptomatic patients, those with acute coronary syndromes, Takotsubo syndrome, other cardiomyopathies, end-stage chronic kidney disease, and heart-transplant recipients were excluded from the analysis. The primary composite endpoint was all-cause death and acute myocardial infarction (AMI). Fifty-four studies met the inclusion criteria, accounting for 35,039 patients with mean age of 56 years, 51% men, and a 5-year median follow-up.

The annual incidence of the composite primary endpoint was 0.98% (95% CI 0.77–1.19). There was considerable heterogeneity among studies which demanded secondary analyses to explore its sources. These analyses showed an association between the incidence of events with the presence of dyslipidemia, diabetes and hypertension, but failed to reveal any significant association with age, sex, smoking history or obesity. There were significant differences according to the type of coronary artery involvement. In studies including patients with less-than-obstructive coronary artery disease (stenosis < 50%), the incidence of the primary outcome was 1.32% compared with 0.52% in studies including only patients with angina and entirely normal coronary arteries ($p < 0.01$). Although there was no significant difference in the incidence of events between studies that required documentation of ischemia and those that did not, in studies where documentation was required, the incidence of events was higher when myocardial ischemia was defined by using imaging techniques (1.52% person-years) than in those which used an exercise stress test (0.56% person-years). Studies enrolling patients with typical angina showed a trend towards a higher incidence of the primary outcome than those enrolling patients with undefined angina.

Mortality at one year was 0.65%. Again, angina with non-obstructive coronary artery disease was associated with significantly higher all-cause mortality (0.74/100 person-years) compared with absence of coronary artery disease (0.28/100 person-years), $p < 0.01$. The annual incidence of non-fatal AMI and of cardiovascular hospitalization was 0.32% and 2.62%, respectively, with a considerable heterogeneity among studies.

For a long time, the presence of angina in the absence of significant coronary artery disease was undoubtedly considered an inconvenience that did not obscure the prognosis. This meta-analysis differs from previous reports as it considered stricter selection criteria, excluding asymptomatic patients or acute coronary syndromes, focusing on the condition of interest. It confirms that the incidence of events in patients without significant coronary artery disease is higher than in the general population but lower than in those with obstructive coronary artery disease. The existence of a gradient (more events with more severe disease) is confirmed with the evidence of worse prognosis in the presence of angina when there is at least some coronary artery disease, and more confirmed evidence of a certain degree of ischemia. It is possible that we are in the presence of greater prognostic risk due to a combination of atherothrombosis and endothelial dysfunction. The heterogeneity of the results suggests that not all "anginas with normal coronary arteries" represent the same. So, what can we consider when dealing with these patients? Undoubtedly, risk factors should be managed more aggressively, particularly when there is some solid evidence of ischemia, or when the atherosclerotic disease becomes evident. Although a meta-analysis of individual data is certainly preferred (this is not the case), the information we present is rich and not negligible.

Left atrial appendage occlusion in the setting of cardiac surgery

Yao X, Gersh BJ, Holmes DR, Jr., Melduni RM, Johnsrud DO, Sangaralingham LR, et al. Association of Surgical Left Atrial Appendage Occlusion With Subsequent Stroke and Mortality Among Patients Undergoing Cardiac Surgery. **JAMA 2018;319:2116-26. http://doi.org/crmz**

Many patients with history of cardiac surgery have or had atrial fibrillation (AF). Because thrombi in the left atrial appendage are common, surgical occlusion of

the left atrial appendage is sometimes performed during surgery to reduce long-term risk of stroke. Some observational studies suggest a favorable effect of this procedure "added" to the primary indication of surgery, but the information available is not conclusive. It is also debated whether it is essential for patients to be fibrillated at the time of surgery to perform left atrial appendage occlusion or whether it is only necessary that patients have a history of AF even though they are at sinus rhythm at the moment of surgery.

A large cohort study performed at the Mayo Clinic provides relevant information on this topic. The study used information from an administrative database of the United States comprising patients with private insurance and Medicare beneficiaries, >18 years old, who underwent their first coronary artery bypass or heart valve surgery (replacement or repair) between 2009 and 2017. The primary endpoint was ischemic stroke or systemic embolism and all-cause mortality. The secondary endpoints were postoperative AF within 30 days after surgery (in patients with sinus rhythm at the moment of surgery) and long-term AF-related health utilization.

A total of 75,782 patients were included; 71% were men and mean age was 66 years; 33.9% had preexisting AF and 89% presented a CHA2DS2-Vasc score ≥ 2. Left atrial appendage closure was performed to 5.8% of the patients during surgery. The factors associated with the performance of this procedure included a history of AF, valve surgery and the use of oral anticoagulants before the surgery. A one-to-one propensity score matching was used to balance patients (based on 76 variables) in order to compare patients with versus those without left atrial appendage occlusion. The final cohort was made up of 8,590 patients, 4,295 with and 4,292 without left atrial appendage occlusion. Among these patients, 25.1% had no prior history of AF.

Left atrial appendage occlusion was associated with lower incidence of ischemic stroke or systemic embolism (1.14% vs. 1.59% events per year; HR, 0.73; 95% CI, 0.56-0.96) and mortality (3.01% vs. 4.30% events per year; HR, 0.71 95% CI, 0.60-0.84). The use of oral anticoagulants during follow-up was similar in patients with and without left atrial appendage occlusion, ruling out anticoagulation as the difference in the outcomes. Left atrial appendage occlusion was associated with higher rates of AF-related outpatient visits and the rate of hospitalization was slightly higher (0.36 vs. 0.32 events per person-year; p = 0.002).

Among patients with prior AF, the benefit of left atrial appendage occlusion was evident; in these patients, the annual incidence of stroke was 1.11% and 3.22% for mortality vs.1.71% and 4.93%, respectively, in those who did not undergo the procedure (p = 0.01 and p < 0.01 for both comparisons). However, there were no differences in the incidence of ischemic stroke/systemic embolism in AF patients treated with oral anticoagulants compared with those undergoing the occlusion procedure. The differences were not significant in patients without AF undergoing or not the occlusion procedure: for stroke/systemic embolism 1.23% vs. 1.26% per year, and for mortality 2.30% vs. 2.49% per year, respectively. Yet, the study failed to demonstrate statistical interaction between prior AF and the procedure.

Of interest, the rate of AF 30 days after surgery was greater in patients without AF during surgery with vs. without left atrial appendage occlusion: 27.7% vs. 20.2 % (HR 1.46; 95% CI, 1.22-1.73). In fact, in a multivariate analysis which considered all the patients in the database and not only those included in the propensity score analysis, in more than 50,000 patients without prior AF, left atrial appendage occlusion was an independent predictor of postoperative AF, with a HR of 1.48.

A first observation to take into account is that at the time of the coronary artery or heart valve surgery, 33% of the patients were with AF. As a result of the intention to match patients with and without left atrial appendage occlusion, the proportion of AF increased to 75% as this procedure is considered in AF patients. However, the use of anticoagulants before surgery in this selected population was only 30%, demonstrating an inadequate approach in most patients. How much could the use have been after surgery? What would have happened if such indication was high? Would these results be the same? We must remember that the intervention did not produce a significant effect in AF patients treated with oral anticoagulants. Was it due to their small number, or because surgery has little to add if the treatment is correct? In the population considered, the higher number of visits in the following year and the higher incidence of AF in patients without prior AF are a matter of concern, but obviously these figures lose relevance compared with the reduction in mortality. We should not forget that this is an observational study based on information retrieved from an administrative database. The use of the propensity score is an attempt to mimic a randomized study, which is clearly not the case, because the score is constructed with known variables, but not with those unknown. An ongoing randomized study is being carried out but includes only patients with AF undergoing coronary artery bypass surgery. An additional limitation is that the study does not distinguish the different forms of left atrial occlusion: excision or exclusion. In conclusion, it seems that left atrial appendage occlusion should be considered especially in AF patients undergoing coronary artery bypass surgery with strong reasons against anticoagulation therapy, or practical limitations.

Is it necessary to perform an ECG when screening for cardiovascular disease in asymptomatic persons?

Jonas DE, Reddy S, Middleton JC, Barclay C, Green J, Baker C et al. Screening for Cardiovascular Disease Risk With Resting or Exercise Electrocardiography: Evidence Report and Systematic Review for the US Preventive Services Task Force. **JAMA 2018;319:2315-28. http://doi.org/crm2**

Male sex, age, hypertension, diabetes, dyslipidemia, and smoking habits are considered to determine cardiovascular risk. Risk prediction equations, such as the Framingham Risk Score (FRS) or the Equation recommended by the AHA/ACC do not consider electrocardiography (ECG) findings. Yet, baseline or exercise ECG are common in cardiology practice. Many physicians consider that the information of the ECG complements the one provided by the clinical variables mentioned. But, is it really so?

In 2012, the US Preventive Services Task Force (USPSTF), a panel of experts dedicated to making recommendations on diagnostic or therapeutic measures to be performed in asymptomatic individuals to prevent adverse medical events, recommended against screening with ECG in asymptomatic adults at low risk for cardiovascular events, and stated that the need for screening for those at intermediate or high risk was uncertain. Since then, new studies have been published, introducing the need for updating this recommendation. A systematic review with reclassification of the evidence available requested by the USPSTF has been recently published.

Three questions were asked. To answer these questions, the review included English-language studies rated as good quality according to predefined criteria. Randomized clinical trials and nonrandomized controlled intervention studies comparing risk stratification using traditional risk factors alone vs. stratification using traditional risk factors plus ECG were eligible. Studies that included asymptomatic patients or with history of cardiovascular events were excluded.

The first question was: Does the addition of screening with resting or exercise ECG in asymptomatic persons improve health outcomes compared with traditional risk factor assessment alone? Does improvement in health outcomes vary for subgroups defined by baseline risk?

Only two randomized trials with a total of 1,151 participants that evaluated screening with exercise ECG (one using cycle ergometer and one using treadmill) in asymptomatic adults aged 50 to 75 years with diabetes could answer this question. The use of exercise ECG did not demonstrate significant reduction in the primary outcome (all-cause mortality, cardiovascular mortality, myocardial infarction, stroke or heart failure).

The second question focused on the ability of a model adding ECG to the traditional clinical variables to improve calibration ability (agreement between observed and predicted outcome), discrimination ability (to distinguish between persons who will and will not have an event) and reclassification ability (to correctly reassign persons into clinically meaningful risk categories).

Among the 14 studies included to answer this question, 5 cohort studies (n=9,582) evaluated exercise ECG. Data were not consistent. There was no precise information on the improvement in calibration and those studies reporting an effect on discrimination (explored with the area under the ROC curve) showed little significant improvement (increase between 0.02 and 0.03 with the use of ECG). Only one study explored reclassification and reported a reclassification improvement of 9.6% (18.9% in the intermediate risk group). Nine other studies (n=68,475) evaluated the usefulness of resting ECG. The overall information was imprecise and heterogeneous; some studies suggested non-significant changes in calibration, discrimination and reclassification, while others reported clear improvement.

The third question investigated the eventual harms of screening with ECG in asymptomatic persons. The answer was found in one of the two randomized studies mentioned in question 1. Twenty out of 262 participants in the group assigned to exercise ECG had positive exercise treadmill test findings. Among those 20 participants, 17 underwent coronary angiography and 12 a revascularization procedure. One of this 12 patients presented non-fatal AMI as a complication of the intervention.

In conclusion, the evidence to answer the three questions was not strong. There was considerable heterogeneity and inconsistency in the results. No studies explored the usefulness of exercise ECG in low-risk persons. In view of the excessive risk of events associated with invasive studies performed due to ECG findings, the USPSTF holds the recommendation against ECG screening in this subgroup of persons. In moderate to high-risk patients (based on data from the 1,511 diabetic patients mentioned above) there is no firm evidence of a favorable impact, and the improvement of the traditional prognostic models with the addition of ECG data is at least questionable. Thus, as there is still no consistent information for these patients, the decision is not to give a definite recommendation.

The basic problem that emerges in light of this systematic review is that the studies conducted so far on this subject have been carried out with different models, follow-up and definitions. And such heterogeneity of populations and designs is translated into an undeniable heterogeneity in the results. Which is the justification for not adding an ECG to screening when the risk is low? The limited improvement in discrimination ability and in inducing favorable changes in prognosis, while it may suggest the possibility of generating invasive studies with the undesirable consequence of some complication. On the other hand, and it is worth stopping here, although some studies have demonstrated improvement in the prognostic ability (particularly when all the abnormalities are considered) in moderate to high risk patients, we cannot recommend a uniform behavior. It is precisely in patients with moderate risk that the highest rate of reclassification occurs, driving them to low risk or high risk categories. It is then in this field where the individual clinical evaluation, the medical history, the physical examination and heuristics, will lead us to decide one way or another. Just as an example, the presence of hy-

pertension may lead to higher use of ECG. Again, it is clear that the simplest and most elementary practices which we understand are driven by common sense do not often have solid bases. It is extremely illustrative that with the uncountable number of ECGs performed on millions and millions of people each year, simple questions about its usefulness cannot be answered.

An easy way to predict late cardiogenic shock in patients with ST-segment elevation acute coronary syndrome

Auffret V, Cottin Y, Leurent G, Gilard M, Beer JC, Zabalawi A, et al. Predicting the development of in-hospital cardiogenic shock in patients with ST-segment elevation myocardial infarction treated by primary percutaneous coronary intervention: the ORBI risk score. **Eur Heart J 2018;39:2090-102. http://doi.org/crm3**

Despite the widespread use of early invasive strategies, cardiogenic shock (CS) is still a common complication of ST-segment elevation myocardial infarction (STEMI), present in 5% to 15% of the cases according to different publications. Mortality at one month ranges between 40% and 45%. We can make a difference between CS as an initial form of STEMI presentation, and CS as a complication of hospitalization. As the latter implies worse outcome, getting ahead of its presentation is essential to implement measures that attenuate its adverse impact. A recently published score predicts the incidence of in-hospital CS in STEMI patients undergoing percutaneous coronary intervention.

The score was built using the information retrieved from the prospective registry ORBI conducted in Brittany, France. Between 2006 and 2015, patients without CS on admission and treated with primary percutaneous coronary intervention were included in this analysis. Although the classic definition of CS considers hemodynamic measurements, as these are rarely available in routine practice, CS was defined using clinical criteria. Cardiogenic shock was defined as systolic blood pressure (SBP) ≤90mmHg for >30 minutes following exclusion of hypovolemia as its cause, and with clinical evidence of hypoperfusion, inotropic dependence, or mechanical left ventricular support to correct this situation. A total of 6,838 patients were considered, with median age of 62 years. The incidence of CS was 4.3% with in-hospital mortality rate of 43.7%.

On multivariate analysis, 11 variables were defined as independent predictors of CS and were used to generate the score: age >70 years (2 points), prior stroke (2 points), anterior MI (1 point), presentation as cardiac arrest (3 points), first medical contact to primary percutaneous coronary intervention >90 minutes (2 points), heart rate >90 beats/ minute on admission (3 points), SBP <125 mm Hg and pulse pressure < 45 mm Hg on admission (4 points), Killip class II (2 points) or III (6 points), culprit lesion of the left main coronary artery (5 points) and glycemia >180 mg/dl (3 points). The score ranged from 0 to 36 points. The optimal cut-off point identifying high-risk of in-hospital CS was a score of 8 (sensitivity 73.6%; specificity 79.5%) A score ≤7 was considered as low-risk for CS, <4%; one between 8 and 10 corresponded to low-to-intermediate risk, ≥4% and <10%; a value of 11 or 12 to intermediate-to-high risk, ≥10% and <15%, and a score ≥13 corresponded to high risk of CS, ≥15%. In the cohort of the ORBI registry, 77.4%, 13.5%, 4.3% and 4.8% of the patients presented these risk categories, respectively. And the performance of the score was adequate: there was an increasing incidence of CS in the 4 categories: 1.3%, 6.6%, 11.7%, and 31.8%. The score demonstrated high discrimination, with an area under the ROC curve of 0.84.

The score was validated in the cohort of the RICO registry from the Cote-d'Or region, which included similar patients. These patients were two years older and had more prevalence of comorbidities than those in the derivation cohort. The incidence of in-hospital CS was higher (8.3%) but in-hospital mortality associated with CS was lower (35.5%). The distribution of the risk categories in this case was 68.3%, 15%, 7% and 9.7% of the patients, respectively. The performance of the score was similar to that of the derivation cohort. The incidence of CS was 3.1%, 10.6%, 18.1% and 34.1%. The area under the ROC curve was 0.80, slightly inferior to the one of the ORBIT registry.

When CS is the form of presentation of MI, the diagnosis and management are clear. In contrast, the late presentation of CS is more insidious, and undoubtedly the lack of predicting the event, the delayed diagnosis, and the idea that the worst is over (especially when percutaneous coronary intervention of the culprit artery has already been performed at the initial stage) play an important role in the subsequent poor outcome. The present score included variables that are easy to obtain and allows for an acceptable definition of the risk of in-hospital CS. Of interest, the score does not consider hemodynamic variables and does not require determining lactate levels or documenting residual TIMI flow. The value of age, HR, SBP, glycemia on admission, and initial manifestations of heart failure is emphasized again. Any of these variables add more points to the score than the presence of anterior MI. Which is the usefulness of the score? From justifying a longer stay in the intensive care unit, to being more careful when indicating beta-blockers or angiotensin-converting enzyme inhibitors, to supporting the idea of the need for complete revascularization during hospitalization. An additional merit of the authors is that they validated the score in a population different from the one it was developed. Validation is usually carried out in the same setting in which derivation is performed: the score is derived, for example, from one part of the population studied and validated in the remaining part. Thus, its performance is logically expected to be correct. Validation in another population is what differentiates more credible scores.

Dual vs. triple antithrombotic therapy in patients with atrial fibrillation: which is better?

Golwala HB, Cannon CP, Steg PG, Doros G, Qamar A, Ellis SG, et al. Safety and efficacy of dual vs. triple antithrombotic therapy in patients with atrial fibrillation following percutaneous coronary intervention: a systematic review and meta-analysis of randomized clinical trials. **Eur Heart J 2018;39:1726-35a. http://doi.org/gdn454**

In patients with atrial fibrillation (AF), the use of oral anticoagulation (OAC) produces a significant reduction in the risk of cerebral and peripheral thromboembolic events. Dual antiplatelet therapy (DAPT) with aspirin and a P2Y12 inhibitor reduces the incidence of major cardiovascular and cerebrovascular events and stent thrombosis in patients undergoing percutaneous coronary intervention. Corollary: in AF patients undergoing percutaneous coronary interventions, triple antithrombotic therapy (TAT) with a combination of DAPT plus OAC would be necessary. Yet, TAT is also associated with increased risk of bleeding. This has led to investigate whether dual antithrombotic therapy (DAT), defined as a combination of one antiplatelet agent and an OAC could preserve the protection of TAT, but reducing the risk of bleeding.

The WOEST study (n=563) compared TAT with warfarin, aspirin and clopidogrel vs. DAT with warfarin and clopidogrel in patients with indication of percutaneous coronary intervention and need for anticoagulation (almost 70% with AF). Dual antiplatelet therapy was associated with a significantly lower incidence of bleeding without increasing the risk of ischemic events (although the power for efficacy assessment was insufficient). In the PIONEER AF-PC study (n=2,124), performed in AF patients who had undergone a percutaneous coronary intervention, DAT with rivaroxaban (15 mg daily) and a P2Y12 inhibitor, and TAT with rivaroxaban (5 mg daily) plus DAPT, were superior to conventional TAT with a vitamin K antagonist plus DAPT to reduce major bleeding without increasing the risk of ischemic events. In the ISAR-TRIPLE trial (n=614) patients who underwent drug eluting stent implantation treated with OAC and aspirin, were randomized to either 6-week or 6-month clopidogrel therapy, which means TAT initially for all the patients and DAT (aspirin plus OAC) vs. TAT from week 6 onwards. There were no differences in the rate of bleeding or ischemic events between both groups. Finally, in the RE-DUAL PCI trial (n=2,725), patients with paroxysmal, persistent or permanent AF who had successfully undergone a percutaneous coronary intervention were randomly assigned to receive one of three treatments: DAT with dabigatran (D) (110 mg twice daily) plus a P2Y12 inhibitor (110-mg D group), DAT with dabigatran (150 mg twice daily) plus a P2Y12 inhibitor (150-mg D group), or TAT with warfarin (with INR range between 2 and 3) plus aspirin and a P2Y12 inhibitor. In this group, aspirin was discontinued after 1 or 3 months in patients in whom a bare-metal stent or a drug-eluting stent, respectively, had been implanted. All the patients in the three groups received the P2Y12 inhibitor for at least 12 months after randomization. The incidence of major bleeding was significantly lower with DAT plus any of the dabigatran doses compared with TAT. The results did not show noninferiority for the incidence of ischemic events for each DAT group vs. the TAT group; but the combination of both DAT groups was noninferior to TAT. The study failed to demonstrate noninferiority for a composite endpoint of thromboembolic events and mortality.

A meta-analysis of these four studies has been recently published. The PIONEER AF-PCI trial rivaroxaban 5 mg arm (n = 709) was not included in the analysis as this is not an approved dose for thromboembolic protection in patients with AF. A total of 5,317 patients were included in the meta-analysis, 3,039 corresponding to the DAT arm. Mean follow-up was between 9 and 14 months, and mean age was 71 years. About 47% patients in the DAT arm and 45% patients in the TAT arm underwent percutaneous coronary intervention for acute coronary syndrome. Approximately 75% of patients in the DAT arm had a CHA_2DS_2VASc score ≥ 2 and 66% had a HAS BLED score ≥ 3. In the TAT score, 82% had a CHA_2DS_2VASc score >2 and 71% had a HAS BLED score ≥ 3.

Patients in the DAT arm demonstrated a reduction in major or minor bleeding TIMI risk (4.3% vs. 9.0%; HR 0.53, 95% CI, 0.36–0.85). The HR for intracranial bleeding was 0.58, although not achieving statistical significance. The incidence of major cardiovascular events (MACE) defined by each study was not different in both arms: 10.4% with DAT vs. 10% with TAT. The individual endpoints of all-cause mortality, cardiac mortality, stent thrombosis or stroke did not differ between the two groups. The incidence of bleeding or MACE did not differ when dabigatran 110 mg or 150 mg doses were analyzed separately.

This meta-analysis confirms the reduction in the incidence bleeding reported by previous studies and has sufficient power to show a similar effect on the risk of thromboembolic events. Although TAT is more effective in reducing the incidence of ischemic events, it should be noted that bleeding leads to treatment discontinuation, so that, paradoxically, its greater power to prevent thrombosis eventually produces an opposite effect: more bleeding with the same protection. In addition, the risk of thrombosis is lower with the novel stents, and the risk of gastrointestinal bleeding is lower with clopidogrel vs. aspirin. The fact that this is not a meta-analysis of individual data and that there is presence of heterogeneity among studies with different populations and treatments are limitations to the study. Some important baseline characteristics, as renal function, have not been considered. The ideal combination of antiplatelet agent and anticoagulant is not clear: is it aspirin or clopidogrel?, acenocumarol, warfarin or new oral anticoagulants? Finally, the

most appropriate decision in each case will come from the balance between ischemic and bleeding risk and the characteristics of the lesion, the complications of the procedure and the patient's conditions.

The importance of peripheral vascular disease: an analysis of the COMPASS trial

Anand SS, Caron F, Eikelboom JW, Bosch J, Dyal L, Aboyans V, et al. Major Adverse Limb Events and Mortality in Patients With Peripheral Artery Disease: The COMPASS Trial. **J Am Coll Cardiol 2018;71:2306-15. http://doi.org/gdn454**

A significant number of patients with cardiovascular disease also present peripheral artery disease (PAD). The prognostic implication of PAD and the events associated with this condition are not always taken into account. A sub-analysis of the COMPASS trial is an attempt to solve this issue.

The COMPASS trial analyzed whether the use of rivaroxaban in stable patients with coronary artery disease or PAD improved the outcome versus standard therapy. The study compared rivaroxaban alone or associated with aspirin versus aspirin alone. A total of included 27,395 patients with stable coronary artery disease, PAD or both were included, and were randomly assigned to one of three groups: rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily) with aspirin placebo, or aspirin (100 mg once daily) with rivaroxaban placebo twice daily. The primary efficacy outcome was the composite of cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction. The main safety outcome included fatal bleeding, symptomatic bleeding into a critical organ, perioperative bleeding requiring reoperation, and bleeding leading to hospitalization. When 50% of the primary efficacy events had occurred, a formal interim analyses of efficacy demonstrated statistically significant effect in the group of rivaroxaban plus aspirin versus aspirin alone, and the study was discontinued. The annual incidence of the composite primary outcome was 4.1% in the rivaroxaban 2.5 mg twice daily plus aspirin group vs. 5.4% in those who were assigned to aspirin plus rivaroxaban placebo (HR, 0.76; 95% CI, 0.66-0.86; p <0.0001). There was a significant reduction in all-cause mortality, but the incidence of major bleeding was greater. The combined risk of ischemic events and bleeding was lower with rivaroxaban plus aspirin than with aspirin alone (4.7% vs. 5.9%; HR, 0.80; 95% CI, 0.70-0.91). The comparison of rivaroxaban 5 mg twice daily with aspirin-matched placebo vs. aspirin and rivaroxaban-matched placebo did not show a significant difference in the primary efficacy outcome, but the rate of major bleeding was higher.

The analysis here presented corresponds to the 6,391 patients of the COMPASS trial with PAD. Mean age was 67.6 years and 27.9% were women. One third of the patients had prior history of peripheral revascularization and 5% of amputation. A history of coronary artery disease was present in 65.9% of the patients, 75% were current smokers or former smokers and almost 45% were diabetics; 69.7% were taking angiotensin-converting enzyme inhibitors or angiotensin receptor blocker medications and 82.3% were receiving statins. The primary outcome of this sub-study was the incidence of major adverse limb events (MALE), defined as acute lower limb ischemia (confirmed by limb arteriography or imaging and leading to an acute pharmacologic intervention, peripheral artery surgery, peripheral angioplasty or amputation within 30 days of onset of symptoms) or chronic limb ischemia (defined as continuing ischemic pain or intermittent claudication with pain at rest and/or throphic lesions leading to intervention).

Major adverse limb events occurred in 2% of the patients (n=128). The following independent predictors of MALE were identified: severe symptoms at rest (HR, 4.79; 95% CI 2.99-7.69), history of revascularization (HR, 2.44; 95% CI 1.71-3.50) or amputation (HR, 3.77; 95% CI 2.40-5.93) and randomization to the aspirin alone arm (HR, 1.63; 95% CI 1.15-2.31).

After MALE, patients presented an adverse outcome in the following year: 95% were hospitalized, 22.9% had amputation due to vascular causes, 3.8% presented major cardiovascular events and 8.7% died. The presence of MALE multiplied the risk of hospitalization by 7, the risk of amputation by 197 and that of all-cause mortality by 3. Interestingly, while the risk of death did not change after a MALE event in participants randomized to receive rivaroxaban and aspirin combination, there was a 6-fold risk of death after a MALE event for participants randomized to receive aspirin alone.

Compared with aspirin alone, participants randomized to receive rivaroxaban 2.5 mg twice daily and aspirin combination were less likely to suffer a MALE (HR 0.57) and amputation (HR 0.42). On the contrary, rivaroxaban 5 mg twice daily showed only a trend toward reduction in MALE, and no significant reduction in amputations.

The prognostic implication of PAD is not always taken into account. We are used to assessing major cardiovascular events, but we do not consider the role of MALE in patients' outcome. While this study provides rich information, some of its findings are obvious. It is more likely that among those with PAD, the risk of MALE will be higher for those with symptoms at rest or who have already undergone a major limb intervention, revascularization or amputation. But the magnitude of the number of short-term events following MALE is still striking: 95% of hospitalizations, nearly 4% risk of major cardiovascular events (cardiac mortality, non-fatal myocardial infarction or non-fatal stroke) and almost 9% of mortality. The association of MALE with major cardiovascular events reflects the extent and severity of the systemic cardiovascular disease. In addition, it should be noted that the risk of all-cause mortality far exceeded that of cardiovascular

mortality, which means that beyond the risk of cardiovascular events, these patients are at very high risk of other type of events (as renal dysfunction, cancer, etc.).The extremely high risk of amputation is a kind of self-fulfilling prophecy in patients with PAD (in one third of cases with a previous revascularization procedure) who have another severe event. A limitation of this study is the low number of events producing incidence rates with wide confidence intervals.

Worsening renal function in patients hospitalized due to heart failure is not necessarily associated with tubular injury

Ahmad T, Jackson K, Rao VS, Tang WHW, Brisco-Bacik MA, Chen HH, et al. Worsening Renal Function in Patients With Acute Heart Failure Undergoing Aggressive Diuresis Is Not Associated With Tubular Injury. **Circulation 2018;137:2016-28. http://doi.org/crtr**

In the setting of acute heart failure (AHF) hospitalizations, approximately 25% to 30% of patients have worsening renal function (WRF), defined as increase in serum creatinine of more than 0.3 mg/dL, or with other methods, increase in serum creatinine of more than 0.5 mg/dL, or 25% or 50% increase in the serum creatinine level compared with the value on admission, or 20% to 25% reduction in glomerular filtration rate or 0.3 mg/dL increase in cystatin C. In 2014, Damman et al. published a meta-analysis of 23 studies including 38,554 patients with acute heart failure, 23% of which had WRF. After a mean follow-up of almost 14 months, but with high dispersion, WRF was a predictor of mortality (OR 1.75; 95% CI 1.47-2.08). However, some lines of investigation suggest that not every WRF should be equally considered, and that its significance is not unequivocal. In this sense, a substudy of the ROSE study is clearly descriptive. The study comprised 360 patients who were hospitalized for the treatment of AHF with median left ventricular ejection fraction of 33% and mean glomerular filtration rate of 42 ml/min/1,73 m2. All the patients were treated with open-label, intravenous (IV) furosemide with a total daily dose equal to 2.5 times the total daily oral dose they were receiving during 7 days before admission, to achieve a significant reduction of systemic congestion. The aim of the study was to compare the effect of two drugs which are considered to be "protective" of kidney function in the setting of aggressive treatment with diuretics. Participants were randomized to "diuretic dose" dopamine (2 μg/kg/min), nesiritide 5 ng/kg/min or placebo. Worsening renal functioning was defined as ≥20% reduction in glomerular filtration rate at 72-hours of admission. Creatinine and cystatin C levels were measured as expression of glomerular filtration rate and three kidney tubular injury biomarkers were determined: neutrophil gelatinase-associated lipocalin (NGAL), kidney injury molecule 1 (KIM-1) and N-acetyl-beta-D-glucosaminidase (NAG).

This analysis reports the information of 283 patients. Patients received a median 560 mg of furosemide equivalents which induced a median urine output of 8.42 l over the 72-hour intervention period. Twenty-one percent of the patients presented WRF. The baseline characteristics of the patients with or without WRF were similar, except for lower creatinine levels in the group with WRF (mean 1.48 vs. 1.67 mg/dL, p = 0.02). Baseline tubular injury biomarkers levels and median daily furosemide dose were also similar. As we know, there was no difference in the incidence of WRF in the three treatment arms of the ROSE study, a strong blow on the idea that routine use of the pharmacological interventions evaluated may be beneficial to protect renal function in the setting of AHF. Therefore, the information of the three arms was analyzed as a whole in this sub-study. The most interesting finding is the absence of significant differences in the levels of tubular injury biomarkers in patients with or without WRF. While KIN1 and NAG levels did not vary over the study period, NGAL levels tended to decrease. Only NGAL demonstrated a statistically significant but very low correlation coefficient with the change in cystatin C (r=0.14), representing an association between a tubular injury biomarker with a glomerular function biomarker. There was no correlation between the change in NAG or KIM-1 with the change in cystatin C. Similar results were found when examining the change in creatinine with biomarkers. Over a median follow-up of 6 months, 19.4% of the patients died. A paradoxical result was obtained after adjustment for baseline covariates and treatments: there was a slight but statistically significant association between higher biomarker levels during hospitalization and lower mortality at 6 months (a 10 to 12% reduction per 10% increase in biomarker level, and a 20% reduction when the three biomarkers were considered together). Worsening renal function was not a predictor of adverse outcome.

Testani et al. have already demonstrated that patients with hemoconcentration during treatment with intravenous diuretics (defined by an increase in hematocrit, plasma proteins or albumin levels) are more likely to present WRF. However, hemoconcentration is associated with improved survival at 6 months. Worsening renal function in the setting of hospitalization does not seem to be unequivocally associated with adverse outcome: different studies demonstrate that when WRF expresses aggressive decongestion, it may be related with improved prognosis. We will certainly need to make progress in understanding the intrinsic meaning of WRF and how to define it. As we can see, the use of creatinine has drawbacks and false positives. For the time being, tubular injury biomarkers do not seem to be the gold standard in terms of their predictive ability, discussed in studies evaluating the validity of tests. Cardiorenal syndrome is still an elusive entity.