

JORGE THIERER ^{MTSAC}**SYNTAX score II: a useful tool to decide type of revascularization therapy**

Farooq V, van Klaveren D, Steyerberg EW, Meliga E, Vergouwe Y, Chieffo A et al. Anatomical and clinical characteristics to guide decision making between coronary artery bypass surgery and percutaneous coronary intervention for individual patients: development and validation of SYNTAX score II. *Lancet* 2013;381:639-50.

The SYNTAX score (SS), based on the anatomical characteristics of coronary artery disease, is recommended by practice guidelines to decide between percutaneous coronary intervention (PCI) with drug-eluting stent or coronary artery bypass graft (CABG) surgery in patients with unprotected left main coronary artery stenosis or three-vessel disease. The score has been criticized for considering only anatomical variables, without taking into account other factors that may influence the results of both procedures.

Therefore, the SYNTAX score II (SS II) was developed using baseline features and 4-year follow-up information recorded in the SYNTAX study. In addition to SS and the presence or absence of left main coronary artery disease, this novel score considers age, gender, creatinine clearance, left ventricular ejection fraction, chronic obstructive lung disease and peripheral vascular disease. The predictive accuracy of the score for mortality was validated in the study population and in a multinational registry.

In patients with left main coronary artery disease, SS II yielded similar mortality for PCI or CABG surgery in 79.7% of patients, which was significantly lower with CABG surgery in 11.5% and with PCI in 8.8% of patients. With SS II < 23, the score predicted significantly lower mortality with PCI in 18.2% of patients and with CABG surgery in 2.7%. With SS II > 33, these figures were reversed: 0.7% vs. 19.2%.

In patients with three-vessel disease, the SS II yielded similar mortality for PCI or CABG surgery in 58.8% of patients. This prediction was significantly lower with CABG surgery in 40.7% and with PCI in 0.5% of patients. With SS II < 23, the score predicted significantly lower mortality with CABG surgery in 19.2% of patients and with PCI in 1.4%. With SS II > 33, the differences were greater: 68.1% vs. 0%.

Younger patients, female sex and reduced ventricular function tipped the scale in favor of CABG surgery, requiring lower SS to achieve similar predicted mortality than PCI. Conversely, older age, left main coronary artery disease, and pulmonary disease favored PCI requiring higher SS to achieve similar

CABG predicted mortality.

The application of the SS II to daily practice still seems difficult; as in most patients the outcome is similar with any of both procedures. The clinical value of the publication is that it reminds us of the presence of other variables beyond anatomy which should be considered at the moment of deciding which approach to use.

Abdominal aortic aneurysm: natural history and adequate surveillance

Bown MJ, Sweeting MJ, Brown LC, Powell J, Thompson S. Surveillance intervals for small abdominal aortic aneurysms: a meta-analysis. *JAMA* 2013;309:806-13.

Abdominal aortic aneurysms (AAA) with a diameter > 5.5 mm should undergo surgery as they have high risk of rupture with a survival rate ≤ 20%. In smaller aneurysms, mortality due to rupture is lower than surgical mortality. The duration of ultrasound surveillance intervals to prevent late indication of surgery is not clear. The meta-analysis presented here evaluates the velocity of progression of small AAA to reach 5.5 cm in diameter and the associated risk of rupture.

Repeated individual follow-up ultrasound measurements were analyzed in 15471 patients (13728 men) from 18 studies with AAA measuring 3-5.4 cm at the time of diagnosis. Data were censored when diameter was ≥ 5.5 cm, non-rupture-related death occurred, an elective AAA operation was decided, or at the end of the available follow-up period in each data set. The average follow-up ranged from 1 to 8 years.

In male patients, AAA of 3.0-cm had an estimated mean growth rate of 1.28 mm per year and the mean time of having 10% chance of reaching 5.5 cm was 7.4 years. When the aneurysm diameter was 5.0 cm, the mean estimated growth rate was 3.6 mm per year and the mean time of having 10% chance of reaching 5.5 cm was 0.7 years. Rate of rupture ranged from 0 to 0.77 % per year. Each 5-mm increase in baseline AAA diameter resulted in 0.6-mm increase in progression rate per year and in almost twofold increase in risk of rupture. For AAA diameters in the range of 3.0 cm to 4.5 cm, the average time to reach a rupture risk of 1% was at least 2 years, and 1.4 years for an AAA diameter of 5 cm.

Based on this data, the surveillance intervals could be of 2 to 3 years for men with AAAs measuring 3.0 to 3.9 cm, 1 to 2 years with AAAs ranging from 4.0 to 4.4 cm, and 6 months to 1 year for those with AAAs

between 4.5 and 5.4 cm.

Surveillance should be stricter in women as the rupture rate was at least 4 times higher than that of men despite similar growth rate. The cutoff value to indicate surgery in women might be lower, though there is lack of evidence from randomized studies.

This meta-analysis contributes to reveal the natural history of AAA and define the need of its surveillance. It also confirms that small AAAs take years to progress. Of importance, as substantial heterogeneity was found among the results, the lowest proposed surveillance interval should be considered in the first place.

Independent effect and interaction of statin therapy and fitness in the outcome of dyslipidemic patients

Kokkinos PF, Faselis C, Myers J, Panagiotakos D, Doumas M. Interactive effects of fitness and statin treatment on mortality risk in veterans with dyslipidaemia: a cohort study. *Lancet* 2013;381:394-9.

Several randomized trials have demonstrated that statins improve the outcome of dyslipidemic patients in primary and secondary cardiovascular disease prevention. In turn, data from epidemiological studies suggest that fitness is associated with a better outcome in apparently healthy subjects and in persons with cardiovascular disease. A cohort study was conducted by the Veteran Affairs Medical Centers in the USA to answer the question about the combined effects of fitness and statin treatment.

The cohort included 10043 dyslipidemic men who underwent an exercise stress test either as part of a routine evaluation or to assess exercise-induced ischemia between 1986 and 2011. The presence or absence of treatment with statins at the moment of enrollment was also considered.

Mean age was 58.8 years. Fifty-one percent of men were treated with statins. These subjects tended to be older and had higher prevalences of cardiovascular disease, smoking habits, hypertension, diabetes, and use of aspirin, β blockers and angiotensin-converting enzyme inhibitors. During a median follow-up of 10 years, mortality was significantly higher in subjects not treated with statins: 27.7% vs. 18.5%. After adjusting for age, baseline conditions and additional drug therapy, treatment with statins and fitness were independent predictors of survival. Adjusted mortality risk was also significantly lower for patients taking statins than for those not taking statins (HR 0.65, 95% CI 0.59–0.71). For every 1-MET increase in fitness, adjusted mortality decreased by 12%, with statistically significant interaction: mortality decreased by 17% in patients taking statins and 11% in those not taking statins. After excluding patients who died within the first 2-year followup in whom low fitness might be explained by underlying diseases, the results remained unchanged. Mortality rate in patients treated with statins with fitness ≤ 5 METs was similar to

that of patients not treated with statins with fitness of 5.1 - 7 METs.

This study demonstrates the importance of the combination of statins and fitness in primary and secondary prevention in dyslipidemic patients. However, as the study was not randomized for any of the two conditions, other factors (especially concerning fitness) might be in part responsible for the magnitude of the association with mortality.

Tobacco use in women: prognostic value and importance of giving-up

Pirie K, Peto R, Reeves GK, Green J, Beral V. The 21st century hazards of smoking and benefits of stopping: a prospective study of one million women in the UK. *Lancet* 2013;381:133-41.

Smoking habits spread lately in women compared to men, reaching the highest peak in the second half of the 20th century. Probably, the real risk of tobacco use in women has been underestimated by studies conducted in the last century. The Million Women Study, focused primarily on breast cancer, recruited women between 50 and 69 years in the United Kingdom from 1996 and 2006. They were asked, among other topics, whether they were current or ex-smokers, and in case of smokers at study entry, how many cigarettes they smoked daily. At the 3-year resurvey, women were asked about their current smoking status and at what age they had started or stopped smoking regularly. Follow-up continued until the beginning of 2011. Women with history of cancer, cardiovascular disease, cerebrovascular disease, current respiratory disease treatment, or who had stopped smoking after the age of 55 were excluded from the study.

The analysis included 1180652 women with average age of 55 years, 20% of which were current smokers and 28% ex-smokers. Mortality rate was of 6% after a mean follow-up of 12 years.

The adjusted mortality RR of those who had been current smokers in the initial survey compared to never-smokers was 2.76, (95% CI 2.71–2.81) and those who were still smoking at the 3-year resurvey had a mortality RR of 2.97 (95% CI 2.88–3.07). The RR was 2 in women smoking fewer than ten cigarettes per day in the initial survey, and over 3 in those smoking more than 20 cigarettes, a value that increased the earlier the smoking habit. The RR was significantly greater in current smokers, particularly for lung cancer and chronic obstructive lung disease. Mortality RR for coronary artery disease decreased with age: 6.6 for women between 50 and 59 years and 3.3 for those > 70 years. The probability of death before the age of 80 years was 53% for current smokers and 22% for non-smokers.

Ex-smokers had greater risk than non-smokers, but significantly lower than current smokers: all-mortality RR was 1.56 (95% CI 1.49-1.64) for women who had stopped smoking between the age 45 and

54 years, 1.20 (95% CI 1.14-1.26) for those who had stopped smoking between 35 and 44 years, and 1.05 (95% CI 1.00-1.11) for those who had stopped smoking between 25 and 34 years.

Damage caused by smoking is unquestionable, even in women smoking a small number of cigarettes and for a few years. However, the benefits of cessation, even during middle-aged, can prevent a great number of deaths attributed to smoking.

Is right bundle branch block a trivial finding in healthy people?

Bussink BE, Holst AG, Jespersen L, Deckers JW, Jensen GB, Prescott E. Right bundle branch block: prevalence, risk factors, and outcome in the general population: results from the Copenhagen City Heart Study. *Eur Heart J* 2013;34:138-46.

The prevalence of right bundle branch block (RBBB) increases with age. It is higher in people with hypertension, diabetes, heart disease or lung disease in whom it may be associated with an adverse outcome. The presence of RBBB in healthy asymptomatic subjects is considered a benign finding. Incomplete right bundle branch block (IRBBB) is more common and has similar considerations.

Data from a prospective cohort study including 18974 randomized subjects, performed in Copenhagen between 1976 and 2003, questions this statement. Right bundle branch block was defined as QRS \geq 120 ms, with R' wave $>$ R wave in V1 or V2 or right QRS axis deviation with R wave \geq 60 ms in V1 or V2; or QRS with S wave $>$ R wave in LI and LII. IRBBB was defined as QRS $<$ 120 ms with R' wave $>$ R wave in V1 or V2.

After excluding subjects with previous myocardial infarction or heart failure and those with left bundle branch block, 18441 subjects were considered for study analysis, with a median follow-up of 20.5 years. The prevalence of IRBBB was 4.7% in men and 2.3% in women, and that of RBBB was 1.4% in men and 0.5% in women. The prevalence of RBBB increased with age, reaching 14.3% in men $>$ 80 years, and was associated with higher blood pressure levels in men and high cholesterol levels in women. At the 5-year follow-up, the incidence of IRBBB was 2.4% and that of RBBB 0.5%.

The adjusted HR of RBBB for all-cause mortality was 1.24 (95% CI 1.05-1.47), mainly due to cardiovascular mortality (HR 1.56, 95% CI 1.23-1.99). Right bundle branch block was associated with need of definitive pacemaker insertion in 7% of cases and increased risk of myocardial infarction. The presence of IRBBB was not associated with any adverse outcome.

This is the largest study conducted on RBBB, with the highest number of observations and follow-up period performed to date, confirming its low prevalence in the general population and its association with male gender and increasing age. The study reveals the prognostic value of RBBB and suggests that its occurrence

justifies a thorough evaluation for risk factors or underlying cardiovascular disease.

Extended use of dabigatran, warfarin, or placebo in venous thromboembolism

Schulman S, Kearon C, Kakkar AK, Schellong S, Eriksson H, Baanstra D et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. *N Engl J Med* 2013;368:709-18.

Dabigatran is a direct thrombin inhibitor. At a dose of 150 mg twice daily, it has been shown to be non-inferior to warfarin during the first 6 months of treatment of venous thromboembolism (VTE) and has been associated with a lower rate of clinically relevant nonmajor bleeding. Recently, two multicenter, randomized, double-blind clinical trials were published comparing dabigatran vs. warfarin (RE-MEDY), and dabigatran vs. placebo (RE-SONATE) in patients with VTE who had completed at least 3 months of anticoagulant therapy.

In both studies, the primary efficacy outcome was symptomatic recurrence or fatal VTE. Safety outcomes included major bleeding and clinically relevant nonmajor bleeding. Patients were eligible if they had symptomatic deep-vein thrombosis (DVT) or pulmonary embolism under approved oral anticoagulation therapy or dabigatran.

The RE-MEDY study was designed to prove that dabigatran is not inferior to warfarin and the RE-SONATE study was designed to demonstrate that dabigatran was superior to placebo. In both studies, average age was around 55 years and two-thirds of the population presented DVT as index event.

In the RE-MEDY study, 1430 patients were assigned to dabigatran and 1246 to warfarin. The primary efficacy outcome was confirmed in 1.8% patients with dabigatran and in 1.3% with warfarin; HR 1.44 (95% CI 0.78- 2.64), with a p value =0.01 for non inferiority. In the warfarin group, the INR was in the therapeutic range (2.0 to 3.0) for a median time of 65.3 %. The incidence of major bleeding or clinically relevant nonmajor bleeding was lower in the dabigatran group; HR 0.54 (95 % CI 0.41-0.71), but the incidence of acute coronary syndrome was significantly higher (0.9% vs. 0.2 %).

In the RE-SONATE study, 681 patients were assigned to dabigatran and 662 to placebo. The primary efficacy outcome was confirmed in 0.4% patients with dabigatran and in 5.6% with placebo; HR 0.08 (95 % CI 0.02- 0.25), but the incidence of major bleeding or clinically relevant nonmajor bleeding was significantly higher in the dabigatran group; HR 2.92 (95 % CI 1.52-5.60).

Dabigatran is non-inferior to warfarin and superior to placebo to prevent recurrent thromboembolic events. It is also safer than warfarin but with higher risk of bleeding compared to placebo. The higher risk of acute coronary syndrome should be considered at the moment of selecting patients.

The cycle for polyunsaturated fatty acids in atrial fibrillation prevention is closed

Macchia A, Grancelli H, Varini S, Nul D, Laffaye N, Mariani J et al. Omega-3 fatty acids for the prevention of recurrent symptomatic atrial fibrillation: results of the FORWARD (Randomized Trial to Assess Efficacy of PUFA for the Maintenance of Sinus Rhythm in Persistent Atrial Fibrillation) trial. *J Am Coll Cardiol* 2013;61:463-8.

Mariani J, Doval H, Nul D, Varini S, Grancelli H, Ferrante D et al. N-3 polyunsaturated fatty acids to prevent atrial fibrillation: updated systematic review and meta-analysis of randomized controlled trials. *J Am Heart Assoc* 2013; 2: 1-13

Atrial fibrillation (AF) increases mortality and thromboembolism, and affects quality of life. Some studies suggest that N-3 polyunsaturated fatty acids (N-3 PUFA) may decrease the incidence of AF and prevent recurrences. The recently published FORWARD clinical trial was a randomized, double-blind, placebo-controlled study performed in Argentina to evaluate the efficacy of n-3 PUFA to maintain sinus rhythm in patients with previous AF.

The study included 586 patients in sinus rhythm with at least two episodes of symptomatic AF in the previous 6 months, the last episode occurring between 3 and 90 days prior to randomization, or either electrical or pharmacological cardioversion due to persistent AF in the previous 3 to 28 days before randomization. To avoid the inclusion of patients with lone AF, all subjects < 65 years of age should have moderate-to-high risk of stroke.

Patients were randomly allocated to n-3 PUFA (containing 850 to 882 mg of eicosapentaenoic acid/docosahexaenoic acid) per day or placebo.

The primary efficacy outcome was the time to symptomatic or documented asymptomatic AF recurrence. The secondary outcome was the composite of all-cause mortality, nonfatal stroke, nonfatal acute myocardial infarction, systemic embolism, heart failure, or major bleeding.

Seventy-three percent of patients required cardioversion, 9.4% presented \geq two episodes of AF within 6 months before randomization, and 17.6% had both criteria. Average age was 66.1 years, with high prevalence of hypertension (91.4%) and low prevalence of heart failure (14.1%). Previous treatment with amiodarone was present in 63.5% of patients and 60.2% were receiving beta blockers. There were no significant differences in the incidence of recurrent symptomatic AF (18.9% with placebo vs. 24% with n-3 PUFA) or in the composite endpoint (6.7% with n-3 AGPI vs. 5.5% with placebo).

In patients with previous AF, n-3 PUFA do not prevent recurrent AF. This finding was confirmed by a meta-analysis that incorporated this study and also evaluated the effect of n-3 PUFA on postoperative AF (4667 patients).

Is serelaxin a justified hope or just an illusion for the treatment of heart failure?

Teerlink JR, Cotter G, Davison BA, Felker G, Filipatos G, Greenberg B et al. Serelaxin, recombinant human relaxin-2, for treatment of acute heart failure (RELAX-AHF): a randomised, placebo-controlled trial. *Lancet* 2013;381:29-39.

Serelaxin is a recombinant form of human relaxin 2. Serelaxin receptors are found in the vessels and the heart. It produces vasodilation and has anti-remodeling, anti-apoptotic and anti-inflammatory effects.

The RELAX-AHF study was a randomized, double-blind, placebo-controlled trial evaluating serelaxin effects in acute heart failure. The study enrolled patients admitted to hospital within 16 hours after onset of symptoms with dyspnea, congestion on chest X-rays, BNP \geq 350 pg/ml or NT-proBNP \geq 1400 pg/ml, systolic blood pressure > 125 mm Hg and creatinine clearance between 30 and 75 ml/min/1.73 m². Patients could be included after receiving at least 40 mg of furosemide but no other intravenous drugs to treat heart failure, except nitrates if systolic blood pressure was > 150 mm Hg. Patients were randomly assigned to 48-h intravenous infusion of serelaxin (30 μ g/kg per day) or placebo. The study had two primary efficacy endpoints: change in the sensation of breathlessness in a visual analogue scale between admission and day 5 and the proportion of patients with improvement of dyspnea measured in a Likert scale at 6, 12 and 24 hours. The secondary efficacy endpoints were days alive and out of hospital at 60 days and a composite of cardiovascular mortality, readmission due to heart failure or kidney failure before day 60. Other additional efficacy endpoints were duration of hospitalization and rate of events at 180 days.

A total of 580 patients were randomly assigned to placebo and 581 to active treatment; mean age was 72 years, average blood pressure was 142/82 and mean left ventricular ejection fraction was 38.7%. Serelaxin improved the visual analogue scale primary endpoint of dyspnea but had no significant effect on either the other primary endpoint nor in both secondary endpoints (at 60 days, there were 27 cardiovascular deaths and 50 rehospitalizations with placebo, and 19 deaths y 60 rehospitalizations with serelaxin). However, serelaxin reduced cardiovascular mortality at 180 days (35 vs. 55 deaths) and all-cause mortality (42 vs. 55 deaths).

Serelaxin significantly improved only one out of the four most important endpoints; however, the reduction in mortality at 6 months gives rise to several questions. Was this finding achieved by chance? Is this effect due to the drug or could it be expected with any other vasodilator as nitroglycerin or sodium nitroprusside, when compared to placebo? Was it appropriate to compare serelaxin to placebo? All these questions should be answered by future research.